HEALTH EFFECTS
OF PROJECT SHAD
BIOLOGICAL
AGENT COXIELLA
BURNETII [Q-FEVER]

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SPECIAL NOTE ON PSYCHOGENIC SEQUELAE OF PERCEIVED EXPOSURE TO BIOCHEMICAL WARFARE AGENTS

This report deals primarily with the biological health challenges engendered by the agent that is the subject of the report. Nevertheless, this report also incorporates by reference and attachment a supplement "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents".

The supplement addresses and describes a growing body of health effects research and interest centered upon the psychogenic sequelae of the stress from actual or perceived exposure to chemical and biological weaponry. As known exposure to agents in Project SHAD logically includes the exposed person also possessing a perception of exposure to biochemical warfare agents, the psychogenic consequences of the perceived exposure to may constitute relevant and valid health effects of the exposure to any agent used in Project SHAD, possibly also including simulants and tracers. Therefore a general supplement has been created to address possible psychogenic effects of perceived exposure.

Because such health effects are part of a recent and growing concern, it is expected that the supplement may be revised and expanded over the course of this contract to reflect the actively evolving literature and interest in the issue.
SPECIAL NOTE ON CITATIONS AND AUTHORITIES

Reference to particular works shall be by the name of the principal author (or editor, where appropriate) and appended in parentheses to the sentence or paragraph which cites the information or quotation from that particular work or authority.

The year of publication may be appended to clarify which of multiple sources of the same principal author/editor is being cited.

The citation in the above format will be to an authority listed in the Bibliography at the end of this report.
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I. EXECUTIVE SUMMARY

*Coxiella burnetii* (CB), the etiologic agent of Q fever, is a pleomorphic, Gram-negative, obligate intracellular coccobacillus, typically 0.2-0.4 µm wide and 0.4-1.0 µm long. In the 1950s, CB was investigated as a potential biowarfare agent and a stock of the microbe was maintained as part of the United States' biological warfare arsenal until the arsenal was destroyed in the early 1970s.

The term “Q-fever” was first proposed in 1937, by Edward Holbrook Derrick, the Director of the Laboratory of Microbiology and Pathology of the Queensland Health Department, to describe an outbreak of febrile illness among abattoir workers in Queensland, Australia. Derrick provided infectious material to F. Macfarlane Burnet (who would later win a Nobel Prize in Medicine for work in immunology) who with Mavis Freeman was able to reproduce the disease in guinea pigs, mice and monkeys as well as visualize an intracellular organism that appeared rickettsial in nature. (Burnet) Independently, in 1936 Herald Cox, working at the Rocky Mountain Labs in Hamilton Montana was able to transmit a febrile illness to guinea pigs from ticks collected at Nine Mile, Montana. Cox also demonstrated that the organism displayed properties consistent with a virus or rickettsia and was able to propagate the infectious agent in embryonated eggs. The agent isolated by both groups was shown to be the same microorganism after R. Eugene Dyer, the Director of NIH, became infected with the organism while working at the Rocky Mountain Laboratory. Dyer received material from Burnet and demonstrated that animals infected with Burnet’s Q-fever strain were protected from challenge by strains isolated for his own blood. (Maurin)

CB is incapable of axenic growth but can be grown in-vitro in a number of cell lines including macrophage-like cells, fibroblasts and Vero cells. Monocytes-macrophages, however, are the only cells CB appears to target in-vivo. CB entry into monocytes-macrophages is mediated through interactions between the bacteria’s lipopolysaccharide (LPS) and a integrin complex consisting of alpha(v)beta(3) integrin and CR3, a complement receptor. CB initially enters phagosomes that then fuse rapidly with lysosomes to form large acidic vacuoles. CB appears to require acidic vacuoles for replication. The replication of CB is very slow for a bacterium with a doubling time of approximately 20 hours (Maurin).

CB has a complex intracellular lifecycle leading to the formation of both small-cell and large-cell variants. Small-cell variants (SCV; spore-like), the extracellular form of CB, are metabolically inactive and resistant to both chemical and physical inactivation. The bacterium will remain infectious in natural environments for several weeks. (Scott, McCaul) In addition to a spore-like transformation, CB undergoes phase variation akin to the smooth to rough transition of other Gram-negative bacteria. During acute Q-fever the predominant antibody response is to phase II antigens and during chronic Q-fever the predominant response is to phase I antigens. There are no morphological differences between phase I and phase II bacteria, but there are differences in the composition of LPS, buoyant density, and affinity for basic dyes.
Q-fever is a zoonosis with a large reservoir that includes domestic and wild mammals, birds and ticks. Ruminants, such as goats, sheep and cattle are the most frequent source of human exposure but domestic dogs and cats can be a source in urban environments. Many animals appear to be chronically infected but asymptomatic. Chronically infected animals constantly shed CB in their feces, urine and milk with substantial shedding occurring during parturition. Human transmission occurs principally from aerosols of shedded bacteria but ingestion of high doses of CB can also result in infection. Q-fever is geographically diverse in spread, with epidemics seen throughout the world with exception of New Zealand (Greenslade). Persons who work with animals, particularly goats or sheep or animal products are at highest risk of infection. There is an increasing awareness that the prevalence of Q-fever is underreported and underestimated. (Besalgic)

The study of natural human exposures indicate that approximately 60% of patients infected with CB seroconvert without any clinical manifestations and only 2% are hospitalized after primary infection (Scheld). There are three major clinical manifestations seen in acute Q-fever: a self-limited or isolated febrile illness, pneumonia and hepatits and more than one of these manifestations can be seen during a single exposure. The incubation time between exposure and acute clinical manifestations can range from 13-32 days. Both the incubation time and type of manifestation appear to be related to dose, route of exposure and strain (Williams).

Self-limited febrile illness caused by CB usually consists of a high fever accompanied by a severe headache. Fever typically increases to a plateau of 39 to 40°C over 2-4 days and then rapidly disappears after 5 to 14 days. Almost all patients who present with Q-fever pneumonia also have fevers and headaches. Fatigue, myalgic and arthralgic pain, chest pains, dry cough, and moderate gastroenteric disturbances are also seen. Q-fever hepatitis is often only detected by increases in liver enzymes. Hepatitis is also frequently accompanied by fever and increases in several cytokines, less frequently by abdominal pain, anorexia, nausea, vomiting, and diarrhea, and occasionally by progressive jaundice. Myocarditis, pericarditis, meningoencephalitis, bone marrow necrosis, hemophagocytosis, hemolytic anemia, transient hypoplastic anemia, erythema nodosum and skin rash can also be manifestations of acute Q fever. Autoantibodies are also frequently seen during acute Q-fever. The route of exposure may also influence the clinical presentation with pneumonia being more common following aerosol exposure and hepatitis being more common following ingestion (Maurin).

Although complications such as pyrurria, spleen rupture, rapid fatal pneumonia, encephalitis, acute renal failure, acute respiratory distress, multiple organ failure, and congestive heart failure are occasionally seen, mortality from acute infection is nevertheless low (approximately 1%) (Kazar, Raoult 2000). Pregnancy can also be compromised, CB causes placentitis with resultant spontaneous abortion, premature birth and low birth weight commonly seen (Hellmeyer, Raoult 2000, Maurin). Several studies have also indicated that chronic fatigue syndrome is more frequently in acute Q-fever patients 5 years post-infection than in case controls (Ayres).
T-cell immunity appears to be largely responsible for the control of CB infections although it is not clear if eradication is achieved in most cases. CB is able to survive within macrophages withstanding low pH and reactive oxygen intermediates. Persistence, recurrence or reemergence of CB is a constant worry following acute infection. A significant decrease in CD4+ T-cells has been associated chronic Q-fever endocarditis (Sabatier). A recent large study in France indicates that chronic Q-fever will evolve in 1.5% of patients with acute Q-fever. Q-fever endocarditis is the most frequent manifestation of chronic Q-fever. Vascular and osteoarticular infection, chronic hepatitis and pericarditis, adenopathies, hepatomegaly, splenomegaly, clubbing of digits, purpuric rash and arterial embolisms are also seen in chronic Q-fever. The shift to chronic Q-fever is favored in patients with heart valve disease and/or immunosuppression. The death rate for Q-fever endocarditis can be as high as 60% but is substantially reduced if diagnosed and treated early (Maurin, Raoult 2000).

Diagnosis is usually performed by serology after a culture-negative presentation of a fever when other possible Q-fever symptoms, exposure risks (e.g., animal contact), and biomarkers are present. Commercial kits that detect antibodies to different phases of CB are available using complement fixation, immunofluorescence or ELISA formats. Electron microscopy and DNA detection schemes are used in research laboratories. Several of the immunodominant epitopes of CB have now been identified and cloned (Zhang).

Doxycycline administered at 200 mg daily over 14 days is the standard therapy for acute Q-fever. Fluoroquinolones, macrolides and co-trimoxazole are also effective alternatives. CB is resistant to both β-lactams and aminoglycosides. The treatment of chronic Q-fever is more problematic. Doxycycline/fluoroquinolones combination therapy over an extended period of time was shown to effective but relapse rates of over 50% prompted a need for a new therapy. Chloroquine, which raises the pH of acidic vesicles was chosen to be combined with doxycycline. An 18 month regimen of 100 mg b.i.d. of doxycycline and 200 mg t.i.d. of chloroquine is the currently recommended for the treatment of chronic Q-fever (Maurin).

A safe, efficacious vaccine against Q-fever has been developed in Australia. A formalin inactivated preparation of CB commonly referred to as Q-Vax, prepared from the phase I form of C. burnetti Henzerling strain, appears to provide 100% protection from natural exposure over a period of five years (Ackland).

This health effects report details the microbiology, epidemiology, clinical course, and treatment of Coxiella burnetii Q-fever infection. (Given the diffuse and evolving state of study of Q-fever, it is likely, however, that the last word on CB infection is far from being written.) A presentation of some of the deficiencies in the secondary health effects literature, including federal government advisories on Project SHAD agents, will also be provided. A supplementary table listing CB health effects also follows. A bibliography containing abstracts and some annotation concludes this review. A review of possible psychogenic effects arising from the subjective perception of exposure to biological or chemical warfare agents will supplement this report.
II. BACKGROUND DATA

A. Microbiology of *Coxiella burnetii*

Alternate name: *Rickettsia burnetii* (Gallaher), Various Department of Defense Project SHAD Project documents use abbreviations "CB" and "OU".

Kingdom: Peubacterial  
Phylum: Proteobacteriae  
Order: Gamma  
Genus: *Coxiella*  
Species: *Burnetii*  
Shape: Coccal  
Stain: Gram-negative  
Variant isolates: small cell variant, large cell variant, Hamilton, Vacca, Rasche, Biotzere, Corazon, Dod, Nine Nile, Priscilla. European and North American strains are regarded as different in pulsed-field gel electrophoresis. Infectious CB strains in North America are believed to be different from those in Europe.  
Sources: Marrie 2000, Thiele, Yeaman, Turkington, Wilson, Maurin, Williams.

Burnet and Cox separately identified the pathogen of Q-fever in 1937. (Maurin, Marrie 2000) The original name, *Rickettsia burnetii* has sometimes continued to appear in the literature. (Gallaher) Although initially included in the Rickettsial family, CB is the only member of its genus. It is also a member of the gamma subset of the Proteobacteriae. (Marrie 2000)

Genomics

The full genome of CB has recently been sequenced. (Marrie 2004).

B. Epidemiology

Disease Name: Q-fever  
Alternate Names: Australian Q-fever, Abbatoir fever, Nine mile fever, Balkan influenza.  
Discovery: Derrick, 1937  
Common Vectors: Zoonotic, Human-to-human (rare)  
Location of Outbreaks: Worldwide  
Sources: Maurin, Marrie 2000, Richardus, Harris.

The "Q" in Q-fever has been reported to stand for “query” or Queensland, the state in Australia where Q-fever was first recognized. The alternate names reflect its worldwide prevalence. After the discovery of Q-fever in Australia, epidemic outbreaks have since been observed in Africa, Europe, Asia, and North America. At least 51 countries have
reported its presence. Even so, it is widely regarded as underdiagnosed and underreported because of its self-limited course, the global lack of reporting requirements, and its diverse variety of symptoms. (Palmer, Javier Alvarez Gutierrez, Haldane, Salamand, Beslagic, Hellin, Sahagun, Bartelink, Maurin, Marrie 2000) Because of its potential as a biological agent (it was part of the US arsenal until 1972), its occurrence has been required to be reported to the Centers for Disease Control since 1999. CB is considered a "category B" bioterrorism agent. (Artenstein)

**Exposure**

CB is prevalent in animal bodies, fluids and excrement, as suggested by its alternate name "abbatoir fever". (Wilson, Turkington) It exists predominantly in cattle, sheep, and goats, but also has been found in household pets, livestock, marsupials, birds, fish, and arthropods (especially ticks). (Maurin)

The transmission often comes from CB being aerosolized in animal fluids (milk, urine, amniotic fluid, blood), as well as inhaled through dust, straw, and other means. Handling wild animals (e.g. rabbit skinning), drinking raw milk or cheese, and contact with birthing pets and other animals are believed also to be means of transmission. Laboratory mishandling of CB has also caused outbreaks. (Marrie 2000, Maurin, Artenstein)

Human-to-human exposure and infection have been reported but are very rare. (Harris, Richardus) Household and sexual transmission are reported, as well as one case through an autopsy and another through blood transfusion. The animal and human placenta appears to hold large amounts of CB and pregnancies and fetuses are frequently endagered. Clothing can also carry CB and infect those in contact. (Marrie 2000, Lumio, Maurin)

**C. Pathogenesis & Microbial Diagnosis**

**Pathogenic Characteristics**

CB is an obligate intracellular organism which takes up residence in the phagolysosome of nucleated cells. It is acidophilic. Safety considerations due to high infectivity have limited the analysis of CB. Laboratories that routinely handle CB cultures must operate at biosafety level 3. (Maurin, Marrie 2000)

**Infectivity**

A single organism of CB can give rise to human infection. But the amount and nature of the organisms contacted, the health condition of the individual, and the route of exposure can determine the incubation, virulence, syndrome, duration, and outcome of a Q-fever infection. As the mechanisms of CB infective action remain largely "unknown" (Brooks) and “obscure” (Harris), a full picture does not yet exist. Nevertheless, it is generally clear that aerosol contact leads to entry through the lungs and systemic distribution thereafter.
Consumption of contaminated fluids like raw milk appears to lead to systemic distribution through the digestive tract. (Raoul 2000, Tissot-Dupont)

Incubation

Two to three weeks is the generally understood period of incubation though it can vary according to the amount of pathogens in the exposure. (Marrie 2000).

