RECENT UPDATES ON Q FEVER: DIAGNOSIS AND TREATMENT

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Summary

Q or "query" fever is a zoonosis caused by the organism Coxiella burnetii. Cattle, sheep and goats are the most common reservoirs of this organism. The placenta of infected animals contains high numbers (up to 10^9/g) of C. burnetii. Aerosols occur at the time of parturition and man becomes infected following inhalation of the microorganism. The spectrum of illness in man is wide and consists of acute and chronic forms. Acute Q fever is most often a self-limited flu-like illness but may include pneumonia, hepatitis, or meningoencephalitis. Chronic Q fever almost always means endocarditis and rarely osteomyelitis. Chronic Q fever is not known to occur in animals other than man. An increased abortion and stillbirth rate are seen in infected domestic ungulates. Four provinces (Nova Scotia, New Brunswick, Ontario and Alberta) reported cases of Q fever in 1989. A vaccine for Q fever has recently been licensed in Australia.

keywords: Q fever, agent, C. burnetii, infection, epidemiology.

Introduction

History

In August 1935, Dr. E. H. Derrick (MD, Melbourne university, 1922), the Director of the Laboratory of Microbiology and Pathology of the Queensland Health Department at Brisbane, Australia, was asked to investigate an outbreak of undiagnosed febrile illness among abattoir workers in Brisbane [1]. This illness he named "Q" for "Query" fever. Derrick inoculated guinea pigs with blood or urine from the "Q" fever patients. The guinea pigs became febrile. Derrick was unable to isolate the agent responsible for the fever so he sent a saline emulsion of infected guinea pig liver to Macfarlane Burnet in Melbourne. Burnet was able to isolate organisms which "appeared to be of rickettsial nature" [2]. At about the same time Drs. Herald Rea Cox and Gordon Davis at Rocky Mountain Laboratory, Montana were working on the possible vectors of Rocky Mountain spotted fever and tularemia. Davis had ticks (the suspected vectors) feed on guinea pigs; the guinea pigs became ill. In May 1938, Dr. Rolla Dyer, the Director of the National Institute of Health visited Cox in Montana to challenge Cox's report that he had cultivated rickettsiae in large numbers in embryonated eggs. Ten days later he became ill with retro-orbital pain, fever, chills and sweats. Five mL of his blood drawn on the sixth day of his
illness resulted in fever when injected into guinea pigs. Subsequent studies showed that this agent was identical to the Nine Mile agent isolated from ticks. In April 1938, Burnet sent Dyer spleens mice infected with the Q fever agent; Dyer showed that the Q fever agent was identical to Nine Mile agent (3). Cox named the Nine Mile agent Rickettsia diaporica (diaporica means having the property or ability to pass through) a reference to the filterable property of the agent (4). Meantime in Australia, Derrick proposed the name of Rickettsia burnetii for the Q fever agent (5). In 1948 Cornelius B. Philip proposed that R. burnetii be considered as the single species of a distinct genus since it was now apparent that this organism was unique among the rickettsiae (6). He proposed the name Coxiella (6). The Q fever agent is now known as Coxiella burnetii. Cox and Burnet both died in 1986 (3).

Figure 1. It shows the chest radiograph of a patient with Q fever pneumonia. Note three opacities in the right lung and two in the left.

Epidemiology

The initial description of Q fever as an illness occurring among abattoir workers (1) was a strong portender of the epidemiology of this illness. The epidemiology of Q fever in man is linked to the epidemiology of Q fever in animals. Q fever is a zoonosis. Of all the animals infected by C. burnetii, man is the animal to usually develop illness as a result of infection (7). Man becomes infected following inhalation of C. burnetii. The desiccation-resistant organism is shed from infected animals, usually cattle, sheep, goats or cats, especially at the time of parturition. Air samples are positive for weeks following parturition and viable organisms are present in the soil for periods of up to 150 days (8). Two characteristics of the organism are important in the epidemiology of the disease. These are its ability to withstand harsh environmental conditions, probably as a result of spore formation (9), and its extraordinary virulence for man. A single organism can cause disease in man (10). Coxiella burnetii has been a very successful pathogen. By 1955 Q fever had been reported from 51 countries on five continents (11). From the very beginning, outbreaks have dominated the epidemiology of Q fever. These can occur even following indirect exposure to contaminated aerosols, as was the case when 415 residents of a Swiss valley, who lived along a road over which sheep travelled to and from mountain pastures, developed Q fever (12).

