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Coxiella burnetii pneumonia

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Coxiella burnetii *pneumonia. T.J. Marrie. ©ERS Journals Ltd 2003.*
ABSTRACT: This report reviews the pulmonary and extrapulmonary manifestation of infections due to *Coxiella burnetii*.

Q fever, a zoonosis, is due to infection with *C. burnetii*. This spore-forming microorganism is a small Gram-negative coccobacillus that is an obligate intracellular parasite. The most common animal reservoirs are goats, cattle, sheep, cats, and occasionally dogs. The organism reaches high concentrations in the placenta of infected animals. Aerosolisation occurs at the time of parturition and infection follows inhalation of this aerosol. There are three distinct clinical syndromes of the acute form of the illness: nonspecific febrile illness, pneumonia, and hepatitis. The chronic form of Q fever is almost always endocarditis, but occasionally it is manifest as hepatitis, osteomyelitis or endovascular infection.

The pneumonic form of the illness can range from very mild-to-severe pneumonia requiring assisted ventilation. Multiple round opacities are a common finding on chest radiography. Treatment with doxycycline or a fluoroquinolone is preferred. Susceptibility to macrolides is variable.

In conclusion, *Coxiella burnetii* pneumonia should be considered when there is a suitable exposure history and when outbreaks of a pneumonic illness are being investigated.
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In August 1935, E.H. Derrick, a pathologist, who was Director of the Laboratory of Microbiology and Pathology at the Queensland Health Department, Brisbane, Australia, was contacted by the Director General of Health and Medical Services for Queensland and instructed to investigate an outbreak of an undiagnosed febrile illness among workers at the Cannon Hill abattoir in Brisbane [1].

DERRICK [2] noted that this illness lasted 7–24 days and was characterised by fever, headache, malaise, anorexia and myalgia. Blood cultures were negative and serum samples had no antibodies to influenza, typhus, leptospirosis, typhoid and paratyphoid. DERRICK [2] named the illness Q (for query) fever.

Subsequent investigations in Australia and in the USA resulted in the isolation of the aetiological agent of Q fever. It was eventually named *Coxiella burnetii* in honour of Burnet and Cox, the two scientists who played an important part in its discovery.

Early on there was no indication that *C. burnetii* was a respiratory pathogen.

Coxiella burnetii

C. burnetii is a pleomorphic coccobacillus with a Gram-negative cell wall that measures 0.2×0.7 μm and is an obligate intracellular microorganism [3]. *C. burnetii* undergoes phase variation, which is akin to the smooth-to-rough transition of lipopolysaccharide (LPS) of Gram-negative bacteria [4]. In experimentally infected animals the first antibody produced is to *C. burnetii* protein (phase II antigen), and later, antibody is produced to *C. burnetii* LPS (phase I antigen). There is also a phase intermediate between phase I and phase II [5, 6]. In infected humans the predominant antibody response in acute Q fever is to phase II and in chronic Q fever it is to phase I antigen. There is no morphological difference between phase I and phase II cells, although they do differ in the sugar composition of their LPS [7], their buoyant density in caesium chloride, and in their affinity for basic dyes. The LPS of *C. burnetii* is nontoxic to chick embryos at doses of >80 $\mu g \cdot embryo^{-1}$ in contrast to *Salmonella typhimurium* LPS which is toxic in nanogram amounts [6].

Spore-like formation explains why *C. burnetii* is so successful as a pathogen. It can survive for 7–10 months on walls at 15–20°C, for >1 month on meat in cold storage and for >40 months in skimmed milk at room temperature [8].

Epidemiology

Q fever is a zoonosis and direct or indirect contact with animals is important in its epidemiology. Cattle, sheep and goats are the primary reservoirs of Q fever for man; however, many different species of animals in different countries are infected with *C. burnetii* [9]. *C. burnetii* has been identified in arthropods, fish, birds, rodents, marsupials and livestock [3].