Antigen Phasing

CB presence in the body is characterized by antigen phasing. Of these two phases, phase I is more virulent. Reactivation of less harmful phase II CB into phase I CB has been observed in animals. (Maurin, Marrie 2000)

Latency/Persistence

Q-fever has a chronic Q-fever sequel is believed to be relatively rare – approximately 10% or less, though asymptomatic or underreported cases may vary that. It is suggested that CB may survive the recovery period of an acute episode primarily by remaining alive in the bone marrow. The theory is that the immature cells in the monocyte-macrophage lineage may be not be sufficiently activated to fight Coxiella bacteria. (Harris) Signs of CB DNA presence in bone marrow and the persistence of phase II antigens have been noted for over a decade after a primary infection. (Reilly, Harris) Placental persistence after infection has been shown to last over two years, and in blood after one year. (Wilson)

Microbial Diagnosis

It is generally recommended that Q-fever be suspected when symptomatology consistent with Q-fever (e.g. fever, atypical pneumonia, granulomatous hepatitis, endocarditis with pre-existing valvular condition, etc. see section A) is combined with culture negative results on standard laboratory tests. (Maurin, Marrie 2000, Broqui 1994, Bernt, Brosch) Laboratory culturing of CB is considered too dangerous for standard culturing (biosafety level 3 required). (Marrie 2000, Maurin) Therefore, other methods, typically serological, are used for diagnosis.

The most common techniques for determining CB infection or presence are these:

- Complement Fixation
- Microagglutination
- Indirect Immunofluorescence assay (IFA)
- Enzyme-linked Immunosorbent Assay (ELISA)
- Immunohistochemical Staining
- DNA detection methods (PCR, etc.)
Complement Fixation is the most common serology method used. (Marrie 2000, Berri, Peter)

A standard diagnostic measure in IFA is an increase of four times in titer between acute and convalescent serum samples. (Marrie 2000)

## III. SYNDROMES, COMPLICATIONS, & BIOLOGIC FINDINGS OF COXIELLA BURNETII INFECTION

### A. General

**Non-Specificity**

Q-fever is generally described as a non-specific febrile illness. The non-specificity probably cannot be overstated. A constant refrain in the literature is that as a result Q-fever is probably greatly underreported, understudied, and underdiagnosed. (Reilly, Palmer, Maurin, Marrie 2000) Even the most common manifestation from which it gets its name, a fever, is not present in asymptomatic and many chronic incidences. (Nebreda, Ko, Broqui 1993)

Effects when they occur are multi-systemic. The symptoms, complications, and biological findings thus can be quite varied. (Tringali, Jansenius) As a leading Q-fever expert observes, "the spectrum of manifestations of infection due to *C. burnetii* continues to expand." (Marrie 2004)

**Main manifestations: acute & chronic**

Despite the variety of effects, certain typical features of symptomatic infection can be described. Q-fever manifests normally in two forms, acute (also called primary) Q-fever and chronic Q-fever. (There also exists a somewhat intermediate form called Q-fever chronic fatigue syndrome which, when it appears, is an immediate sequela to an acute episode.)

**Age & gender**

In general, male gender and increasing age seem to add to the risk of developing symptomatic Q fever and having more severe effects and prognoses. (Maltezon, Raoult 2000, Maurin)

**Special vulnerability of those with immunosuppression**

Persons with debilitated immune systems are especially susceptible to Q-fever and its effects. Typically these are persons with acquired immune deficiency syndrome (AIDS),
chronic alcoholism, cancer, chronic myeloid leukemia, renal transplantation, corticosteroid therapy, postpartum status and chronic alcoholism. (The vulnerability exists because CB maintains itself in phagolysosomes, similar to other micro-organisms which target immunosuppressed hosts.) (Bronqui 1993, Marrie 2000) It is argued that Q fever should be "added to the spectrum of diseases that occur more frequently during HIV infection." (Maurin, Marrie 2000)

**Mortality**

Q-fever is normally not fatal; the death rate among observed acute infections is about 1%. (Maurin, Marrie 2002) Among chronic cases, the mortality rate is much higher, though in both acute and chronic cases, mortality is usually associated with another debilitating health condition. A review of several studies suggests that the main Q-fever chronic manifestation, endocarditis, has in the past had a mortality rate as high as 65% but that has been lowered to 10% in many cases because of earlier intervention and better therapy. (Siegman-Igra, Maurin, Marrie 2000, Raoult 2000)

**Chief characteristic symptom: fever**

By far the most characteristic sign of Q-fever is a fever. It appears in both the acute and chronic forms, though the fever appears almost universally in the former condition (when the *Coxiella burnetii* infection is symptomatic). The fever can run as high as 104 degrees F (39-40 degrees C) or more. Females are more likely than males to present with a fever alone. (Marrie 2002, Maurin)

**B. Acute Effects**

**General acute presentations**

The common presenting signs and rates of occurrence with acute fever are a fever of 39-40°C (100%), fatigue (98%), chills (88%), sweats (84%), myalgia (68%), nausea (49%), vomiting (25%), pleuritic chest pain (28%), diarrhea (21%). Arthralgia and weight loss are reported as well. A severe headache is common but is especially associated with acute Q-fever pneumonia. (Marrie 2000)

Various forms of rashes are known to occur – macropapular exanthema, purpuric red trunk papules being observed in an umber of cases -- but only recently have these been regarded as part of Q-fever presentation. (Jansenius, Maurin) Other commonly reported symptoms, such as dry cough, are associated with the additional syndromes that may occur after infection. (Marrie 2002)

The additional syndromes of acute Q-fever are typically respiratory and hepatic, the former manifesting as pneumonia primarily, and the latter as forms of hepatitis. Figures can vary by study and region but the two syndromes each seem to occur in about one-half to two-thirds of the cases, sometimes (about 20%) both at the same time. (Maurin,
Raoult 2000) Other systems can be involved as symptoms or complications in acute Q-fever, though much less frequently. Of these, the neurologic and cardiovascular systems are especially significant. Effects on these latter conditions tend to be more threatening to overall health. (Broqui 1994, Raoult 2000, Shah)

**General Acute Biologic Findings**

Normal leukocyte count is extremely common in acute Q-fever patients (90%). (Maurin) Cytokine overproduction is a classic set of findings: tumor necrosis factor (TNF), interleukin (IL)-6, IL-12, and IL-10 are increased in patients with different clinical presentations of acute Q fever, but even patients with uncomplicated acute Q-fever exhibited increased release of the 4 cytokines. (Honstettre 2003, Maurin, Marrie 2000)

Other somewhat less common general acute biologic effects include smooth muscle antibodies, antiphospholipase antibodies, elevated erythrocryte sedimentation rate, increased gamma-glutamyl transferase levels, and increased transaminase levels. Rarer still, but also observed, are increased creatinine levels, increased lactate-dehydrogenase levels, increased alkaline phosphatase levels, increased bilirubin levels, and thrombocytopenia. (Maurin)

**Pneumonia**

Three types of pneumonia have been identified as effects of acute Q-fever. These are pneumonia as incidental finding in a febrile illness, atypical pneumonia, and rapidly progressive pneumonia. The last is the most encountered manifestation of pneumonia. (Marrie 2000) Fatality is rare, and is usually associated with another active debilitating health condition. (Maurin) Urso reports a case of deadly infection with severe intrahemorrhagic and focal necrotizing pneumonia associated with necrotizing bronchitis, histocytes, lymphocytes, plasma cells in alveoli.

When pneumonia does occur, the most noticed presentation is "inspiratory crackles." (Marrie 2000) Atypical pneumonia usually manifests with a dry non-productive cough (28% of Q-fever pneumonia). (Torres, Marrie 2000, Maurin) Rapidly progressive pneumonia mimics Legionnaire's disease in its progress. Severe cases of Q-fever pneumonia are known which have required ventilation. (Torres, Marrie 2000, Maurin)

**Biologic findings in acute Q-fever pneumonia**

Pulmonary consolidation signs are seen in the rapidly progressive form of pneumonia. Five percent of pulmonary manifestations also include splenomegaly. Lumbar puncture readings are usually normal although occasionally the CB pathogen is found. (Marrie 2000) A study by Pierce showed on transbronchial biopsy the presence of small coccobacilli within alveolar macrophages.

Radiographic examination does not always yield consistent results. Nonsegmental and segmental pleural-based opacities are found, but multiple rounded opacities can be
present also (especially in exposure through feline placentitis). Other features are small pleural effusions, atelectasis, increase in reticular markings, hilar adenopathy may occur (Baret, Marrie 2000, Maurin). One study noted "unique lobar or segmental alveolar opacity" involving more likely the lower lobes, but multiple or interstitial opacities were found as well. (Caron)

Complications in acute Q-fever pneumonia

Other systems may experience effects due to pneumonia. Encephalitis, renal failure, congestive heart failure and myocarditis are suggested as possible complications. (Maurin)

Mortality in acute Q-fever pneumonia

Mortality is generally less than 3% and is associated with prior heart and lung conditions in the patient. (Maurin, Soubrane, Siegman-Igra)

Acute Q-fever hepatitis

Hepatitis manifests in Q-fever usually as a standard infectious hepatitis manifestation, as an incident of Q-fever pneumonia, or most commonly as a granulomatous form, usually discovered on biopsy during a fever of uncertain origin. (Marrie 2000, Maurin) It has been suggested from a French study that hepatitis is a more likely result of infection via consumption of unpasteurized milk. (Tissot-Dupont)

Presentation of acute Q-fever hepatitis usually consists only of other non-specific symptoms of Q-fever infection (fever, headache, etc.). Hepatitis is generally only discovered on biopsy. Biologic findings are usually determinative and descriptive of acute Q-fever hepatitis and its characteristics. Jaundice, however, can be part of the presentation but it is not especially common. (Marrie 2000) One acute Q-fever hepatitis case was associated with transient ischemic attacks. (Ferrante)

Biologic findings in acute Q-fever hepatitis

The most characteristic finding is the presence of fibrin-ring granulomas, called "doughnut lesions". (Erhardt, Marrie 2000) Kupffer cells are regarded as the target of CB liver infection. Hepatic lesions and effects also include portal triaditis, Kupffer cell hyperplasia, and moderate fatty changes. (Maurin) Anemia is a noted association with acute Q-fever hepatitis. (Arrebola-Garcia)

The increase of cytokines associated with Q-fever generally have been found to be even higher in patients with acute Q-fever hepatitis than in patients with just fever or pneumonia. An elevated level of liver enzymes is also common: increases in AST, ALT, and alkaline phosphatase are especially noted. (Baret, Maurin) Hyponatremia is frequent though it has not appeared in a majority of the cases. (Maurin)
Acute Q-fever Hepatitis mortality

A fulminating hepatitis from Q-fever has proven fatal in one case. (Reilly)

Cardiac Manifestations: Pericarditis and Myocarditis

Although much rarer (0.5-2% range of acute cases), cardiac involvement in acute Q-fever typically manifests as pericarditis and myocarditis. Endocarditis is the characteristic condition of chronic Q-fever, though pericarditis appears in the chronic form of Q-fever as well. (Marrie 2002) Most of these conditions are only discovered on laboratory diagnosis, though chest pains are associated. In severe cases, tachycardia, cardiac failure, and hypoxemia needing ventilation are manifestations. (Maurin) Baquero reports cardiac tamponade in a 2 year old.

Pericarditis and myocarditis often occur together. Pleuritis is often associated with pericarditis. (Marrie 2000, Maurin) One myocarditic case produced a hypokinetic left ventricle accompanied by dyspnea (Murcia).

Biological Findings in acute Q-fever pericarditis and myocarditis

Electrocardiogram abnormalities are the only way to ascertain myocarditis. Pericarditis is found the same way but with T-wave abnormalities particularly common on electrocardiogram and pericardial effusion seen on echocardiogram. (Maurin)

Mortality in acute Q-fever cardiac syndromes

Myocarditis in the primary form of Q-fever and has been fatal. Fatality from myocarditis is not necessarily associated with prior debilitated conditions. (Maurin, Fournier 2001) In one case, fatal heart (and subsequent multi-organ) system failure arose in a CB-infected 15-year old male who was only exposed to a pregnant cat. (Chevalier)

Neurological manifestations

Acute Q-fever neurological manifestations tend to be low in frequency although Reilly noted a rate of about 20% in that study cohort. Meningoencephalitis, encephalitis, and encephalomyelitis are the noted syndromes. (Maurin) Severe acute cerebellitis occurred in a child. (Sawaishi) The mechanism of Q-fever neurological effects are unknown. (Brooks)

Neuropsychiatric manifestations are the common clinical indicators. (Bernit, Maurin) Weakness, dementia, behavioral disturbances, recurrent meningismus, reidula parasthesias, left leg sensory loss, seizures, and coma have been known to occur. (Dano, Marrie 2000) Optical neuritis, myelitis, and peripheral neuropathies are possible effects as well. (Maurin, Marrie 2000)
One study showed a case of reversible bilateral abducens nerve paralysis in acute meningoencephalitis. (Shaked) Irritability, agitation, and a glassy-eyed disoriented demeanor have been seen associated with encephalitis. (Maurin) The child with cerebellitis also manifested with a herniated tonsil as a result of a swollen vermis. (Sawaishi)

Diffuse meningeal irritations in acute primary fever have been noted; neck stiffness has been associated with them. (Maurin, Marrie 2000) Blurred vision is a noted residual feature of Q-fever meningitis. (Maurin) Cortical dysfunction has manifested as a persistent headache, a 3 week relapse, and photophobia. (Brooks)

Cerebellar symptoms, cranial nerve palsies, extrapyramidal signs, and the Miller-Fisher form of Guillain-Barré syndrome (areflexia/ophthalmoparesis) are reported to present as part of Q-fever neurological involvement. (Bernit, Maurin, Marrie 2000) A neurological complication from acute Q-fever hepatitis included extrapyramidal signs: cogwheel rigidity and intention tremor in the upper extremities. (Gallaher).