Occasionally, large outbreaks of Q fever may occur and the source of the infection may not be apparent. Recently, May to July 1989, more than 100 cases of Q fever occurred in the West Midlands of England, chiefly Birmingham. No common source has been found but, since
the outbreak coincided with the lambing period of sheep and as the summer was early and dry, it is postulated that wind-borne contaminated dust resulted in the outbreak (13). Institution-related outbreaks have been important from the early days of laboratory work with C. burnetii to the present. From 1938 to 1955, 266 laboratory workers world-wide developed Q fever (14). Since the 1960’s, the epidemiology of institution acquired Q fever has changed. Since then there have been several outbreaks of Q fever due to the use of infected pregnant sheep in research (15-17). Transportation of these infected sheep along heavily travelled corridors has resulted in infection of individuals who were not involved in the research. Some studies have suggested that ingestion of raw (contaminated) milk is a risk factor for the acquisition of Q fever (18-20). Serocconversion, but not disease, did occur following ingestion of raw milk (21).

It is likely that, in some populations, ingestion of infected material accounts for the high seropositivity rate. Ingestion of C. burnetii is probably important in the maintenance of Q fever in the animal population. Cats experimentally infected via the oral route did not become ill, whereas cats infected via the subcutaneous route became febrile and lethargic (22). Percutaneous infection can occur (23,24), but accounts for very few cases of Q fever worldwide. While C. burnetii has been isolated from human placentas (25), there is little to suggest that vertical transmission occurs in man. Person-to-person transmission has been documented but it is very unusual. Pneumonia occurred among two pathologists, a nurse, and an autopsy attendant who performed a postmortem examination on a patient who had died from C. burnetii pneumonia (26). Twelve cases of Q fever occurred at the Institute of Pathology at Tubingen University - person-to-person transmission is assumed to have occurred but the source of the infection was not found (27).

Recently Mann et al (28) described what they feel is person to person transmission of Q fever in a family. I have not observed transmission of Q fever from patients to medical staff. There is no need to isolate patients hospitalized with this illness (29), however precautions should be taken in the handling or postmortem examination of infected cadavers (30). Sexual transmission of C. burnetii has been demonstrated in mice in the laboratory (31), but whether Q fever can be transmitted sexually under natural conditions and in other animal species is unknown. Worldwide, there is a remarkable diversity in the epidemiology of Q fever.

In some areas there always seem to be human cases of Q fever, while in other areas with the same rate of infection in animals, spread to man does not occur (10,32). Q fever in Nova Scotia has also followed exposure to infected rabbits and to the contaminated [by new-born kittens] clothing of a worker in a truck repair facility. Many questions remain unanswered about the epidemiology of pneumonia in Nova Scotia. Why are cats so important in the epidemiology of infection in this province? How do the cats become infected? Pneumonia is the predominant manifestation of Q fever in Nova Scotia - why? We have also found that infected cats have resulted in cases of Q fever in Prince Edward Island and New Brunswick (TJ Marrie - unpublished observations). Whether or not cat-related Q fever is limited to Maritime Canada awaits further study. Q fever occurs throughout the year in Nova Scotia, however only a few cases occur during the winter. Fourteen percent of 1684 Nova Scotians had antibodies (indirect fluorescent antibody test) to phase II C. burnetii antigen. The rate of seropositivity among males and females was equal, but males outnumbered females by 2:1 among the 180 cases of acute Q fever that we have studied so far. The rate of seropositivity was highest among veterinarians - 49% of those tested had antibodies to phase II antigen (31).

It is likely that strain differences of C. burnetii are important in the epidemiology of Q fever. This may explain why the predominant manifestation of Q fever in Nova Scotia is pneumonia, while in Ontario granulomatous hepatitis occurs in addition to other manifestations of Q fever (33-36). This is probably the explanation of why the rate of chronic Q fever (mainly endocarditis) varies from country to country. Chronic Q fever is uncommon in the United States and Australia, whereas it is quite common in England and France.
The organism

Coxiella burnetii is a highly pleomorphic coccobacillus with a gram-negative cell wall. Unlike true rickettsiae it enters the cell by a passive mechanism. Within the cell it survives within the phagolysosome - the low pH of this environment is necessary for the metabolic functioning of C. burnetii. Coxiella burnetii undergoes phase variation. 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 gradual conversion to phase II a virulent forms. These two antigenic phases differ in the sugar composition of their lipopolysaccharides, in their buoyant density in cesium chloride, and in their affinity for hematoxylin and basic fuchsin dyes. Plasmids have been found in both phase I and phase II cells. There are three different plasmid types varying in length from 36 to 45 kilo bases.