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Indeed, it naturally infects >40 species (including 12 genera) of ticks found on five continents [3]. Lice, mites and parasitic flies are also infected [10]. *C. burnetii* localises to the uterus and mammary glands of infected animals [9]. Infected cows can shed *C. burnetii* in milk for up to 32 months [11]. Large concentrations of *C. burnetii* are present in the infected placenta and aerosols are created during parturition [12]. Inhalation of these contaminated aerosols by susceptible humans results in Q fever. This explains why, in many areas, annual outbreaks of Q fever occur around the time of livestock kidding [13, 14]. Pets, including cats, dogs, and rabbits are a new source of *C. burnetii* infection [15–19]. In a recent study, the wild brown rat was implicated as a part of the link in Q fever between farm animals and cats [20]. A family outbreak of Q fever in France was due to *C. burnetii* contaminated pigeon faeces [21].

In some countries, infection of domestic or wild animals results in considerable infection among humans in contact with these animals, whereas in other areas little if any transmission to man occurs [22, 23].

C. burnetii has been an extraordinarily successful pathogen. By 1955, *C. burnetii* was found in 51 countries on five continents [24]. In the 1990s, New Zealand was one of the few countries that was free of *C. burnetii* infection [25]. However, major differences occur in the manifestations of Q fever from country to country. In Nova Scotia, Canada, and in the Basque region of Spain, pneumonia is the predominant manifestation of Q fever [26, 27], while in the Canary Islands (southern Spain) it is fever and hepatitis [28]. In contrast, in the south of France both hepatitis and pneumonia are observed but hepatitis is more frequent than pneumonia [29]. The reasons for these differences are not currently understood. It is noteworthy that in an outbreak of Q fever in Bonavista, Newfoundland that was associated with exposure to infected goats [30], a nonspecific febrile illness was the major manifestation of the infection. However, in cat-related outbreaks in nearby Nova Scotia, pneumonia (whether it is associated with exposure to infected cats, dogs, rabbits) is the exclusive manifestation of *C. burnetii* infection [15–17]. In addition, Q fever in a geographic area may be endemic or epidemic and shift back and forth between these two extremes.

Q fever continues to be a significant infection in many European countries, especially the UK [16, 31], France [29], Germany [32], Greece [33] and many of the Eastern European countries [34].

A review of Q fever in Germany from 1947–1999 revealed a cyclical incidence pattern with peaks occurring every 5–10 yrs [32]. The mean annual incidence ranged from 0.1–3.1 per million in various parts of the country [32]. Forty outbreaks were identified since 1947. Sheep were the source in 24 outbreaks while cattle were implicated in four community outbreaks and two abattoir outbreaks [32].

Some aspects of the epidemiology of Q fever seem to be unique to Europe. British residents who lived along a road over which farm vehicles travelled, developed Q fever as a result of exposure to contaminated straw, manure, or dust from farm vehicles [35]. In a Swiss valley, 415 residents who lived along a road over which sheep travelled to and from mountain pastures developed Q fever [36, 37]. Those persons who lived in six villages close to the road had high rates of infection, ranging from 11.8–35.8% (mean 21.1%) while those who lived in villages off the road had significantly lower rates of infection (range 2.1–6.8% (mean 2.9%)). An outbreak of Q fever involving 58 people in Northern Italy was associated with three flocks of sheep which passed through the area between late May and early June [38]. The prevalence of *C. burnetii* antibodies in these flocks ranged from 45–53%.

Two studies documented that high winds can result in infection with *C. burnetii* up to an 11-mile (18.3 km) distance from the point source [13, 39].

While the aerosol route is the major one whereby humans are infected, rarely is there person-to-person transmission [40–42] and infection *via* contaminated blood or the percutaneous route [43, 44]. Person-to-person transmission is so uncommon that isolation is not recommended for patients who are admitted to hospital for treatment of acute Q fever.

There is a suggestion from epidemiological studies that ingestion of contaminated milk is a risk factor for Q fever infection [45, 46]. However, evidence from experiments where contaminated milk was fed to volunteers is contradictory [47–49]. In a case control study, HATCHETTE *et al.* [30] found that ingestion of pasteurised cheese and tobacco smoking were both risk factors for acquisition of Q fever during an outbreak of Q fever on a caprine cooperative in Newfoundland.