**Biological findings in neurological Q-fever syndromes**

The presence of leukocytes, predominantly mononuclear, in the cerebrospinal fluid (CSF) is one noted finding. (18-1392 cells per mm3) (Marrie 2000). Protein concentrations in the CSF are increased but glucose remains normal. (Maurin) Pleocytosis is reported as well in cerebellitis. (Sawaishi)

Demyelinating polyradiculoneuritis in a 71 yr old has been observed in Q-fever meningoencephalitis. (Marrie 2000). Acute meningoencephalitis shows periodic bilateral complexes in an electroencephaologram (EEG). Moderately severe abnormalities on EEG have indicated generalized cortical dysfunction. (Brooks)

**Hematological effects**

Hematological effects, in addition to the various serological and immune include bone marrow necrosis, histiocytic hemophagocytosis, hemolytic anemia, the simulation of lymphoma, transient hypoplastic anemia, reactive thrombocytosis. (Maurin, Marrie 2000)

**Cholecystitis**

Rolain recorded some cases of acute cholecystitis from Q-fever. Of nine cases, distended gallbladder with biliary sludge but without stones occurred in eight cases but one case had a single stone. Five gallbladders showed inflammation.

**Fatigue syndrome: A mixed appearing condition**

A fatigue syndrome is reported in the cases of many who have recovered from primary Q-fever symptoms. Described as a "persistent debilitating syndrome", it can persist for
several years as a chronic condition, and is evidence of the persistence of the
survivability in the body of CB after the acute episode (Maurin, Harris) Nevertheless, it
is regarded as part of the acute period of Q-fever because serologically it is associated
with no or few anti-phase I antibodies. (Maurin)

Symptoms of this condition include fatigue, sweating, breathlessness on exertion, vision
blurring, bradycardia, arthralgia, myalgia, muscle fasciculation, sleep disturbance, and
painful swollen lymph nodes. (Maurin, Harris, Harvey-Sutton, Kawagawa)

Pregnancy

Placentits can occur during pregnancy. (Marrie 2000, Maurin) High rates of stillbirths,
spontaneous abortions, and low birth weight have been noted, (Tellez, Ludlam, Javier
Diaz, Raoult 2000, Richardus) Vasculitis, vascular thrombosis, placental insufficiency;
direct fetal injury and infection shown in aborted fetuses have been observed. (Maurin)

C. Chronic Effects

General

Coxiella burnetii are known to persist in the system after acute infection and have been
specifically observed to be present for more than a decade. No outer limit of persistence
has been determined and the time between acute infection and chronic infection is not
fixed. It is believed that CB survive in the bone marrow because immature cells in the
monocyte-macrophage lineage are present but not activated enough to destroy the
pathogens. (Harris) Immunocompromised patients are especially vulnerable to Q-fever
persistence. (Maurin)

Acute v. chronic

The Nine Mile and Priscilla strain isolates have been "implicated in two different clinical
disease syndromes, acute and chronic Q fever, respectively." (Yeaman) (More recent
studies indicated that host factors, e.g. immunosuppression, previous cardiac disease,
influence the transition from acute to chronic than bacterial strain.) Rheumatoid factor
has been found significantly elevated in chronic disease but not in primary Q-fever.
fever. (Peacock) The rate of incidence of a chronic illness development from an acute
infection appears to be in the range of 1-2%.

Serology

Serological profiles have been established to distinguish the chronic from the acute form
of Q-fever. (Peter 1980, Maurin) In general, using the complement fixation methods a
titer to phase I antigens of 1:200 or more is indicative of chronic infection; if less, it is
deemed acute. (Maurin, Marrie 2000) Fournier found using immunofluorescence that a
phase I IgG antibody titer greater than or equal to 1:800 is associated specifically with chronic Q-fever endocarditis.

Using the Western immunoblot test, chronic Q-fever was indicated by IgG antibodies to 12 to 15 antigen of phase I CB, but in acute Q-fever the IgG antibodies reacted with 7 to 10 antigens. (Marrie 2000) Chronic Q-fever was also distinguishable in that there were antibodies to antigens of molecular masses 50, 80, 160 kD only present for chronic Q-fever. (Marrie 2000)

Peacock has found on serology testing that "the ratio of anti-phase II to anti-phase I antibodies was greater than 1, greater than or equal to 1, and less than or equal to 1 for primary Q fever, granulomatous hepatitis, and Q fever endocarditis, respectively."

Most noted chronic presentation: endocarditis

Sixty to seventy percent of symptomatic Q-fever in the chronic phase manifests as endocarditis. About half the cases involve the mitral valve, one-third the aortic valve, and about one-sixth of cases involve both. Cardiac failure is present in two-thirds of Q-fever endocarditis cases. Males over 40 appear most susceptible. (Maurin, Marrie 2000)

Pathogenesis of endocarditis

Endocarditis appears almost always in persons with existing valvular or certain other cardiopulmonary defects (dyspnea, acute pulmonary edema, angina, palpitations). (Broqui, Marrie 2000, Maurin) Prosthetic valve endocarditis is an increasingly noted phenomenon. (Sanchez Recalde, Maurin)

Presentation of clinical complications of Coxiella-induced endocarditis

Q-fever's classic presentation, fever, is present in about two-thirds of endocarditis patients. It is often low-grade. Purpuric rash can appear in about one out of five cases. Weakness, malaise, fatigue, weight loss, chills, anorexia, and night sweats are commonly reported. Clubbing of the fingers tends to happen in about one-third of the cases. (Maurin, Marrie 2000)

In more advanced forms of the disease renal insufficiency has occurred. Focal segmental proliferative glomerulonephritis (GN) and diffuse intracapillary proliferative glomerulonephritis. (Vacher, Perez-Fontan)

Hepatomegaly and splenomegaly have been found present in about half the cases. Arterial emboli are a characteristic of about 21% of cases of Q-fever endocarditis. (The neurologic sequelae of chronic Q-fever, as well as possible strokes and mortality itself, are often attributed to the effects of the emboli.) (Maurin)

Biologic findings in Q-fever endocarditis
A chronic inflammatory syndrome typically occurs that is usually reflected in elevated sedimentation rate, and increased gamma globulin concentration. Circulating immune complexes, the presence of rheumatoid factor, and the presence of smooth muscle antibodies are very common biologic findings in Q-fever endocarditis. Thrombocytopenia, anemia, antinuclear antibodies, increased liver enzyme levels (ALT/AST), and increased creatinine levels are less typical but common. Leukocytosis and leukopenia are rarer effects. Also noted are microscopic hematuria, antimitochondrial antibodies, and a positive Coombs' test. (Peacock, Marrie 2000, Maurin)

**Serology of Q-fever endocarditis**

In immunofluorescence assays a phase I IgG antibody titer of 1:800 or more has been shown to be associated with chronic Q-fever endocarditis. (Fournier)

**Mortality in Q-fever endocarditis**

Strong emphasis has been placed upon early detection and intervention. Over the past years, such steps have lowered the mortality rate of Q-fever endocarditis from over 60% to under 10% with effective combination antibiotic therapy. (Raoult 2000, Marrie 2002, Maurin)

**Other cardiac effects**

Maurin observes that pericarditis may also present as a complication of endocarditis. No studies indicate that myocarditis is an effect of chronic Q-fever infection. (See section B's discussion of acute pericarditis for possible manifestations)

**Osteoarticular chronic Q-fever**

Osteomyelitis, osteoarthritis, and spinal osteomyelitis developing from an aortic graft infection have been found. Children with coxitis and spondylodiskitis have had bone infection with Q-fever. Joint prostheses and immunosuppression have given rise to bone infections in adults with chronic Q-fever. Tuberculoid bone lesions on biopsy with no mycobacterial pathogens are the common indicators. (Perez-Ortela, Maurin, Marrie 2000)

**Chronic Q-fever hepatitis**

Hepatic involvement in chronic Q-fever is usually a complication of chronic Q-fever endocarditis. But chronic Q-fever hepatitis does occasionally, though rarely, occur alone. The general non-specific symptomatology of Q-fever – fever, headache, myalgia, etc --. may accompany the condition. (Maurin, Marrie 2000)

Chronic Q-fever hepatitis manifests biologically with lymphocytic infiltration of the liver and foci of spotty necrosis. The characteristic "doughnut lesions" of acute Q-fever are
absent, however. Phase I antibody titers by IFA method in chronic Q-fever hepatitis were 1: 2048 (Yebra)

**Chronic pulmonary effects**

These occur among about 1% of chronic Q-fever victims. Pulmonary fibrosis and pseudotumors are the common manifestation of chronic Q-fever pulmonary pathology. Radiologically, the pseudotumors resemble lung neoplasm. Chronic Q-fever pulmonary pseudotumors have been shown on examination after lung resection to contain mononuclear cells blocking the bronchioles and invading the septa and alveoli.

**Chronic neurologic effects**

Neurologic effects in chronic syndrome do not seem to be different from the acute. (See section B above). It is suspected, however, that they can result from the emboli of chronic Q-fever endocarditis. (Ferrante) Also, since stroke is a possible effect of the emboli, neurologic sequelae to stroke should be considered as the effects of a Q-fever infection complication. (Shaked)

**Vascular**

Generally vascular Q-fever manifests only as a non-specific fever. Weight loss and abdominal pain have been noted as associated symptoms, however. Typically, the vasculitis patients are male with an average age of 66.5. Most had had some kind of previous vascular challenge like an aortic abnormality (e.g., infrarenal anyeurism or vascular graft). Serology is necessary for diagnosis. This condition is very likely to be underrdiagnosed. (Maurin)

**Biologic findings in vascular infection**

A severe inflammatory syndrome is very common with high erythrocyte sedimentation rate and a high C-reactive protein level along with a high fibrinogen level in serum. Unlike the symptom complex of Q-fever endocarditis, however, hyperleukocytosis, thrombocytopenia, and increased liver enzyme levels are not characteristic. (Maurin)

**Psychogenic Effects**

Current medical scholarship urges consideration of psychogenic effects of the subjective trauma arising from exposure to biowarfare agents. This issue is addressed in the Supplement "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents." No study of psychogenic effects of exposure specifically to CB has been found.

**D. Miscellaneous**

Other symptoms have been reported in clinical studies. (Maurin, Marrie 2000, Marrie 2004, Gallaher) They are listed below:
Reproductive system effects

priapism
orchitis
epididymitis

Endocrine effects

vasopressin secretion abnormalities
thyroiditis

Cutaneous/Subcutaneous effects

erythema nodosum
mesenteric panniculitis

Other

splenic rupture
pancreatitis
rhabdomyolysis
hemolytic uremic syndrome

IV. TREATMENT & PREVENTION

Antibiotic therapies

The recommended treatment of acute Q-fever is doxycycline at 200 mg/day for 14 days). Macrolides are recommended for pregnant women. Fluoroquinolones and macrolides are good alternative therapies. Q-fever pneumonia has been treated with erythromycin effectively but its general use is uncertain. (Maurin, Marrie 2000, Caron)

Tetracycline is also somewhat effective in chronic Q-fever endocarditis but the disease's persistence and virulence leads to relapse if the therapy is stopped. Combination therapy is now recommended with chloroquine and doxycycline together for 18 months or more, or doxycycline and ofloxacin together for more than 3 years. Clinical monitoring of lymphocyte ratios (T4/T8) and echocardiograms at a quarterly annual rate are recommended as well for endocarditis. Valve replacement surgery is reserved for hemodynamic complications, and antibiotic therapy should continue thereafter to avoid relapse. (Maurin, Calza, Shishmanov, Marrie 2000)

Vaccines

A variety of vaccines have been attempted, the Russians developed an attenuated version of CB but concerns over the persistence of the organism argue against the use of a live
vaccine. The Australians have developed an effective formalin-inactivated vaccine called Q-Vax has proved to be 100% effective over a 5 years period. (Marrie, Maurin, Kishimoto)

V. SECONDARY SOURCES SURVEY

Many secondary sources present oversights and errors on issues that might arise in clinical and epidemiological evaluation of Coxiella burnetii infection. In some cases, length is a natural limitation. In that regard, it is not uncommon in surveying sources to find whole syndromes (e.g. neurologic, osteoarthritic) overlooked.

Additionally, information and studies on the nature and probability of the persistence of the bacteria in the body, including its transition from an acute to chronic pathogen, are rare.

Below are some other significant oversights by select key sources, including those of the federal government.


No entry for Coxiella burnetii/ Q-fever.

Centers for Disease Control & Prevention (CDC) --“Q-Fever”

The CDC’s online monograph does not mention other chronic effects beyond endocarditis.

Cohen et al, Infectious Diseases. 2000

The chapter on "Bioterrorism and Biodefense" (Artenstein) contains no specific discussion of Coxiella/Q-fever except to list it among bioweapons of moderate priority (category B). Where it appears on a chart which addresses infection control concern it answers “no” to the question of human-to-human transmission, though such transmission, while uncommon, is reported as possible and having occurred. (Milazzo)

Department of Veterans Affairs/Defense

In a Project SHAD-related Fact Sheet attached to a letter dated December 31, 2001, and numbered IL 10-2001-015, entitled “Under Secretary for Health's Information Letter”, CB is described in one paragraph. References indicate that there was reliance on Mandell et al. Principles and Practice of Infectious Diseases (2000), which contains Marrie's
summary chapter on Q-fever. The short summary in the letter accurately reports the most common effects – pneumonia, hepatitis, and endocarditis. It then adds that "generally victims recover, even without treatment"; this might underemphasize the fatality rate of Q-fever endocarditis

The same paragraph currently appears in the Department of Defense's DeploymentLINK website, but with the following cautionary sentence appended: "However, complications, if they ensue, can be very serious and sometimes even life-threatening." (http://deploymentlink.osd.mil/current_issues/shad/shad_glossary.shtml -- March 10, 2004)

**Infectious Diseases Handbook, 5th ed. 2003**

The "Microbiology" section of the entry on *Coxiella burnetii* incorrectly identifies phase I CB as avirulent and phase II CB as virulent, which is the opposite of the known tendencies of the respective phases of CB progression.

**Mandell et al. Principles and Practice of Infectious Diseases, 5th ed. 2000.**

Marrie's summary in this work (Marrie 2000) does not discuss the chronic fatigue syndrome which can follow primary Q-fever. (The fatigue syndrome is significant in its indication of the persistence in the system of *Coxiella* bacteria.) The summary exclusively emphasizes the aerosol transmission of *Coxiella* bacteria when describing "pathogenesis", even though human-to-human transmission is known and oral transmission via raw milk is also known and later discussed in the full course of the same chapter.

The chapter also addresses the Q-fever syndromes and effects in somewhat haphazard fashion. Acute and chronic syndromes are not clearly differentiated. Hepatitis is discussed after chronic endocarditis, for example, when it usually manifests in acute Q-fever.

**Shulman et al. The Biologic & Clinical Basis of Infectious Diseases, 5th ed. 1997.**

The section on Q-fever states incorrectly that "the clinical illness is not associated with rash."