Q fever in animals

Coxiella burnetii can infect a large number of animal species including livestock. These animals rarely become systemically ill from Coxiella burnetii, but abortion and stillbirths may occur. Endocarditis, the major form of chronic Q fever in man, does not seem to occur in other animals. Coxiella burnetii localizes in the uterus and mammary glands of infected animals. In some instances, cattle have been resistant to infection by intranasal, intravenous, and intravaginal inoculation and by feeding contaminated bran, however in other studies intranasal infection of a pregnant cow by means of an atomizer did lead to infection and recovery of the organisms from the placenta. Coxiella burnetii has been recovered from the placentas of naturally infected dairy cows. Similarly, this organism has been isolated from the placentas of naturally infected and experimentally infected sheep, and has been found in the amniotic fluid of these animals. Coxiella burnetii has been transmitted transplacentally in a guinea pig model of infection. Cows have been known to shed C. burnetii in milk for up to 32 months, while sheep shed the organism in feces for 11 to 18 days postpartum. Outbreaks of abortion due to C. burnetii were first reported in goats and later in cattle. Inflammation of the placenta has been demonstrated in sheep and goats in instances where C. burnetii has caused abortion. Histological examination of the placenta shows trophoblasts distended with the bacilli and necrotic villi. Stresses such as overcrowding and the immune suppression of pregnancy are associated with multiplication of C. burnetii in the placenta.

The placentas of infected sheep can contain 109 hamster infective doses per gram of tissue. We have noted that the stillbirth rate among infected cats is high compared with the quoted background rate of 10%. The following additional domestic animal species have been found to be infected by C. burnetii in some areas: pigs, horses, dogs. Infected cattle, sheep and goats are most commonly associated with transmission of Q fever to man. We have shown that cats are the major source of Q fever for humans in Nova Scotia and Prince Edward Island. Dogs have been infrequently associated with transmission of C. burnetii to man; the reasons for this are not readily apparent. Interestingly enough, we could not demonstrate any infection by C. burnetii among dogs in Nova Scotia despite the preeminence of cats in the epidemiology of Q fever in this province. This suggests that the behavior of these animals is important in their acquisition of C. burnetii.

We postulate that cats acquire this infection by ingesting infected mice. Dogs soiled with sheep placenta have passively spread Q fever to their owners. Wild animals may be very important in the epidemiology of Q fever. Dogs are felt to be responsible for introducing C. burnetii to Northern Ireland. Carnivorous birds probably acquire the infection from their
infected prey; granivorous and insectivorous birds feed and roost in close proximity to cattle and probably become infected via the aerosol route. A wide variety of fish, rodents and marsupials have been shown to be infected by C. burnetii. Ticks are probably most important in keeping the cycle of C. burnetii going in nature (4, 6). Coxiella burnetii multiplies in the cells of the midgut of the tick and is excreted in the feces of the tick during feeding. Early in the history of Q fever, Derrick felt that ticks were important in the epidemiology of this disease (7). The different symptoms occur in Q fever as shown in Table no. 1.

Table no. 1. It shows the list of symptoms occur in Q fever

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Percent reporting this symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>88-100</td>
</tr>
<tr>
<td>Fatigue</td>
<td>98-100</td>
</tr>
<tr>
<td>Headache</td>
<td>65-98</td>
</tr>
<tr>
<td>Chills</td>
<td>60-88</td>
</tr>
<tr>
<td>Myalgia</td>
<td>47-69</td>
</tr>
<tr>
<td>Sweats</td>
<td>31-98</td>
</tr>
<tr>
<td>Cough</td>
<td>24-90</td>
</tr>
<tr>
<td>Nausea</td>
<td>22-49</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13-25</td>
</tr>
<tr>
<td>Chest pain</td>
<td>10-34</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5-22</td>
</tr>
<tr>
<td>Sore throat</td>
<td>5-14</td>
</tr>
<tr>
<td>Rash</td>
<td>4-18</td>
</tr>
</tbody>
</table>