The present authors feel that the route of infection may explain the difference in the manifestations of Q fever in some countries *e.g.* pneumonia in Nova Scotia, Canada *versus* hepatitis in Marseille, France. The present authors used five different strains of *C. burnetii* to infect mice *via* the intraperitoneal or intranasal route. Those infected intranasally developed pneumonia only, while those infected intraperitoneally developed hepatitis, splenomegaly and pneumonia. Bronchiolar changes were seen only in mice inoculated intranasally [50]. These data have been reproduced in a guinea pig model of Q fever [51].

Vertical transmission rarely occurs [52, 53] but increased surveillance may reveal additional cases of vertical transmission. Indeed, in the town of Martigues in Southern France, Q fever complicated $\geqslant 1$ in 540 pregnancies [54].

Sexual transmission of Q fever has been demonstrated in mice [55] and viable *C. burnetii* has been demonstrated in bull semen [56]. There is also a suggestion that Q fever can be transmitted sexually in humans [57]. MILAZZO *et al.* [58] reported the case of a 53-yr-old male who developed orchitis as a complication of Q fever. The orchitis had its onset 3 days after the patient had intercourse (29 days after onset of the patient's illness). Fifteen days later the patient's spouse developed Q fever. *C. burnetii* deoxyribonucleic acid (DNA) was identified by polymerase chain reaction (PCR) in the semen of the index case 4 and 15 months after onset of the acute illness

Clinical manifestations of *Coxiella burnetii* infection

The infections due to *C. burnetii* can be divided into the acute and chronic varieties. Chronic Q fever almost always means endocarditis or rarely hepatitis. Chronic Q fever will not be discussed further in this article.

Acute Q fever has three major manifestations: 1) a self limited febrile illness; 2) pneumonia; and 3) hepatitis.

Q fever pneumonia

A panel of experts reviewed the literature on pneumonia and summarised the aetiology of community-acquired pneumonia (CAP) as part of the process of developing the British Thoracic Society recommendations for treatment of CAP [59]. In the UK, 1.2% of 1,137 patients had *C. burnetii* pneumonia, none of the 236 patients in one study of pneumonia treated on an ambulatory basis and none of the 185 patients treated in intensive care unit had this diagnosis [59]. In six studies involving 654 patients from continental Europe who were treated on an ambulatory basis, 0.8% had Q fever pneumonia [59]. In 23 studies involving 6,026 patients

requiring hospitalisation for the treatment of pneumonia in continental Europe, 0.9% had Q fever pneumonia while none of 453 CAP patients hospitalised in Australia and New Zealand had this diagnosis [59]. Surprisingly 2.3% of 1,306 patients hospitalised in North America for the treatment of CAP had Q fever pneumonia [59]. However, all of the cases from the North American series were from one study from Nova Scotia [60]. Furthermore, serological studies were not performed for *C. burnetii* in all of the studies that were reviewed, thus the importance of *C. burnetii* as a cause of CAP may be underestimated.

Symptoms and signs

Almost all patients with Q fever pneumonia complain of fever. A variety of other symptoms are frequently present, however headache is more common than it is in patients with pneumonia due to other aetiologies [61]. Indeed patients with Q fever pneumonia often state that the headache is the most severe pain that they have ever had. Table 1 gives the range of symptoms and signs in patients with Q fever pneumonia as reported in a variety of studies [61, 62]. Table 1 indicates that approximately one-half of the patients with Q fever pneumonia have physical findings suggestive of pneumonia on examination of the chest. Of course that means that half do not, thus a high index of clinical suspicion is often necessary to make a diagnosis of pneumonia in the first instance, and later a diagnosis of Q fever.

The spectrum of illness due to Q fever pneumonia ranges from very mild to very severe. The latter is infrequent but in the author's experience with over 300 cases of Q fever pneumonia ~2% require admission to an intensive care unit. The patient described by ODDO *et al.* [63] is an example of severe respiratory distress syndrome due to Q fever pneumonia that required mechanical ventilation for 21 days.