**Turkington. The Encyclopedia of Infectious Diseases. 2nd ed. 2003.**

The entry on Q-fever incorrectly says there is no human-to-human transmission. It fails to clearly distinguish acute from chronic Q-fever and states without support and in the face of *Coxiella burnetii*’s known persistence that "after one infection, a person becomes immune to Q-fever for life."
A. GENERAL SYMPTOMS

Characteristics of Coxiella Infection
- Many asymptomatic or low symptom cases
- Special vulnerability for the immunocompromised
- Older males more susceptible to infection and severe effects
- An understudied condition, so effects may not be complete or completely understood

Common General Symptoms in Q-fever (may occur in acute or chronic coxiella burnetii infections)
- Fever to 104 degrees F.
- Fatigue
- Chills
- Sweats
- Persistent or Severe Headache
- Myalgia
- Nausea
- Vomiting
- Pleuritic chest pain
- Diarrhea
- Arthralgia
- Weight loss
- Dry cough/productive cough
- Rashes (macropapular exanthema, purpuric red trunk papules)

B. ACUTE EFFECTS

General
- About 3% mortality
- Fever (usually rapid onset)
- Most common presentations other than general symptoms: Pneumonia and Hepatitis
- Infections of the neurologic, cardiovascular systems occur and are more threatening to overall health.
- Normal leukocyte count
- Cytokine overproduction: tumor necrosis factor (TNF), interleukin (IL)-6, IL-12, and IL-10 increased

Other Noted General Characteristic Effects
- Smooth muscle antibodies
- antiphospholipase antibodies
- elevated erythrocyte sedimentation rate
- increased gamma-glutamyl transferase levels,
- increased transaminase levels
- increased creatinine levels
- increased lactate-dehydrogenase levels
- increased alkaline phosphatase levels
- increased bilirubin levels
- thrombocytopenia.

Pneumonia
Mortality is generally less than 3% and is associated with prior heart and lung conditions in the patient.

Common Presentations
- incidental finding in a febrile illness
- atypical pneumonia
- rapidly progressive pneumonia (most common manifestation; mimics Legionnaire's disease)

Noted Effects
- "inspiratory crackles." (most noted)
- dry non-productive cough
- splenomegaly (rare)
- presence of small coccobacilli within alveolar macrophages,
- nonsegmental and segmental pleural-based opacities
- multiple rounded opacities
- small pleural effusions
- atelectasis
- increase in reticular markings
- hilar adenopathy
- "unique lobar or segmental alveolar opacity" (commonly lower lobes)
- multiple or interstitial opacities

**Reported Complications of Acute Q-fever Pneumonia**

- Encephalitis
- Renal failure
- Congestive heart failure
- Myocarditis

**Hepatitis**

A fulminating hepatitis from Q-fever has proven fatal in one case.

- standard infectious hepatitis
- incident of Q-fever pneumonia
- granulomatous form (most common manifestation)

**Presentation**

- general symptoms -- fever, headache, etc.
- fibrin-ring granulomas ("doughnut lesions")
- portal triaditis
- Kupffer cell hyperplasia
- moderate fatty changes
- anemia
- increase of cytokines even greater in hepatitis
- elevated level of liver enzymes: AST, ALT, and alkaline phosphatase
- hyponatremia

**Cardiac Manifestations (0.5-2% of acute Q-fever cases)**

Typically pericarditis and myocarditis, which usually occur together. Fatality from myocarditis not necessarily associated with prior debilitated health conditions

**Presentation**

- general symptoms (e.g. fever, etc.)
- chest pains especially noted
- EKG abnormalities. T-wave abnormalities (associated with pericarditis), pericardial effusion discovered in echocardiogram (pericarditis)

**Complications in severe cases:**

- tachycardia
- cardiac failure
- hypoxemia needing ventilation
- cardiac tamponade (observed in 2 year old)
- pleuritis (with pericarditis)

**Neurological Manifestations**

Neurological manifestations tend to be low though 20% reported in one study. Unknown mechanism. These effects also may occur in chronic Q-fever cases.

- meningoencephalitis
- encephalitis
- encephalomyelitis
- cerebellitis

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*Coxiella Burnetii Health Effects*
Neuropsychiatric manifestations

- Weakness
- persistent headache
- photophobia
- dementia
- behavioral disturbances (including irritability, agitation, and a glassy-eyed disoriented demeanor)
- myelitis
- recurrent meningismus
- reidula parasthesias
- reversible bilateral abducens nerve paralysis
- peripheral neuropathy (e.g., left leg sensory loss)
- seizures
- coma
- optical neuritis
- blurred vision (noted residual symptom)
- herniated tonsil from swollen vermis (cerebellitis)
- Neck stiffness (associated with diffuse meningeal irritations)
- extrapyramidal signs e.g.: cogwheel rigidity and intention tremor in the upper extremities.
- leukocytes, predominantly mononuclear, in CSF
- CSF protein concentrations increased
- Pleocytosis (in cerebellitis)
- Cerebellar symptoms
- cranial nerve palsy
- Miller-Fisher type of Guillain-Barre syndrome (areflexia/ophthalmoparesis)
- Demyelinating polyradiculoneuritis in meningoencephalitis (one case reported)
- Periodic bilateral complexes in EEG (acute meningoencephalitis)

Hematological Effects

- bone marrow necrosis
- histiocytic hemophagocytosis
- hemolytic anemia
- simulation of lymphoma
- transient hypoplastic anemia
- reactive thrombocytosis.

Fatigue Syndrome

Described as a "persistent debilitating syndrome" which follows for an indefinite period an acute episode.

- fatigue
- sweating
- breathlessness on exertion
- vision blurring
- bradycardia
- arthralgia
- myalgia
- muscle fasciculation
- painful swollen lymph nodes
- sleep disturbance.

Sleep disturbance

Pregnancy

- placentitis
- spontaneous abortions
- high rates of stillbirths
- low birth weight
- vasculitis
- vascular thrombosis
- placental insufficiency
- direct fetal injury
- fetal infection

C. CHRONIC EFFECTS

The outer limit of chronic effects of CB infection is not established. Endocarditis is the most noted chronic effect. General symptoms can show in chronic as well as acute infection. Serology is used to distinguish acute and chronic infection. Rheumatoid factor is also significantly elevated in chronic, as opposed to acute, cases

Serology

- Complement Fixation:
  Titer to phase I antigens of > 1:200 = chronic, less acute
  Microfluorescence:
phase I IgG antibody titer ≥ 1:800 = chronic Q-fever endocarditis.

- Western immunoblot test:
  Chronic = IgG antibodies reacting to 12 to 15 antigen of phase I CB
  Acute = IgG antibodies reacting to 7 to 10 antigens. (Marrie 97)

- Antibodies to antigens of molecular masses 50, 80, 160 kD only present for chronic Q-fever

- General: Ratio of anti-phase II to anti-phase I antibodies > 1 = primary/acute, ≥ 1 = granulomatous hepatitis, and ≤ 1 = Q fever endocarditis

**Most Noted Chronic Presentation: Endocarditis**

**General**

- 60-70% of chronic Q-fever = endocarditis.
- Males over 40 appear most susceptible
- Occurs usually with existing valvular or certain other cardiopulmonary defects (dyspnea, acute pulmonary edema, angina, palpitations). Prosthetic valve endocarditis is well-observed too.
- Mortality can be high (over 60%) but better intervention may be lowering that.

**Involvements**

- mitral valve (more common)
- aortic valve (less common)
- both (rarer)

**Symptoms**

General Q_fever symptoms present often.

- fever low-grade
- purpuric rash (occasionally)
- weakness
- malaise
- fatigue
- weight loss
- chills
- anorexia
- night sweats

**Additional effects:**

- clubbing of the fingers
- renal insufficiency: (glomerulonephritis)
- hepatomegaly
- splenomegaly
- arterial emboli (believed responsible for neurologic sequelae of chronic Q-fever and fatality)
- possible strokes (role of emboli?)
- cardiac failure
- increased liver enzyme levels (ALT/AST)
- increased creatinine levels less typical
- leukocytosis (rare)
- leukopenia (rare)
- microscopic hematuria
- antimitochondrial antibodies
- positive Coombs’ test.

**Serology**

- Microfluorescence: phase I IgG antibody titer ≥ 1:800

  **Possible additional cardiac complication**

- Pericarditis

**Osteoarticular Chronic Q-fever**
Joint prostheses and immunocompromise have given rise to bone infections in adults.

- osteomyelitis
- osteoarthritis,
- spinal osteomyelitis developing from an aortic graft infection
- coxitis and spondylodiskitis with bone infection (noted in children).
- tuberculoid bone lesions with no mycobacterial presence

**Chronic Q-fever hepatitis**

Hepatitis rarely occurs alone in chronic Q-fever.

- General symptoms
- lymphocytic infiltration
- foci of spotty necrosis
- (Note: no doughnut lesions)

**Serology**

- IFA: Phase I antibody titers = 1: 2048

**Chronic Pulmonary Effects (1% of chronic Q-fever)**

- Pulmonary fibrosis
- Pseudotumors

**Presentation & Findings**

- fever and general symptoms
- pseudotumors resemble lung neoplasm (radiology).
  - mononuclear cells blocking bronchioles and invading the septa and alveoli in pseudotumor manifestation

**Chronic Neurologic Effects**

Neurologic effects in chronic syndrome do not seem to be different from the acute (see above section A). They may result from the emboli of chronic Q-fever endocarditis. As stroke is a possible effect of the emboli, neurologic sequelae to stroke should be considered as possible effect of Q-fever.

**Chronic Vascular Effects**

Commonly affecting males with average age of 66.5 and previous vascular challenge like an aortic abnormality (infrarenal aneurysm or vascular graft).

**Presentation**

- non-specific fever
- weight loss (especially observed with these effects)
- abdominal pain (especially observed also)

**Biologic findings in vascular infection**

- severe inflammatory syndrome: high erythrocyte sedimentation rate, a high C-reactive protein level, high fibrinogen level.
- Not present: hyperleukocytosis, thrombocytopenia, and increased liver enzyme levels.

**Potential Psychogenic Effects**

Modern scholarship has noted that psychiatric conditions may result from the subjective awareness of being exposed to biowarfare agents. This issue is separately treated in the Supplement "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents"
D. OTHER EFFECTS OCCASIONALLY OBSERVED

Reproductive System Effects

- priapism
- orchitis
- epididymitis

Endocrine Effects

- vasopressin secretion abnormalities
- thyroiditis

Cutaneous/Subcutaneous Effects

- erythema nodosum
- mesenteric panniculitis

Lymphatic

- Mediastinal lymphadenopathy

Other

- Rhabdomyolysis
- hemolytic uremic syndrome

Endocarditis is a rare, but sometimes fatal, complication of Q fever. Its diagnosis is difficult and it is based on non-specific cardiac findings and a high title of phase I antibodies. The treatment is based on tetracyclines alone or in combination with cotrimoxazole, for long periods of time. The therapeutic efficacy is evaluated by the measurement of phase I antibodies, every three months. The relapses are frequent despite the long period of antibiotic therapy. We report what is probably the first case of Q fever prosthesis endocarditis in Portugal, as a complication following an acute episode of Q fever.

The authors describe some aspects of “difficult to treat” infections, pointing out, on the basis of their experience, infective endocarditis (IE) and nosocomial infections in compromised host. Among difficult-to-treat IE, the authors stress: 1) the peculiar etiopathological features and the frequent causative pathogens multi-resistance on early post-surgical IE; 2) the problems in detecting and management of IE by HACEK group microorganisms; 3) the problems related to other unusual agents IE, with particular regard to nutritionally deficient variants of S. viridans and to Coxiella burnetii. Among nosocomial infections in compromised host, Authors underline the relationship between either nosocomial flora or surgical/instrumental practices and possible underlying immunodeficiencies. Clinical and diagnostic remarks of sepsis, pneumonitis, meningitis, enteritis in neutropenic patients are then stressed, pointing out their atypical presentations and severe prognosis.

The authors report their experience on etiological and clinical aspects of infective endocarditis (IE). A series of 182 consecutive patients, including 83 cases of medical IE, 73 cases of IE in intravenous drug abusers (DA), 22 cases of IE on late prosthetic valves and 4 cases of IE on early prosthetic valves were evaluated since 1976. Medical IE occurred frequently in the elderly patients and in most of the cases (80%) involved natural valves with underlying abnormalities, either rheumatic (42%) or degenerative.
(33%) or malphormative (25%). Pre-existing valvular pathology was not needed for IE in DA, occurring in 13%, mainly due to a previous IE. In most of the cases IE in DA was a staphylococcal IE (80%) and a right-sided IE (77%). Streptococci were frequent agent both in medical and late prosthetic valves IE (55%); however, a wide pattern of microorganisms, including &quot;unusual&quot; pathogens like nutritionally variant Streptococci, Haemophylus parainfluenzae, Haemophylus paraphrophylus, Coxiella burnetii and the so-called &quot;non pathogen microorganisms&quot; (e.g. Neisseria sicca) was identified as etiological agent. As regards the clinical approach and diagnosis, the Authors underline some atypical clinical presentations of IE: the pulmonary presentation, occurring in right-sided IE, mainly in DA; the neurological presentation, suggesting staphylococcal etiology and left-sided IE; the vasculitis presentation, miming connective tissue diseases; the cardiac presentation, observed in aortic localization (1 case). One or more severe complications occurred in 65% of the patients, contributing to adverse outcomes. (ABSTRACT TRUNCATED AT 250 WORDS)


BACKGROUND: Seventy five patients older than 60 years with a community acquired pneumonia followed up in an outpatient clinic, were prospectively studied in order to determine the incidence of atypical agents, clinical-radiological characteristics, progression and the differences with pneumonia in younger patients. METHOD: Clinical-radiological evaluation protocols were activated in the first visit and in two subsequent controls. Etiological diagnosis was made by means of serology (in the first visit and three weeks later). RESULTS: Initially, 85 patients older than 60 years were included of which 75 non hospitalized were fully followed up. Also, in the comparative study, 216 outpatient clinic patients 60 years old or younger were followed up during the same period. In the first group the frequency of atypical agents was 33.3%. The most frequently isolated bacteria was Coxiella burnetii (13.3%) followed by virus and Legionella pneumophila. No case of Mycoplasma pneumoniae was diagnosed. The most frequent radiological onset was alveolar infiltrate (85%). The comparative study between the two populations (older or younger than 60 years), found few clinical differences (dyspnea more frequent in older, feverish chill in younger) and auscultation (crackles more frequent in older). We did not find differences remaining clinical-radiological or laboratory data. Most patients presented a favourable clinical and radiological progression. Only 2 patients needed hospital admission (2.7%). CONCLUSIONS: In outpatient clinic patients older than 60 years with community acquired pneumonia a high number of atypical agents have been found. The clinical-radiological evolution was satisfactory for most of them. Age was not a decisive element in determining hospital admissions.