Q fever in man

Man is the only animal known to almost always develop illness following infection with C. burnetii (8). Several clinical syndromes result from this infection these are:
1. A self-limited febrile illness
2. Pneumonia
3. Hepatitis
4. Endocarditis
5. Osteomyelitis
6. Q fever in infancy
7. Neurological manifestations
8. Complications of acute Q fever

While some C. burnetii infections are totally asymptomatic, the majority are mild self-limited febrile illnesses. It is difficult to know just what proportion of Q fever is truly asymptomatic. Luoto et al found no overt cases of Q fever among 315 residents in 90 infected premises in Rasalli County, Montana; 22 persons seroconverted in one year. Minor illnesses were encountered but none were identifiable as Q fever infection. How many of these minor illnesses were due to Q fever is unknown since these subjects were not investigated to determine the etiology of their minor illness. Stoeneer and co-workers studied families with infected and non-infected herds in two areas of the state of Idaho. While seropositivity to C. burnetii was significantly greater among subjects with positive herds, the incidence of disabling febrile illness of two days or more was not greater. Even when illnesses probably due to influenza were excluded, there was no difference between the two groups. Acute Q fever, which may be manifest as pyrexia of unknown origin, pneumonia or hepatitis, is almost always of abrupt onset. The manifestations of acute Q fever vary from country to country (9-11) (Table 1).
Severe headache is a characteristic feature, so much so that it prompts a lumbar puncture to rule out meningitis in some patients. Headache is more common with Q fever pneumonia than it is in pneumonia due to other agents (17). Physical examination may be normal apart from an elevated temperature. Hepatomegaly and splenomegaly may be present (28). We have not noted these findings in patients with cat-associated Q fever. However, 51070 of 111 patients with Q fever in Australia had hepatomegaly and 3007 had splenomegaly (27), while 11% of 180 patients studied in northern California had hepatomegaly and 4% had splenomegaly (26). Relative bradycardia pulse inappropriately slow for the degree of fever has been reported by some workers (29).

This feature however has been inadequately studied. Pneumonia has been the predominant manifestation of Q fever in Nova Scotia. It accounted for 2.9% of patients with community-acquired pneumonia admitted to an urban hospital, while it caused 20% of pneumonias admitted to rural hospitals in this province. Coxiella burnetii causes an "atypical" pneumonia. This term is used to distinguish this form of pneumonia from those due to conventional bacteria, e.g. Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, and aerobic gram negative bacilli. Patients with atypical pneumonia usually have a nonproductive cough and the radiographic findings tend to be more extensive than the physical findings would suggest. Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae, and various respiratory tract viruses are other causes of atypical pneumonia. Severe C. burnetii pneumonia cannot be distinguished from that due to Mycoplasma or Legionella on clinical and radiographic grounds. The chest radiographs will frequently show multiple rounded opacities in patients with Q fever pneumonia following exposure to infected parturient cats. Other features include increased reticular markings and atelectasis. Pleural effusions occur in 26% of patients and, rarely, caviation of pulmonary nodular opacities has occurred (26). The white blood cell count is increased in of patients with acute Q fever it is normal in the remainder. Thrombocytosis during the recovery phase of Q fever pneumonia is common. Abnormal liver function tests are present in about half of the patients rarely jaundice may be one of the presenting manifestations of acute Q fever.

### Chronic Q fever

The strains of C. burnetii that cause chronic Q fever in man are probably different from those that cause acute disease (31, 32). The major manifestation of chronic Q fever is endocarditis. An abnormal native heart valve or a prosthetic valve is usually infected, although infection of vascular grafts or aneurysms may also occur (33, 34). Another important predisposing factor is paralysis of specific cell-mediated immunity. Lymphocytes from patients with Q fever endocarditis are unresponsive to C. burnetii antigens however this may be a secondary rather than a primary phenomenon. Phase I antibodies and antibodies in the IgA fraction predominate in Q fever endocarditis this is not so in acute Q fever. While chronic Q fever has been reported from many countries, the proportion of cases of chronic Q fever to acute Q fever varies considerably from country to country. In the United Kingdom, Q fever endocarditis accounts for 117 of all cases of Q fever, whereas this entity is extremely rare in the United States. The clinical presentation of chronic Q fever is usually that of “culture-negative endocarditis”. In areas where there is little clinical experience with this illness, diagnosis is usually delayed. Symptoms include malaise, weakness, fatigue, weight loss, chills, fever, anorexia and night sweats (35, 40). However these patients are often febrile by the time they consult a physician. The physical findings are nonspecific clumping of the fingers and toes is found in 1/3 of cases. Hepatomegaly is also common. A purpuric rash is noted on the extremities in 2007 of cases. This is due to circulating immune complexes. Anemia is common, as is an elevated
erythrocyte sedimentation rate. The globulins are increased in about 90% of patients, sometimes markedly so. Rheumatoid factor is present and cryoglobulins are positive. Phase I antibody titers that are equal to or greater than the phase II antibody titers suggest chronic Q fever.