It is not uncommon for a variety of extrapulmonary manifestations to be evident at the time of presentation or to appear during the course of the illness. These include bone marrow necrosis [64], haemophagocytosis [65], haemolytic anaemia [66], lymphadenopathy mimicking lymphoma [67], transient hypoplastic anaemia [68], splenic rupture [69], and erythema nodosum [70]. Neurological manifestations include confusion, meningitis, meningoencephalitis, optic neuritis, and demyelinating polyradiculoneuritis [71–79]. Pericarditis and myocarditis are also manifestations of Q fever that may occur in patients with pneumonia [80].

Table 1. – Symptoms and signs of Q fever pneumonia

Symptom	
Fever	82–100
Anorexia	75–80
Headache	35–100
Cough	60–70
Chills	40–88
Pleuritic chest pain	50–60
Rigors	30–40
Productive cough	30–40
Myalgia	30–40
Arthralgia	30–40
Confusion	30–40
Mean temperature °C	38.4–38.7
Crackles	40–50
Consolidation	25–30

Data are presented as percentage unless otherwise stated.

Table 2. – Radiographic manifestations of *Coxiella burnetii* pneumonia in 272 patients

Feature	n	Patients with this feature %
Rounded opacity	17	6.3
Multiple rounded opacities	7	0.3
Pleural effusion	27	9.9
Atelectasis	12	4.4
Bilateral opacities	21	7.7
Air bronchogram	70	25.7
Lower lobes involved	100	36.7
Segmental consolidation	17	6.3

Data from [85–88].

Laboratory investigations

The total white blood cell count is usually normal, with 25% of patients having an elevated count. However, lymphopaenia is common. Thrombocytopaenia may be present in 10% of the patients at the time of presentation, however, thrombocytosis is usually seen in the recovery phase of the illness. Occasionally platelet counts of 1 million$\times 10^9$ L^{-1} are seen. A low serum sodium concentration may be present, usually as a result of inappropriate secretion of antidiuretic hormone. Mild elevation of liver function tests is not uncommon. Microscopic haematuria is present in ~50% of patients with Q fever pneumonia. A variety of autoantibodies have been described in acute Q fever including antimitochondrial antibodies [81], anticardiolipin antibodies [82, 83] and antismooth muscle antibodies [84].

Chest radiographic manifestations of Q fever pneumonia

Table 2 and figures 1–3 summarise radiological features of Q fever pneumonia. Multiple rounded opacities are very suggestive of Q fever pneumonia in some geographic areas such as Nova Scotia, Canada. Other conditions, such as septic pulmonary emboli due to tricuspid valve infective endocarditis, can also present as multiple rounded pulmonary opacities,

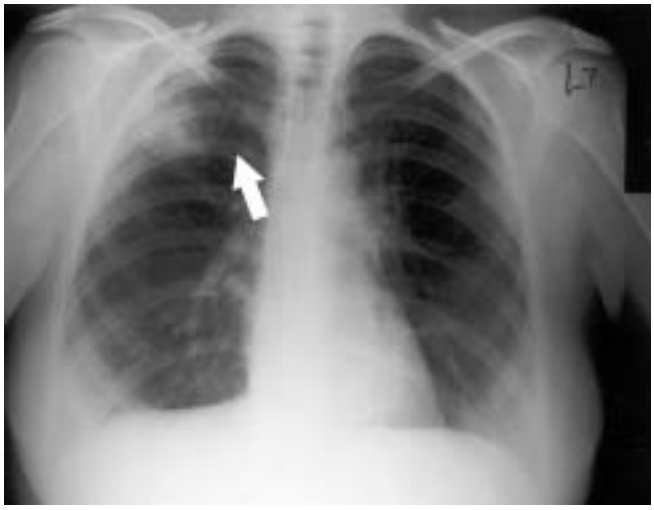

Fig. 1. – Chest radiograph of a young female who developed Q fever pneumonia following exposure to an infected parturient cat. Note the right upper lobe opacity (arrow).