Q fever, a worldwide zoonosis caused by Coxiella burnetii, has many manifestations in humans. Endocarditis is the most serious complication of Q fever. Animal models are limited to acute pulmonary or hepatic disease and reproductive disorders. An appropriate experimental animal model for Q fever endocarditis does not yet exist. In this study, severe combined immunodeficient (SCID) mice infected with C. burnetii showed persistent clinical symptoms and died, whereas immunocompetent mice similarly infected became asymptomatic and survived. The SCID mice examined in this study had severe chronic lesions in their primary organs: the heart, lung, spleen, liver, and kidney. The heart lesions of the SCID mice were similar to those in humans with chronic Q fever endocarditis: they had focal calcification and expanded macrophages containing C. burnetii. The 50% lethal dose of C. burnetii in SCID mice was at least 10(8) times less than that in immunocompetent mice. The SCID mouse is highly susceptible to C. burnetii, and the immunodeficiency of the host enhances the severity of Q fever. This animal model could provide a new tool for the study of chronic Q fever and Q fever in immunodeficient hosts.

Arrebola García et al. 1993. [Hepatic granulomatosis caused by Q fever: a cause of erroneous tuberculosis diagnosis]. An.Med.Interna. 10(12): 595-598. We present the case of a 31-year-old man hospitalized for the study of a fever syndrome. The patient developed acute respiratory failure, with anemia and hepatic affection. In the histological examination of the liver and bone marrow, the presence of granulomas suggesting a tuberculous etiology was demonstrated. Antibodies IgG anti-Coxiella burnetii were detected, using indirect immunofluorescence, at the level of 1/200, with latter seroconversion to 1/800. Therapy with doxycycline was administered (200 mg/day during 14 days). Fever subsided in 24 hours and the other clinico-biochemical disorders disappeared in the following days. After the literature review, we conclude that Q fever must be taken into account for the differential diagnosis of any granulomatous disease observed in the liver and/or bone marrow. We can confirm that any granuloma is specific of just one pathological entity. The diagnosis must be always supported by other clinical, supplementary and serological data.

Ascher et al. 1983. Initial clinical and immunologic evaluation of a new phase I Q fever vaccine and skin test in humans. J.Infect.Dis. 148(2): 214-222. A new phase I Q fever skin test was administered to 74 subjects. Thirty-eight had less than 8 mm and 36 had greater than or equal to 10 mm erythema at 24 hr. Only 14 had circulating antibody. Three skin test-positive and 17 skin test-negative, seronegative individuals subsequently received 6 or 30 micrograms of vaccine in a single dose. All skin test-positive individuals and one skin test-negative individual developed mild local reactions. Seventeen of 18 recipients developed fluorescent antibody to phase II antigen, and five developed positive phase II complement fixation titers. Serial assays of specific lymphocyte proliferation (LT) performed in 15 individuals revealed an increase in phase II LT in nine and an increase in phase I LT in six. All local reactions occurred in individuals with preexisting phase II LT. On the basis of these results, this vaccine and
skin-test preparation appear safe, effective, and promising for eventual use in at-risk personnel.


PURPOSE: Prosthetic valve endocarditis is a dangerous complication of valvular surgery (3-6%). Among involved pathogens, Coxiella burnetii is an occasional agent, though isolated with increasing frequency. We report our experience with this peculiar endocarditis and lay stress on specific diagnostic and therapeutic difficulties.

METHODS: Between 1990 and 1995, six patients retrospectively met the diagnosis criteria for definite endocarditis due to Coxiella burnetii. RESULTS: Five Algerian men and one French woman presented with prosthetic valve endocarditis with negative blood cultures (on bioprosthesis: four cases, on mechanical valve: two cases). The main clinical and biological feature was febrile congestive heart failure with hepatomegaly, splenomegaly, hepatic and renal abnormalities, inflammatory syndrome, hypergammaglobulinemia, anemia and lymphopenia. Serological testing for Coxiella burnetii provided diagnosis in all cases. Echocardiography displayed vegetations in all cases. Valvular replacement was performed in four patients. With antibiotic therapy including doxycycline or hydroxychloroquine, quinolones or rifampicine, all patients experienced complete clinical, biological and echographic remission. CONCLUSION: Q fever prosthetic valve endocarditis presents as a systemic disorder occurring in patients with valvular heart disease. From now on, early diagnosis and efficient medical treatment may provide permanent prosthetic sterilization.

**Ayres 1991.** Post-infection fatigue syndrome following Q fever. *QJM.* 91:105-23


Acute Coxiella burnetii infection is most commonly a mild and self-limiting disease with fever, pneumonia and hepatitis. Endocarditis is the most frequent clinical presentation of chronic infection. We report a 2-year-old child with Q fever who presented with acute pericarditis and cardiac tamponade and who developed a chronic hepatic infection.


Q fever is a worldwide zoonosis but is not often a common cause of fever among travellers returning from the tropics. We report a case of acute Q fever, revealed by a pneumonia and acquired by a traveller in French Guyana. The chest radiography showed alveolar opacities and pleural effusion. Biological abnormalities were elevated liver enzyme levels and thrombocytopenia. The patient improved or the third day of antibiotic treatment. She mentioned that 3 other people she lived with during her trip had been diagnosed with Q fever. A common source outbreak was then suspected. They all stayed
in the same farm in French Guyana. Animal exposure occurred there, in particular with a goat and a dog (both were parturient). The disease was probably transmitted by airborne dust to our patient, as no other vectors of transmission were found. Since the clinical presentation of Q fever is not specific, in order for the physician to diagnose it, he must have an awareness of the disease. Our case emphasised that looking for risk factors of Coxiella burnetii exposures is particularly important. Amongst them, the most important seems to be contact with farm animals. The clinician should thus try to trace such a possible contact when treating a case of traveler's Q fever.


Q fever is a zoonosis caused by Coxiella burnetii, an obligate intracellular bacterium. Domestic ungulates and parturient cats are the primary reservoirs of infection. The animals excrete the bacterium in urine, faeces, milk and amniotic fluid. After desiccation the micro-organism spreads via aerosols. After inhalation or ingestion and an incubation period of 2-6 weeks acute Q fever may develop with atypical pneumonia and hepatitis as major clinical symptoms. The infection also may present as a flu-like illness or remain asymptomatic. Generally, the prognosis is favourable. However, endocarditis or another chronic form of Q fever occasionally develops with possibly fatal outcome. Diagnosis relies upon serologic testing with an indirect immunofluorescence method. Doxycycline is the antibiotic of choice in the treatment of Q fever. Endocarditis needs therapy for years with the addition of rifampin or hydroxychloroquine. Q fever is poorly recognised due to the variety of clinical presentations.


Chronic forms of Q fever (endocarditis) are rare, but are responsible for severe and desperately recurrent infections, resulting in multiple valve replacements with a reserved prognosis. The authors report the case of a 35-year-old patient with a known history of rheumatic fever, who developed blood culture negative infectious endocarditis on a mitral bioprosthesis. The diagnosis of Q fever was based on serological arguments. Despite long-term antibiotic therapy, serology remained strongly positive and was associated with repeated mitral valve disinsertion. The patient died immediately after the fourth operation in a context of haemodynamic failure. This clinical case emphasizes the importance of performing Q fever serology in any case of culture negative endocarditis and the therapeutic difficulties encountered in chronic recurrent endocarditis.

Infective endocarditis due to fastidious microorganisms is commonly encountered in clinical practice. Some organisms such as fungi account for up to 15% of cases of prosthetic valve infective endocarditis, whereas organisms of the HACEK group (Haemophilus parainfluenzae, H. aphrophilus, and H. paraphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae) cause 3% of community-acquired cases of infective endocarditis. Special techniques are necessary to identify these microorganisms. A history of contact with mammals or birds may suggest infection caused by *Coxiella burnetii* (Q fever), Brucella species, or *Chlamydia psittaci*. A nosocomial cluster of postsurgical infective endocarditis may be caused by * Legionella* species or *Mycobacterium* species. If risk factors that are commonly associated with fungal infections (cardiac surgical treatment, prolonged hospitalization, indwelling central venous catheters, and long-term antibiotic use) are present, fungal endocarditis is possible. Patients with endocarditis and a history of periodontal disease or dental work in whom routine blood cultures are negative might have infection due to nutritionally variant streptococci or bacteria of the HACEK group. Communication between the microbiologist and the clinician is of crucial importance for identification of these microorganisms early during the course of the infection before complications such as embolization or valvular failure occur. In this article, we review the microbiologic and clinical features of these organisms and provide recommendations for diagnosis and treatment.


**BACKGROUND:** Q fever is characterized by its clinical polymorphism; neurological involvement has occasionally been described. In the course of acute Q fever, neurological manifestations may include aseptic meningitis, encephalitis or encephalomyelitis, and peripheral neuropathy. **OBJECTIVE:** To review and evaluate cases of acute Q fever with neurological symptoms diagnosed in our laboratory. **METHODS:** A total of 1269 acute Q fever cases were recorded from January 1985 to January 2000 in our laboratory and were reviewed for neurological complications. Patients were considered to have acute Q fever when serological procedures showed *Coxiella burnetii* phase II titers of 1:200 or higher for IgG and 1:50 or higher for IgM. Those patients who underwent a lumbar puncture for cerebrospinal fluid analysis or who had abnormal neurological symptoms were selected for this study. We describe the clinical, epidemiological, and biological features of these cases. We also review the literature and compare our cases with those previously reported. **RESULTS:** Among the 45 patients selected, 14 were excluded because they had normal cerebrospinal fluid and no neurological symptoms. Two were excluded because there were no clinical or epidemiological data. Three major clinical syndromes were observed: meningoencephalitis or encephalitis in 17 cases; meningitis in 8; and myelitis and peripheral neuropathy in 4. Encephalitic signs were not specific, but behavior or psychiatric disturbances were common. **CONCLUSIONS:** Q fever should be included in the differential diagnosis of acute neurological disease in a patient with a fever. Serological testing should be performed in cases of meningoencephalitis, lymphocytic...
meningitis, and peripheral neuropathy, including Guillain-Barre syndrome and myelitis.


Two abortions associated with Coxiella burnetii occurred in a group of 34 pregnant ewes. The seroprevalence of C. burnetii infection was studied by using an ELISA and the immunofluorescence (IF) assay was applied to the contents of vaginal swabs. In addition, a PCR assay, with primers based on a transposon-like repetitive region of the C. burnetii genome (trans-PcR), was used for the highly sensitive and specific detection of C. burnetii in vaginal swabs, milk and faeces. Of the 34 animals tested at parturition, eight (24 per cent) were positive by ELISA, 11 (32 per cent) were positive by IF, and 15 (44 per cent) were positive when the vaginal swab extract was subjected to the trans-PCR assay. C. burnetii was therefore detected by PCR in the vaginal swabs of seven seronegative ewes. However, five weeks after lambing, 16 (47 per cent) of the animals tested were ELISA positive but only two animals (6 per cent) were positive by PCR. Among the ELISA- and PCR-positive animals, eight (25 per cent) shed coxiella in their milk and six (18 per cent) did so in their faeces.


Q-fever is widely spread antropoozoosis caused by Coxiellae burnetti, an intracellular compulsory microbe parasite. Two characteristics of Coxiellae burnetti are of crucial importance for appearance of Q-fever, especially in the circumstances when the cause of infection remains unclear. The first one is a high resistance of Coxiellae burnetti to environment changes and the second one is a small size of the infectious dose. The clinical manifestations of Q-fever can vary, so the making of diagnosis is still based on serology, with Phase I and Phase II antibodies and the difference between the acute and the chronic form of the disease. Serologic diagnostics presents the method of choice with Q-fever (IFT) in serums of patients with clinical suspicion to Coxiellae burnetti infection. We have tested the serums of patients from Canton of Sarajevo which were coming to our laboratory from January 2001-December 2001. Out of 58 processed serums the specific IgM antibodies were found in 10 serums and specific IgG antibodies in 27 serums.

Q-Fever nowadays presents the most diffuse disease in the world, caused by the microorganisms from the family Risickettiaceae. This disease is Coxiellae burnetii. The laboratory diagnosis of the Q-Fever can be stated either by the isolation of the cause from the patient material, either by the proving of the specifically antibodies. The serologic diagnostics presents the choile method in Q-Fever. The aim of this work is to illustrate the results of the detection of the serum in patients with the clinical symptoms at the infection Coxiellom burnetii. We tested the sera of the patient from the region of the Federation Bosnia and Herzegovina, which arrived in our laboratory in the period of November 2000 till May 2001. From the total 174 prepared sera specific IgM of the antibodies we found in cases, and the specific IgG of the antibodies in 54 sera.

We initiated a prospective study with a group of practitioners to assess the etiology, clinical presentation, and outcome of community-acquired pneumonia in patients diagnosed in the outpatient setting. All patients with signs and symptoms suggestive of pneumonia and an infiltrate on chest X-ray underwent an extensive standard workup and were followed over 4 weeks. Over a 4-year period, 184 patients were eligible, of whom 170 (age range, 15-96 yr; median, 43 yr) were included and analyzed. In 78 (46%), no etiologic agent could be demonstrated. In the remaining 92 patients, 107 etiologic agents were implicated: 43 were due to "pyogenic" bacteria (39 Streptococcus pneumoniae, 3 Haemophilus spp., 1 Streptococcus spp.), 39 were due to "atypical" bacteria (24 Mycoplasma pneumoniae, 9 Chlamydia pneumoniae, 4 Coxiella burnetii, 2 Legionella spp.), and 25 were due to viruses (20 influenza viruses and 5 other respiratory viruses). There were only a few statistically significant clinical differences between the different etiologic categories (higher age and comorbidities in viral or in episodes of undetermined etiology, higher neutrophil counts in "pyogenic" episodes, more frequent bilateral and interstitial infiltrates in viral episodes). There were 2 deaths, both in patients with advanced age (83 and 86 years old), and several comorbidities. Only 14 patients (8.2%) required hospitalization. In 6 patients (3.4%), the pneumonia episode uncovered a local neoplasia. This study shows that most cases of community-acquired pneumonia have a favorable outcome and can be successfully managed in an outpatient setting. Moreover, in the absence of rapid and reliable clinical or laboratory tests to establish a definite etiologic diagnosis at presentation, the spectrum of the etiologic agents suggest that initial antibiotic therapy should cover both S. pneumoniae and atypical bacteria, as well as possible influenza viruses during the epidemic season.