**Diagnosis**

In most instances, the diagnosis is confirmed serologically since most laboratories do not have the facilities to work with C. burnetii. The microagglutination, complement fixation, microimmunofluorescence, and the enzyme-linked immunosorbent assay (ELISA) have all been used for this purpose. The ELISA is the most sensitive, but the IFA is easier to perform. A fourfold rise in antibody titer between acute and convalescent phase serum samples is diagnostic of acute Q fever. IgM antibodies can persist for six to eight months in some patients, so determination of IgM antibodies on a single serum should not be used in the diagnosis of acute Q fever. In chronic Q fever, the antibody titers are usually much higher than those seen in acute Q fever, and phase I antibodies are higher than or equal to phase II antibody titers. In acute Q fever, the phase II antibody response predominates.

**Treatment**

Acute Q fever is readily treated with tetracycline. In vitro susceptibility testing of C. burnetii has been carried out by Yeaman et al using persistently infected L929 fibroblast cells. In this system the most active agents were quinolones and rifampin. Chloramphenicol, doxycycline and trimethoprim had some activity, while tetracycline, gentamicin, streptomycin, erythromycin, sulfamethoxazole, penicillin G and polymyxin B had minimal to no activity. Some workers have reported that erythromycin is effective in the treatment of C. burnetii pneumonia this has not been our experience. In uncontrolled clinical trials we have found that rifampin is very effective in the treatment of acute Q fever. The treatment of chronic Q fever is difficult. It is probably best to use two antibiotics for at least two years. Some authorities recommend treating chronic Q fever for life. Strain differences may be very important in the management of chronic Q fever. The Priscilla isolate is less sensitive than the Nine Mile isolate to quinolones and it is resistant to rifampin. We have treated eight patients with chronic Q fever with two years of tetracycline and cotrimoxazole; there have been no relapses. Surgical replacement of the infected valve is frequently necessary. The decision to replace the infected valve is made primarily on the basis of hemodynamic changes (increasing valvular insufficiency or stenosis).

**Prevention**

Early vaccines were complicated by occasional severe reactions consisting of an indurated mass at the vaccination site and the formation of a sterile abscess which was complicated by fistula formation requiring excision. Coxiella burnetii persists at the injection site resulting in prolonged antigenic stimulation. It was concluded that previously sensitized persons were at risk for severe reactions and that potential vaccines should be screened for previous sensitization. In 1964, Ormsbee and co-workers showed that a phase I C. burnetii vaccine was 100 to 300 times more potent in protecting guinea pigs against experimental infection than a vaccine made from phase II cells. The next step in the development of a Q fever vaccine was to develop methods to purify the C. burnetii phase I cells from yolk sac material and lipid. In recent years (1981 onwards) Marmion has used a formalin-inactivated C. burnetii phase I whole cell vaccine made from strain Henzerling. This vaccine has been shown to be protective. The rate of serious reactions to this vaccine was low. One percent of 2682 vaccines developed an abscess at the inoculation site. Other measures that are of use in the prevention of Q fever are: using only seronegative pregnant sheep in research facilities and control of ectoparasites on livestock. The management of infected
animals is important. In Cyprus, the prevalence of Q fever among sheep and goats was reduced by destroying infected aborted material, isolating infected dams and disinfecting the premises (50, 51).}

### Conclusion

Q fever is present in Canada and while the number of cases varies from year to year, veterinarians and physicians must be aware of the epidemiology of this disease. Probably the best approach to management of Q fever is to investigate outbreaks and apply appropriate control measures if necessary. Serological surveys of cattle, sheep and goats should be done periodically to monitor the endemic level of the presence of C. burnetii in a region as measured by seropositivity among the traditional reservoirs of this organism for man.

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