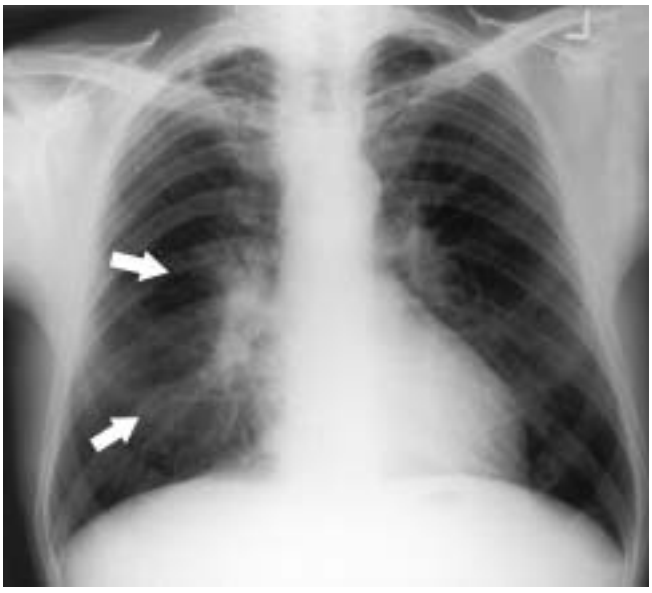

Fig. 2. – Right perihilar opacity in a patient with Q fever pneumonia (arrows).

although history and physical examination serve to distinguish the two. In many instances, however, there is nothing distinctive about Q fever pneumonia on chest radiographs.

Laboratory diagnosis of Q fever pneumonia

In most instances the laboratory diagnosis of *C. burnetii* infection is serological. The complement fixation [89] and indirect immunofluorescence antibody tests are available [90, 91]. The latter is best. An enzyme-linked immunoassay is also available in some centres [90]. A four-fold or greater rise in antibody between acute and convalescent samples is diagnostic. In general, a 2-week interval between the acute and convalescent sample is sufficient. Diagnosis based on a single serum sample is not ideal, however, a phase II immunoglobulin (Ig)M titre of >1:64 or a phase II IgG titre of >1:256 by indirect fluorescent antibody (IFA) is strong evidence of recent *C. burnetii* infection using the IFA test.

C. burnetii can be isolated in embryonated eggs or in tissue culture. Most laboratories are not able to work with *C. burnetii* because of its extreme infectiousness. The shell vial technique is useful for isolating *C. burnetii* and for determining antibiotic susceptibility [92]. *C. burnetii* has been isolated from the blood of ~15% of patients with Q fever pneumonia (using tissue culture in a shell vial technique), sampled prior to antibiotic therapy, and during the first few days of disease, and in 50% of patients with Q fever endocarditis [93].

PCR can be used to amplify *C. burnetii* DNA from tissue [94, 95]. This technique can be modified so that the amount of *C. burnetii* in tissue can be quantified [95, 96].

Treatment

Determination of antimicrobial susceptibility of *C. burnetii* has been problematic, since it is an intracellular pathogen. However, there is a long history of efforts to provide antimicrobial susceptibility data about *C. burnetii*. Three model systems have been used: chick embryos, guinea pigs, and cell cultures. In general tetracyclines, quinolones, rifampin, telithromycin and clarithromycin are active against *C. burnetii* [97]. Some strains are susceptible to erythromycin, others are not [97].

SOBRADILLO *et al.* [98] carried out a prospective, randomised, double-blind study of doxycycline and erythromycin in the treatment of pneumonia presumed to be due to Q fever in the Basque region of Spain. Forty-eight patients were proven by serological studies to have Q fever; 23 received 100 mg doxycycline twice daily, and 25 received erythromycin (500 mg every 6 h) for 10 days. Fever resolution was more rapid in the doxycycline-treated group (3±1.6 days *versus* 4.3±2 days for erythromycin-treated patients; p=0.05). The erythromycin-treated group had more gastrointestinal adverse effects (11 *versus* two for the doxycycline-treated patients; p<0.01). By day 40, the chest radiograph was normal in 47 of the 48 patients. The authors concluded that doxycycline was more effective than erythromycin, but they recognised the self-limiting and benign nature of most cases of pneumonia due to Q fever. KUZMAN *et al.* [99] studied 64 patients with Q fever pneumonia. Twenty-two patients were treated with azithromycin (total dose 1.5 g administered over 3–5 days), 15 with doxycycline (100 mg *b.i.d.* for 10–14 days) and 15 received a variety of other antibiotics. The mean duration of fever was 2.5 days in the azithromycin-treated group, 2 days in the doxycycline-treated group, and 3.5 days in the patients who received other antibiotics. All patients were cured. A retrospective review of 130 patients with Q fever pneumonia treated between 1989–1995 was carried out by KOFTERIDS *et al.* [33].