Acute infection with Coxiella burnetii usually results in a self-limited illness, but it can occasionally cause chronic endocarditis or hepatitis. Headache is a common presenting symptom of acute infection with this agent, but specific neurological abnormalities are rare. We report the case of a patient with acute Q fever that caused frank encephalitis. We also review the literature on central nervous system disease attributable to C. burnetii.
The MAR-test results including titer levels of 1:4 and higher revealed 92% positive reactions in the district of Santa Cruz/Santiago and 77% positive reactions in 6 villages of Santo Antao. The submitted examinations prove the agent Coxiella burnetii's existence responsible for different clinical pictures observed on the Cape Verde Islands.

PURPOSE: Cardiac valves that were resected from patients with Q fever endocarditis were examined by immunohistologic methods to correlate the presence of Coxiella burnetii in the valves with the histopathologic, serologic, microbiologic, and clinical findings. PATIENTS: Seventeen patients with serologic and microbiologic or clinical evidence of Q fever endocarditis who presented with cardiac failure secondary to valvular dysfunction and required valve replacement surgery were selected from the clinical records of the Unite des Rickettsies, Marseille, France. METHODS: Clinical data were collected by questionnaire. Serologic characterization was performed by indirect immunofluorescent antibody testing; shell vial cultivation of C burnetii was performed from resected valves and blood when available; and pathologic and immunohistologic testing for localization of C burneti in resected valves were performed by standard methods using both polyclonal and monoclonal C burneti antibodies. RESULTS: Demographic and clinical findings were typical of patients with Q fever endocarditis. Pure chronic inflammation or mixtures of acute and chronic inflammation were the most frequent inflammatory patterns present and were associated with fibrin deposition, necrosis, and fibrosis. Well-formed granulomas were not present, but the granulomatous inflammation observed in 6 of these 17 patients was associated with foreign body reactions or with valvular calcifications secondary to preexisting valvular damage and could not be directly attributed to infection. C burnetii were present nearly exclusively in macrophages in sites of inflammation and valvular injury and only in the vegetations. Immunohistologic results confirmed the valve culture results in 10 of 14 cases. CONCLUSION: The pathologic findings in the valves of patients with Q fever endocarditis are nonspecific. The presence of empty or foamy macrophages is suggestive of infection by C burnetii; however, definitive identification rests upon the demonstration of the organism in the tissue by immunohistology. Q fever endocarditis probably results from infection of previously damaged heart valves. The finding of the absence of granulomas in these cases contrasts with the pathologic findings in patients with acute, self-limited Q fever and suggests an aberrant host immune response that permits persistence of the bacterium and chronic, prolonged valvular infection and injury. The pathologic findings and distribution of C burnetii in the damaged valve tissues explain the clinical findings of valve failure and occasional embolic episodes, as well as the frequent ability to isolate C burnetii from the peripheral blood of infected patients. Immunohistology may be a valuable diagnostic tool in places where serology and culture are not available.
OBJECTIVE: Chronic Q fever is seldom recognized; before 1989, only 234 cases had been reported in the literature. The 92 cases of chronic Q fever collected at the French National Reference Center for Rickettsioses from 1982 through 1990 represent the largest series ever reported. PATIENTS: The patients included in the study were diagnosed between July 31, 1982, and August 1, 1990, at the French National Reference Center for Rickettsioses as having chronic Q fever by the following criteria: presence of antibody against Coxiella burnetii phase I antigen at a titer greater than or equal to 800 for IgG and 50 for IgA by the indirect immunofluorescence test. Epidemiologic, clinical, laboratory, and treatment data were collected from 39 different collaborative hospitals throughout France. MAIN OUTCOME MEASURE: For each serologically selected patient, a computerized questionnaire was utilized to record 188 different items of demographic, epidemiologic, clinical, laboratory, and therapeutic data, which were analyzed. RESULTS: Chronic Q fever occurs more frequently in city dwellers than in rural inhabitants, and exposure to domestic ruminants and raw milk is an important feature. Immunocompromising conditions (20.2%) and underlying heart disease (88.4%) or vascular disease are the most important risk factors to consider in potential cases of chronic Q fever. The mortality in these patients with endocarditis was high (23.5%). The clinical spectrum of 84 patients included 57 cases of endocarditis, three cases of vascular prosthesis infection, three cases of aneurysmal infection, three cases of osteoarthritis, four cases with lung localizations, nine asymptomatic cases, three cases of hepatitis, and two cases with cutaneous forms of the disease. CONCLUSIONS: In patients with unexplained fever, negative blood cultures, and a history of underlying vascular or cardiac disease, Q fever should be considered.

The etiologic diagnosis of infective endocarditis is easily made in the presence of continuous bacteremia with gram-positive cocci. However, the blood culture may contain a bacterium rarely associated with endocarditis, such as Lactobacillus spp., Klebsiella spp., or nontoxigenic Corynebacterium, Salmonella, Gemella, Campylobacter, Aeromonas, Yersinia, Nocardia, Pasteurella, Listeria, or Erysipelothrix spp., that requires further investigation to establish the relationship with endocarditis, or the blood culture may be uninformative despite a supportive clinical evaluation. In the latter case, the etiologic agents are either fastidious extracellular or intracellular bacteria. Fastidious extracellular bacteria such as Abiotrophia, HACEK group bacteria, Clostridium, Brucella, Legionella, Mycobacterium, and Bartonella spp. need supplemented media, prolonged incubation time, and special culture conditions. Intracellular bacteria such as Coxiella burnetii cannot be isolated routinely. The two most prevalent etiologic agents of culture-negative endocarditis are C. burnetti and Bartonella spp. Their diagnosis is usually carried out serologically. A systemic pathologic examination of excised heart
valves including periodic acid-Schiff (PAS) staining and molecular methods has allowed the identification of Whipple's bacillus endocarditis. Pathologic examination of the valve using special staining, such as Warthin-Starry, Gimenez, and PAS, and broad-spectrum PCR should be performed systematically when no etiologic diagnosis is evident through routine laboratory evaluation.


Endocarditis is a rare but severe complication of Q fever, an infectious disease caused by the intracellular pathogen Coxiella burnetii. Heart involvement is the most common clinical presentation of chronic Q fever, and it occurs almost invariably in patients with previous valvular disease or artificial valves, and in the immunocompromised host. The optimal treatment of Q fever endocarditis is still today debated, and recommended duration of treatment varies from one year to one's lifespan. A case of chronic Q fever endocarditis is described in a patient with biological prosthetic aortic valve and aortic homograft, successfully treated with doxycycline and chloroquine for 2 years.


The progression of Q fever to either acute or chronic disease has been attributed both to biological characteristics of the bacteria and to the host immune response. In order to determine whether a specific immunoglobulin G (IgG) subclass distribution could play a diagnostic or prognostic role in Q fever, IgG subclass levels were measured in patients with acute or chronic disease. It was observed that (i) IgG1 and IgG3 levels were elevated in patients with chronic Q fever compared to patients with acute disease or normal controls; (ii) variations over time reflected inverse complementary relationships of subclass levels, such as between IgG1 and IgG3 compared with IgG2 and IgG4, or an inverse relationship between IgG1 and IgG2; (iii) variations in IgG2 and IgG3 total subclass levels during follow-up of patients with chronic Q fever showed a decrease in IgG2 with a concomitant increase in IgG3 two years from disease onset. These findings indicate that measurements of IgG subclasses may be a simple, additional tool useful in the diagnosis of Q fever. This data raises the question of an unusual immunoregulatory mechanism in Q fever that is implicated in the presentation of the clinical disease.


A total of 157 sera from febrile patients in the Philippine General Hospital in Manila, Luzon, and the Northern Samar Provincial Hospital, the Philippines, were used. Serum antibodies against spotted fever group Rickettsia (SFGR) and typhus group Rickettsia
Coxiella Burnetii were detected by indirect immunofluorescence test. Antibody positive rates were 1.3% for SFGR (Rickettsia japonica) and 2.5% for TGR (R. typhus), respectively. Rickettsial antibodies in humans in the Philippines were found for the first time. These results underscore the need for further epidemiological study of clinical rickettsioses in the Philippines.


**STUDY OBJECTIVES:** To emphasize epidemiologic, clinical, or radiologic characteristics whose detection could lead to an early diagnosis and to enhance therapeutic efficacy. **PATIENTS:** Eighty hospitalized patients from 1982 to 1996. **DESIGN:** The diagnosis of Q fever infection was serologically confirmed in all the patients (phase II Coxiella burnetii antibody) using the complement fixation test and/or the indirect immunofluorescence antibody test. **RESULTS:** Patients from rural and urban areas were noted in the same proportion; however, the usual epidemiologic factors such as contact with cats or farm animals were found in 40% of the patients. Mean age+/-SD was 49 +/- 20 years, and there was a higher sex ratio of male to female patients (1:3.44). We found a specific seasonal distribution since 80% of the cases occurred between February and May. Delay before referring to hospital was 8.2 +/-7.8 days, while 69.3% of the patients received an antibiotic treatment that was mainly penicillin or cephalosporin. The dominant clinical features were dry cough and high fever, as the maximal temperature reached more then 40 degrees C in 58% of the patients. Digestive symptoms were rare. WBC count remained within normal range in 80% of the cases with a low proportion of lymphocytes in half of the patients, and the sedimentation rate was usually elevated (55 +/- 34 mm). Altered liver function consisted more frequently in an elevated level of alkaline phosphatase (70% of the cases) than transaminases, while hyponatremia was frequently mentioned (28.2% of the patients). We found radiologic evidence of unique lobar or segmental alveolar opacity involving more likely the lower lobes in 55 patients, and multiple or interstitial opacities in the others. Chest radiographs were considered normal in eight patients. The clinical response was favorable in all the patients with a reduction in fever 4.8 +/- 3.9 days after the start of treatment with the second antibiotic that included mainly erythromycin or quinolones, and chest radiographs returned to normal in 81% of the patients within the first month.


**BACKGROUND:** During one year (1988), a protocol study of the community-acquired pneumonias was carried out in patients referred to the Hospital Virgen del Camino in Pamplona (Health Area I or Northern Navarra), so as to have an epidemiological and microbiological knowledge of this disease in this geographic area. **METHODS:** A clinical protocol, microbiological investigation, 3 blood cultures, Gram stain and sputum culture and serological tests at admission and 20 days later (complement fixing antibodies and indirect immunofluorescence) were carried out. Chest radiographs were carried out on
admission, on the third and seventh hospital days and subsequently depending on the evolution. RESULTS: The causative organism was found in 141 of the 225 included patients (62%). Two or more organisms were identified in 19 (8%). In 84 (38%) no microorganism was found. The results for the causative organisms and their frequency were: Pneumococcus 12%, mycoplasma 12%, other bacteria (including Legionella) 11%, Q fever 8%, viruses 7%, and psitaccosis 4%. In 59% of patients there was an underlying disease and 39% developed complications. 4% of patients died. CONCLUSIONS: 22% of the community acquired pneumonias were cared for in the hospital, representing 6% of the admissions to the Internal Medicine Service. The etiologic diagnosis was made in 62% of the community-acquired pneumonias. 23% were of bacterial origin (including Legionella) and 31% were nonbacterial. There was a high incidence of pneumonias caused by Mycoplasma pneumoniae and Coxiella burnetii.

Congestive heart failure and septic embolism complicate the clinical course of patients with infective endocarditis (IE). This study reviews the clinical records of patients with systemic disease secondary to IE and stratifies their disease severity according to individual risk factors and medical, and surgical interventions. The hospital records of all patients presenting to our institution from 1992 through 1997 with heart valve destruction secondary to IE were reviewed. Ten patients with hemodynamically significant valve lesions were included in this study: seven with aortic valve disease and two with mitral valve disease, and one with combined aortic and mitral valve lesions. All were diagnosed by echocardiogram. All ten patients experienced systemic septic arterial emboli: four intracranial lesions, four visceral lesions, and three extremity arterial occlusive events. Two patients required peripheral arterial repair. Cultures revealed infection secondary to Staphylococcus aureus in five, Streptococcus species in three, Coxiella species in one, and an unidentified organism in one patient. Seven patients underwent valve replacement. Three patients died from their disease processes. Statistical significance was established by Wilcoxon rank analysis with a two-tailed P < 0.05. Patients with IE secondary to staphylococcal infections suffered a more acute and virulent disease process (P = 0.04), with a 40 per cent mortality rate in the first 48 hours. There was no increased incidence of embolization associated with longer duration of symptoms (P = 0.32). Surgical repair conferred improved clinical outcome as compared with no surgical intervention (P = 0.03). Improved patient outcome was associated with nonstaphylococcal infection (P = 0.02), and a successful initial antibiotic regimen (P = 0.03). Peripheral arterial repair was successful in both cases.

INTRODUCTION: The most frequent clinical expression of chronic Q fever is culture-negative endocarditis. Other localizations are rare. EXEGESIS: We report a documented case of chronic Q fever that occurred in a 47-year-old immunocompetent man and was
associated with spleen abscess, in the absence of detectable endocarditis. The spleen abscess was a complication of either a preexisting cyst or a calcified hematoma. Splenic infection with Coxiella burnetii was documented with cultures, polymerase chain reaction and immunohistochemistry. The outcome was favorable after splenectomy and a 21-month antibiotherapy. CONCLUSION: Chronic Q fever may develop in the absence of endocarditis, when a preexisting vascular lesion such as aortic aneurysm exists. A splenic cyst may have played a similar role for this patient.


The zoonotic infections caused by Francisella tularensis and Coxiella burnetii, tularemia and Q fever, respectively, are two less commonly encountered clinical illnesses that are becoming increasingly recognized as epidemiologically important human diseases. The prevalence of tularemia and Q fever can be positively impacted by increased awareness of the clinical entities that arise from infection by these arthropod-borne organisms. Improved recognition of these clinical syndromes will lead to greater diagnostic accuracy in recognizing these diseases in patients. Ultimately, more stringent measures to prevent infection may be required, through raising public awareness, since current therapeutic regimens for these two diseases are limited, and knowledge of the pathogenesis of these two organisms are still in developing stages.