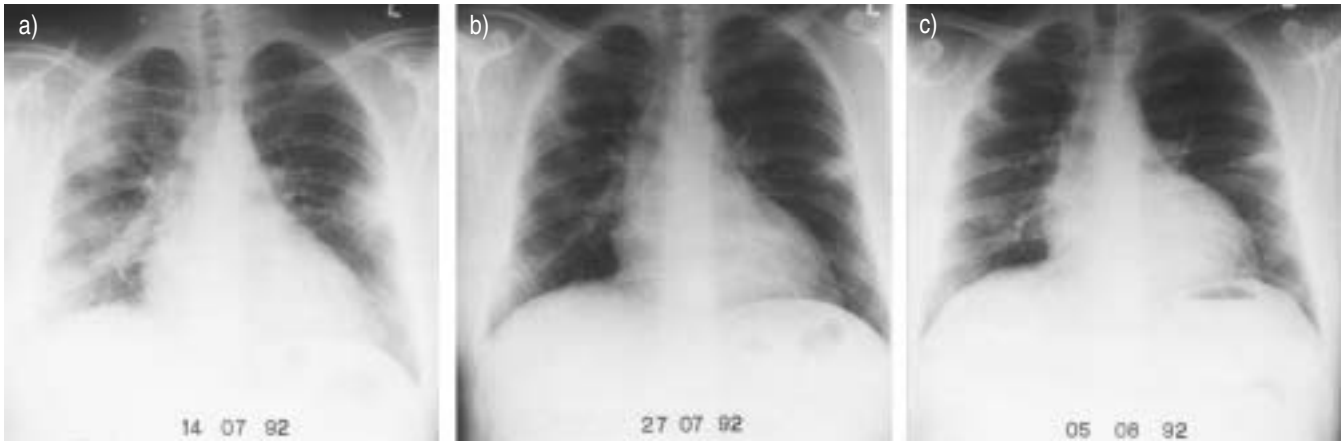

Fig. 3. – a–c) Serial chest radiographs of a patient with Q fever pneumonia. Note the multiple round opacities. c) Considerable resolution has occurred 3 weeks after the first radiograph.

Eleven patients who were treated with tetracycline became afebrile in a mean of 3 days, the 42 patients treated with erythromycin became afebrile in a mean of 4.26 days, and the 28 patients treated with β-lactam agents required 6.8 days to become afebrile. Fifteen per cent of the clarithromycin-treated patients were still febrile at 5 days compared with 35% of the erythromycin-treated patients and none of the tetracycline-treated patients.

A retrospective review of 19 patients with Q fever pneumonia showed that 11 were treated with erythromycin and eight with β-lactam antibiotics. The erythromycin-treated group became afebrile by day 3, while only two of the β-lactam-treated group were afebrile by this time ($p<0.005$) [100].

The treatment of choice for Q fever pneumonia is doxycycline for 10 days. Alternative therapies are a fluoroquinolone or a macrolide plus rifampin. The latter recommendations are based on *in vitro* susceptibility results and anecdotal experience.

Concluding remarks

Clinicians should be aware of the prevalence of *Coxiella burnetii* infections in the area in which they practice. Patients who present with pneumonia should be asked about risk factors for Q fever and if any of these are present, acute and convalescent serum samples should be collected and tested for antibodies to *Coxiella burnetii*. If a diagnosis of Q fever is confirmed Public Health authorities should be notified so that appropriate investigations can be carried out to determine the source of the infection.

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