Enzyme-linked immunosorbent assays (ELISA) for the detection of specific immunoglobulin G (IgG) and IgM antibodies were developed by using purified Coxiella burnetii cells. Variables, including type of microtiter plate, blocking agent, incubation conditions, antigen stability, and substrate type, were examined to achieve optimal ELISA performance. The reliabilities of the assay systems were compared with those of complement fixation (CF) and enhanced immunofluorescence (EIF) tests with 600 human serum samples from defined clinical cases of Q fever, routine samples, and serum specimens from farmers. ELISA and EIF test results agreed in all cases. Dot immunoblotting was also used to test some of these sera and gave a rapid, qualitative result, which agreed with ELISA and EIF test results in all cases. No instances were found in which both ELISA and EIF test results were negative and the CF test results was positive. However approximately 5% of the sera were positive by ELISA and the EIF test while the CF test result was either negative or unreadable because of serum anticomplementary activity. We conclude that dot immunoblotting is a useful screening test, whereas ELISA and the EIF test are both rapid and sensitive tests when used for the serodiagnosis of Q fever and should be considered to be replacements for the CF test.
Meningoencephalitis caused by Coxiella burnetii is exceptional and its clinical presentation is varied. We report a case which presented as transient central neurological deficits and intracranial hypertension without fever. The condition was diagnosed by indirect immunofluorescence.

Human ehrlichiosis, an acute febrile illness caused by Ehrlichia canis or a closely related rickettsial organism, was first identified in 1986. From 1986 through 1988, sera from 85 patients demonstrated a fourfold rise or fall in antibody titer to E. canis. Seven (22%) of 32 patients initially tested during the first week after onset of illness, 17 (68%) of 25 tested during the second week, and all 18 tested during the third week had titers that exceeded the minimum positive titer of greater than or equal to 80. Of the 85 confirmed ehrlichiosis patients, 31 (36.5%) also had indirect fluorescent antibody titers considered diagnostic of infection with Rickettsia rickettsii, Rickettsia typhi, or Coxiella burnetti, but in most these diagnoses were not supported by epidemiologic, clinical, or serologic evidence. These results emphasize that patients suspected of having a tick-borne infection should be tested for antibodies to E. canis as well as for those to other rickettsiae.

Immunoglobulin M (IgM) and IgA responses in patients with acute Q fever were compared by enzyme-linked immunosorbent assay. An increase in both IgM and IgA was observed in paired sera from all 19 patients with acute Q fever, and both IgM and IgA levels showed good correlation with complement fixation test titers. Paired sera from 23 patients with infections other than Q fever were also tested. IgM levels were elevated in three of these patients, while IgA levels were elevated in three different patients (87% specificity for either IgM or IgA). As no patients in the disease control group showed elevated levels of both IgM and IgA, definition of a positive result as elevated levels of both IgM and IgA improved specificity to 100% without a decrease in sensitivity. This study indicates that detection of specific IgA is a useful adjunct to that of IgM in the diagnosis of acute Q fever.

Some cases of late abortion occurring after a Coxiella burnetii infection, more often with a chronic evolution, have already been mentioned in the literature. We reported here two cases of early abortion, contemporaneous of an acute infection due to C. burnetii. Two
patients, after a contact, before and at the beginning of the pregnancy, with an animal susceptible to contaminate human beings by C. burnetii, presented no clinical symptom characteristic of Q fever. The fetal death for the two cases was found out at the 17th week of amenorrhoea. All the investigations in order to search for an abortion etiology remained negative. Only, the specific serologies showed an acute infection due to C. burnetii.

Within the last four years, we have observed five patients with epidemiological, clinical, and serological features that were consistent with Q fever meningoencephalitis. Attempts to isolate Coxiella burnetii from the cerebrospinal fluid of two patients were unsuccessful. Neurological features ranged from coma, general seizures, confusion, to palsy and meningitis. All patients were febrile. These patients were neuroradiologically investigated. Since 1984, four other cases have been reported in the literature. Antibiotics with good penetration into the cerebrospinal fluid, such as new quinolones, may be useful for treatment of confirmed cases. Q fever should be considered as a possible etiology of meningitis in endemic areas, and diagnosis should be confirmed by serology.

Q fever, a worldwide zoonosis caused by Coxiella burnetii, lacks clinical specificity and may present as acute or chronic disease. Because of this polymorphism, serological confirmation is necessary to assess the diagnosis. Although microimmunofluorescence is our reference technique, the cutoff titers that are currently used to make a diagnosis of active or chronic Q fever were determined years ago with limited series of patients and sera. We determined the titers of immunoglobulin G (IgG), IgM, and IgA against both phases (I and II) of Coxiella burnetii. Rheumatoid factor was removed before testing IgM and IgA. We report here the various cutoff titers and the kinetics of antibody development from 2,218 first serum samples of patients, among whom 208 suffered from acute Q fever and 53 had chronic Q fever. In active Q fever, we have defined a low cutoff (phase II IgG titer &lt; or = 100) below which the diagnosis cannot be made and would need further confirmation and confirmed a high cutoff (phase II IgG titer &gt; or = 200 and phase II IgM titer &gt; or = 50) over which the diagnosis can be made. For chronic Q fever diagnosis, phase I IgA titers are not contributive despite previous works claiming their usefulness; a phase I IgG titer of &gt; or = 800 is highly predictive (98%) and sensitive (100%). We have also studied the possibility of rejecting or evoking the diagnosis of chronic Q fever by phase II IgG and IgA titers. This method is useful when phase I testing is not available, but the sensitivity remains low (57%).
The clinical findings during a major epidemic of Q-fever which affected 415 people in the Val de Bagnes (Valais, Switzerland) in the autumn of 1983 are reported. Q-fever symptoms were evident in 191 cases but inconspicuous or absent in 224 cases. The symptoms most frequently reported were prolonged high fever, headaches, severe exhaustion, loss of appetite, cough and myalgia. Amongst disorders which accompany acute Q-fever, pneumonia and granulomatous hepatitis are very frequent, while myopericarditis and glomerulonephritis are less frequently observed. Endocarditis, a later complication of Q-fever, is a severe illness which more frequently affects patients with underlying valvular lesions. New serological techniques now permit more rapid and more accurate diagnosis of both acute and chronic Q-fever.

AIM OF THE STUDY: The purpose of this study was to analyse the clinical and serological follow-up in 21 patients with Q fever endocarditis in Switzerland from 1981 to 1993. PATIENTS AND METHODS: Criteria for Q fever endocarditis were the following: Coxiella burnetii phase I IgG &gt; 1 : 2560 and IgA &gt; 1 : 20 by indirect immunofluorescence. Methods to confirm the diagnosis include immunohistochemical demonstration of C. burnetii by microscopy in valvular material (1 case) and inoculation of this material in experimental animals (10 cases). Information on clinical course of the disease, laboratory abnormalities and treatment were obtained by chart review and a questionnaire sent to physicians who requested the serological tests for Q fever. RESULTS: The average age of the patients was 47 years (15 men and 6 women). 64% of patients had a history of environmental exposure to C. burnetii. The median time of symptomatology before diagnosis was 5 months (1-108). 19/21 patients had valvular lesions, and 2/21 vascular Dacron prosthesis. Most patients presented with fever (18/21), congestive cardiac failure (14/21), weight loss (12/21), anemia (6/19), or thrombocytopenia (6/19). All the patients required antibiotic treatment. Cardiac surgery was performed in 15/21 patients. For 10 patients the geometric mean serological follow-up included at least titers at time of diagnosis (IgG anti-phase I antibodies 1 : 27024, IgA anti-phase I antibodies 1 : 685), at the end of therapy (IgG anti-phase I antibodies 1 : 2941, IgA anti-phase I antibodies 1 : 153) and 6 months after the end of therapy (IgG anti-phase I antibodies 1 : 368, IgA anti-phase I antibodies 1 : 40). The fall in anti-phase I titers was significant. During the clinical and serological outcome (median of 60 months and 69 months respectively) there was no recurrence of endocarditis and antibody titers to C. burnetii phase I remained low. Two patients died during the observation period, one from lung cancer, while the cause of death in the other was unknown. CONCLUSIONS: Serology is the key to Q fever diagnosis. The duration of treatment, and the values to be used to establish cure of endocarditis, are not clearly defined. During the clinical and serological outcome (median of 60 months and 69 months respectively) there was no recurrence of endocarditis and antibody titers to C. burnetii phase I remained low.
Q fever usually presents with high fever, headache and an atypical pneumonia. A case report of a 47-year-old patient with an atypical course of a coxiella infection is described. The dominant clinical symptoms were a liver and bone marrow involvement, whereas pulmonary manifestations were absent. The diagnosis of Q fever in this patient was based on the detection of cytoplasmatic inclusion bodies in macrophages and granulocytes. Furthermore fibrin-ring granulomas ("doughnut lesions") were found in liver tissue specimen and epitheloid-cell granulomas were detected in bone marrow specimen. Complement-fixation antibody titers and PCR resulted unspecific or negative on different occasions during the course of the disease. A confirmation of the diagnosis by complement-fixation antibody test was possible only after recovery from the disease. In Q fever with atypical clinical and serological presentation the screening of blood cells for inclusion bodies and liver or bone marrow tissue for granulomas may be important for establishing the diagnosis.

The authors describe the clinical aspects and epidemiology of Q fever in the Ukrainian SSR and neighbouring territories of the Russian SFSR. Using clinico-epidemiological data as corresponding criteria for the diagnosis of infection by means of adequate laboratory diagnostic tests permitted to increase the detection rate of Q fever.


Acute infection with Coxiella burnetti usually results in a self-limited illness requiring a high index of clinical suspicion for diagnosis. Although headache is a common presentation of acute infection with this agent, focal neurological deficits are considered to be limited to chronic infection, most commonly caused by emboli from endocarditis. We report the case of a soldier returning from Desert Storm who presented with headache and a crescendo pattern of transient ischemic attacks and had serology consistent with an acute Q fever infection. The English-language literature on central nervous system infection caused by Coxiella burnetti is reviewed.

A commercially available enzyme-linked immunosorbent assay (ELISA) for the diagnosis of Q fever (PanBio Coxiella burnetii immunoglobulin M [IgM] ELISA, QFM-200) was compared to the indirect fluorescent antibody test (IFAT) for C. burnetii IgM and the complement fixation test (CFT). The ELISA demonstrated 92% agreement with the reference method (IFAT), and gave a sensitivity of 99% (69 of 70 samples) and a specificity of 88% (106 of 121). Specificity can be increased with confirmation by IFAT. CFT was found to have a specificity of 90% (107 of 119), although it was lacking in sensitivity (73%; 51 of 70). No cross-reactivity was observed in the ELISA with serum samples from patients with mycoplasma (n = 6), chlamydia (n = 5), or legionella (n = 4) infections, although 2 of 5 patients with leptospirosis and 1 of 4 samples containing rheumatoid factor (RF) demonstrated positive results in the ELISA. Results indicate that the performance of the PanBio C. burnetii (Q fever) IgM ELISA (F = 187) is superior to that of CFT (F = 163), and consequently the ELISA should be a useful aid in the diagnosis of acute Q fever.

A novel commercially available enzyme-linked immunosorbent assay (ELISA) for prevaccination screening and diagnosis of Q fever (PanBio Coxiella burnetii immunoglobulin G [IgG] ELISA) was compared to the complement fixation test (CFT), and the indirect fluorescent-antibody test (IFAT) was used to resolve discrepant results between the other two tests. A total of 214 serum samples was tested. The ELISA demonstrated a specificity of 96% (46 of 48 samples) and a sensitivity of 71% (95 of 134 samples). Of the six serum pairs showing CFT seroconversion, three pairs showed a corresponding ELISA seroconversion. No cross-reactivity was observed in the ELISA with serum samples from patients with mycoplasma, brucella, and chlamydia infections. One of the 13 patients with leptospirosis demonstrated a positive result in the ELISA but not in the CFT or the IFAT, and Legionella pneumophila serogroup 4 antibody was found in one of the two sera that were false-positive by ELISA. The results presented in this study suggest that the PanBio Q fever IgG ELISA is a specific alternative method for prevaccination testing and an aid for the diagnosis of Q fever. This test is suitable for use as a screening assay, with CFT and/or IFAT used to confirm negative results.

There is still a low level of clinical awareness regarding Legionnaires' disease 25 years after it was first detected. The causative agents, legionellae, are freshwater bacteria with a fascinating ecology. These bacteria are intracellular pathogens of freshwater protozoa and utilize a similar mechanism to infect human phagocytic cells. There have been major advances in delineating the pathogenesis of legionellae through the identification of genes which allow the organism to bypass the endocytic pathways of both protozoan and human cells. Other bacteria that may share this novel infectious process are Coxiella
burnetti and Brucella spp. More than 40 species and numerous serogroups of legionellae have been identified. Most diagnostic tests are directed at the species that causes most of the reported human cases of legionellosis, *L. pneumophila* serogroup 1. For this reason, information on the incidence of human respiratory disease attributable to other species and serogroups of legionellae is lacking. Improvements in diagnostic tests such as the urine antigen assay have inadvertently caused a decrease in the use of culture to detect infection, resulting in incomplete surveillance for legionellosis. Large, focal outbreaks of Legionnaires’ disease continue to occur worldwide, and there is a critical need for surveillance for travel-related legionellosis in the United States. There is optimism that newly developed guidelines and water treatment practices can greatly reduce the incidence of this preventable illness.


Patients with Q fever and legionellosis may present identical clinical symptom. Differentiation of these diseases is made by serology, mainly the indirect immunofluorescence assay (IFA). Using IFA the authors tested 154 Q fever positive sera from 55 patients with acute Q fever and 28 patients with chronic Q fever for *Legionella pneumophila* antibodies and 57 sera from 57 patients with legionellosis for *Coxiella burnetii* antibodies. Of the 211 sera tested, four sera from different patients had antibodies to both *C. burnetii* and *L. pneumophila*. Using cross-adsorption studies and protein immunoblotting, no cross-reaction between *C. burnetii* and *L. pneumophila* antibodies could be identified. The moderate antibody titers against *L. pneumophila* in two Q fever patients and vice versa for one legionellosis patient are consistent with the incidence of seroprevalence in healthy blood donors and were not due to cross-reactivity. One patient was identified with concurrent Q fever and legionellosis.


Myocarditis has only rarely been described as a manifestation of acute Q fever. Among our series of 1276 patients in whom acute Q fever was diagnosed during 1985--1999, myocarditis was diagnosed in 8. Two patients (25.0%) developed cardiac symptoms during the course of interstitial pneumonia, 2 (25.0%) initially presented with unexplained fever, and 1 (12.5%) presented with febrile cutaneous rash. In 3 patients, cardiac symptoms were inaugural: 1 patient experienced heart failure, and 2 experienced precordial pain. Dilated cardiomyopathy was documented in 7 patients, and 2 (1 of whom had undergone heart transplantation) died despite therapy. In addition, 1 patient was scheduled for heart transplantation because of cardiac insufficiency. When the patients in this study were compared with 32 control patients with acute Q fever, no specific epidemiological or clinical features were associated with this disease except worse prognosis (P=.006). Moreover, among the 12 patients from our series who died as a result of acute Q fever, 2 patients, who were significantly younger than the other 9 patients
(P=.03), had myocarditis. Our study highlights the severity of Coxiella burnetii myocarditis.


Q fever is a potentially severe disease which can occur in large outbreaks of acute infections and is a possible bioterrorism agent. In order to lessen the delay in diagnosing acute Q fever, we compared LightCycler Nested PCR (LCN-PCR), a rapid nested PCR assay that uses serum sampled early during the disease as a specimen and the LightCycler as a thermal cycler, to serology by indirect immunofluorescence. We used the 20-copy htpAB-associated element as the DNA target. The detection sensitivity of this method was one Coxiella burnetii DNA copy. We applied this method to the first serum samples taken from 100 patients diagnosed in our laboratory as having acute Q fever on the basis of clinical manifestations and serology and to 80 controls. The LCN-PCR had a specificity of 100%. The sensitivity was 26% when no antibodies were detected but only 5% with seropositive patients (P < 10⁻²). The technique was most efficient in the first 2 weeks following the onset of symptoms (P = 0.02), when its sensitivity was 24% compared with 14% for serology. With combined use of LCN-PCR and serology within the first 2 weeks, the sensitivity was significantly increased over that with serology alone (P < 10⁻²). Thus, we propose a strategy for improving the early diagnosis of acute Q fever where LCN-PCR should be performed together with serology in the first 2 weeks of the disease but should be reserved for seronegative patients in the next 2 weeks and not used later than 4 weeks following onset, when serology is highly sensitive.


Diagnosis of acute Q fever is usually confirmed by serology, on the basis of anti-phase II antigen immunoglobulin M (IgM) titers of &gt;=1:50 and IgG titers of &gt;=1:200. Phase I antibodies, especially IgG and IgA, are predominant in chronic forms of the disease. However, between January 1982 and June 1998, we observed anti-phase II antigen IgA titers of &gt;=1:200 as the sole or main antibody response in 10 of 1,034 (0.96%) patients with acute Q fever for whom information was available. In order to determine whether specific epidemiological or clinical factors were associated with these serological profiles, we conducted a retrospective case-control study that included completion of a standardized questionnaire, which was given to 40 matched controls who also suffered from acute Q fever. The mean age of patients with elevated phase II IgA titers was significantly higher than that usually observed for patients with acute Q fever (P = 0.026); the patients were also more likely than controls to live in rural areas (P = 0.026) and to have increased levels of transaminase in blood (P = 0.03). Elevated IgA titers are usually associated with chronic Q fever and are directed mainly at phase I antigens. Although the significance of our findings is unexplained, we herein emphasize the fact that IgA antibodies are not specific for chronic forms of Q fever and that they may occasionally be observed in patients with acute disease. Moreover, as such antibody
profiles may not be determined by most laboratories, which test only for total antibody
titers to phase I and II antigens, the three isotype-specific Ig titers should be determined
as the first step in diagnosing Q fever.

36(1): 83-89.
Methods have been developed for the rapid detection of C. burnetii by specific
hybridization of labelled DNA probes to rickettsial plasmid DNA sequences present in
clinical samples. One DNA probe detects all C. burnetii strains, while additional probes
differentiate, between organisms associated with chronic or acute disease. Using these
probes, C. burnetii can be identified in blood, urine, and tissue samples. The plasmid-
derived DNA probes detect as few as 10(4) organisms and less than 1 ng of Coxiella
DNA. Host-cell DNA has no effect on the hybridization signal from C. burnetii DNA,
and these probes do not cross-react with a variety of microorganisms, including both
common laboratory contaminants and organisms that cause clinical symptoms similar to
those of Q fever. The sensitivity of the assay is markedly enhanced when the procedure
employs the polymerase chain reaction (PCR) to amplify C. burnetii DNA. This requires
construction of oligonucleotide primers to DNA sequences flanking the target region of
the DNA being amplified. For C. burnetii detection, several sets of primers have been
prepared. One set is derived from the QpH1 H fragment, a region that is shared by all C.
burnetii plasmids (homologous sequences are also present in the plasmidless strains of C.
burnetii). The H primers detect all strains of C. burnetii. To differentiate between C.
burnetii strains, additional primers, specific for DNA sequences that are unique either to
chronic or acute disease-related strains of C. burnetii are employed. PCR amplifies target
sequences up to 10(6)-fold. When DNA hybridization is used in conjunction with PCR,
the test can detect less than 10 C. burnetii cells.

Second Ed.

Frazier et al. 1990. DNA probes for the identification of Coxiella burnetti strains.
Isolation of Coxiella Burnetii in the standard laboratory setting is hazardous; therefore
most diagnoses are based on retrospective detection of a rising antibody titer to C.
burnetii. As a result, this disease is usually undiagnosed or misdiagnosed. Methods for
the rapid detection of C. burnetii have now been developed that utilize specific
hybridization of labeled DNA probes to nucleic acid in clinical samples. One method
detects the presence of C. burnetii 16S ribosomal RNA (rRNA); another uses plasmid
sequences. We have developed a probe that detects C. burnetii and one that differentiates
between Coxiella strains capable of causing chronic disease and those that cause the
acute form. Using these probes, C. burnetii can be identified in blood, urine, and tissue
samples. The plasmid-derived probes detect as few as 10(4) organisms and less than 1 ng
of Coxiella DNA. A third method differentiates between chronic (endocarditis-causing)
strains and those that cause acute Q fever. This method uses the polymerase chain
reaction (PCR), in which the target regions of DNA are amplified by iterative cycles of
Taq I DNA polymerase chain extension to produce up to a 10(6) amplification of the
target sequences. When Southern blotting is used in conjunction with PCR, the test detects as few as 2-9 C. burnetti cells.


Infections due to Coxiella burnetii, the causative organism of Q fever, are extremely rare in North America. Endocarditis due to the organism has an unusual presentation and poses echocardiographic and laboratory challenges in establishing a diagnosis. We describe the presentation and clinical course of a 40-year-old American man with Q fever endocarditis and briefly discuss the salient issues regarding this entity.


Forty-two children with nontuberculous spondylodiscitis treated between 1966 and 1997 were reviewed, and the clinical, paraclinical, and therapeutic results are presented. The study shows the difficulties of diagnosis and understanding the pathophysiology of the disease. Additional information is provided by new imaging techniques, disc aspiration, and biopsy. The mean age at treatment was 4 years 6 months. The initial clinical presentation was often misleading and the diagnosis was often delayed (42 days average). Standard radiographs and technetium bone scans were important for diagnosis and patient follow-up. Magnetic resonance imaging and needle aspiration of the disc gave an additional reliable aid in differential diagnosis and helped to guide treatment. Bacteria were isolated in 22 of the 35 samples taken (55% Staphylococcus aureus, 27% Kingella kingae; Coxiella burnetii in one sample). The functional outcome is good if treatment is properly carried out. Disc fibrosis and occasional vertebral fusion develop inevitably in the long term. According to these results, nontuberculous spondylodiscitis is truly osteomyelitis of the spine.


We used broad-range eubacterial PCR amplification followed by direct sequencing to identify microbial pathogens in heart valve material from 29 patients with histologically confirmed infective endocarditis and 23 patients free of infective endocarditis. Microorganisms cultured by conventional techniques matched those identified by PCR in 21 cases. PCR alone identified the causative agent in three cases (Streptococcus bovis, Staphylococcus cohnii, and Coxiella burnetii), allowing better patient management. PCR corrected the initial bacteriological diagnosis in three cases (Streptococcus bovis, Streptococcus mutans, and Bartonella henselae). Among the 29 cases of histologically confirmed infective endocarditis, PCR findings were positive in 27 cases and were consistent with the bacterial morphology seen at Gram staining (26 cases) or with the
results obtained by immunohistologic analysis with an anti-C. burnetii monoclonal antibody (one case). In two other cases of histologically confirmed infective endocarditis, PCR remained negative in a blood culture-negative case for which no bacteria were seen at histological analysis and in one case with visualization of cocci and blood cultures positive for Enterococcus faecalis. Ten clinical diagnoses of possible infective endocarditis were ruled out by histopathological analysis of the valves and subsequently by PCR. PCR was negative in 13 of the 14 patients in whom infective endocarditis was rejected on clinical grounds; the other patient was found to have Coxiella burnetii infective endocarditis on the basis of PCR and histopathological analysis and was subsequently included in the group of 29 definite cases. In total, PCR contributed to the diagnosis and management of infective endocarditis in 6 of 29 (20%) cases.

Gikas et al. 2001. Newer macrolides as empiric treatment for acute Q fever infection. Antimicrob.Agents Chemother. 45(12): 3644-3646. The effectiveness of newer macrolides in acute Q fever for 113 patients was recorded. The mean times to defervescence were 2.9 days for doxycycline and 3.3, 3.9, 3.9, and 6.4 days for clarithromycin, roxithromycin, erythromycin, and beta-lactams, respectively (P < 0.01 for macrolides versus beta-lactams). We conclude that macrolides may be an adequate empirical antibiotic therapy for acute Q fever.

Gilmore et al. 2003. Molecular characterization of the sucB gene encoding the immunogenic dihydrolipoamide succinyltransferase protein of Bartonella vinsonii subsp. berkhoffii and Bartonella quintana. Infect.Immun. 71(8): 4818-4822. Members of the genus Bartonella have historically been connected with human disease, such as cat scratch disease, trench fever, and Carrion's disease, and recently have been recognized as emerging pathogens causing other clinical manifestations in humans. However, because little is known about the antigens that elicit antibody production in response to Bartonella infections, this project was undertaken to identify and molecularly characterize these immunogens. Immunologic screening of a Bartonella vinsonii subsp. berkhoffii genomic expression library with anti-Bartonella antibodies led to the identification of the sucB gene, which encodes the enzyme dihydrolipoamide succinyltransferase. Antiserum from a mouse experimentally infected with live Bartonella was reactive against recombinant SucB, indicating the mounting of an anti-SucB response following infection. Antigenic cross-reactivity was observed with antiserum against other Bartonella spp. Antibodies against Coxiella burnetii, Francisella tularensis, and Rickettsia typhi also reacted with our recombinant Bartonella SucB. Potential SucB antigenic cross-reactivity presents a challenge to the development of serodiagnostic tests for other intracellular pathogens that cause diseases such as Q fever, rickettsioses, brucelloses, tularemia, and other bartonelloses.

A subhuman primate model was developed for study of the pathogenesis of infection with Coxiella burnetii. Cynomolgus monkeys (Macaca fascicularis) that were exposed to 10(5) mouse median infectious intraperitoneal doses of C. burnetii in a small-particle aerosol developed clinical signs of illness and pathologic changes characteristic of Q fever infection in humans. All monkeys had radiologic evidence of pneumonia by day 9. Antibodies to C. burnetii were detectable by the indirect fluorescent antibody test by day 7. These data indicate that the cynomolgus monkey is a suitable model for study of the pathogenesis of Q fever infection and may prove valuable in the evaluation of C. burnetii vaccines.


Q fever endocarditis is rarely reported in North America; only four cases have been documented since 1953. In 1981-1982, five cases were identified in the Victoria General Hospital, Halifax, Nova Scotia. Four patients were from widely separated areas of Nova Scotia and one was from Prince Edward Island. Four patients with long-standing valvular abnormalities, including two with prosthetic valves, presented with recurrent febrile episodes. The fifth patient, who was previously well, had recurrent septic embolic episodes. Clinical features and laboratory findings were variable. Diagnosis by serology was confirmed in four patients by culture of Coxiella burnetii from excised tissue. Histopathology varied from nonspecific inflammatory changes to two more distinctive patterns; electron microscopy showed C burnetii in two patients. Therapy with tetracycline and trimethoprim-sulfamethoxazole was beneficial, although three patients required valve replacement for hemodynamic deterioration. Q fever endocarditis may be more common than is recognized, and serological investigations should be performed in all cases of culture-negative endocarditis.


Q fever is caused by C. burnetii, an intracellular obligate bacterium. For clinical confirmation of Q fever, diagnosis of interstitial pneumonia is of significance. The acute disease varies in severity from minor to fatal, with the possibility of serious complications. Chronic endocarditis is a well-known outcome. Symptoms of Q fever can vary; fixing diagnosis is done by serology with the phase I and the phase II antibody. We tested 44 sera of 31 clinically suspect patients. From these, 22 patients were taken to the infection clinic, 8 to the pulmonary clinic, and one to the general hospital. From the 31 patients, 21 patients had one serum, 7 patients, 2 sera, and 3 patients, 3 sera. Blood samples were collected by vein puncture, and serum samples were kept at -20 degrees C until testing. All sera were processed by indirect immunofluorescent assay (IFA) Q fever IgM and IgG. Of 44 processed sera, 21 were seropositive. Specific IgM antibody was found in sera of 6 patients (19.4%), and specific IgG antibody in sera of 16 patients.
In sera of 15 clinically suspect patients (48.3%), no specific anticoxiella antibody was found. From these results we can confirm the importance of serology in laboratory diagnosis and clinical affirmation of suspect Q fever. Indirect immunofluorescent assay (IFA) is reliable and appropriate for daily, routine diagnosis of human Q fever.


After a primary infection Coxiella burnetii may persist covertly in animals and recrudesce at parturition to be shed in the products of conception and the milk. Similar latent persistence and recrudescence occurs in man: namely, infection of placenta, heart valve or mural endocardium, bone or liver. The numbers of organisms, their viability and cellular form, and the underlying organ sites of latent infection for the coxiella are obscure. During investigations of 29 patients with a chronic sequel to acute Q fever, the post-Q fever fatigue syndrome (QFS) [1-3], sensitive conventional and TaqMan-based PCR revealed low levels of C. burnetii DNA in blood mononuclear cells (5/29; 17%), thin needle liver biopsies (2/14; 14%) and, notably, in bone marrow aspirates (13/20; 65%). Irrespective of the ultimate significance of coxiella persistence for QFS, the detection of C. burnetii genomic DNA in bone marrow several years after a primary infection unveils a new pathological dimension for Q fever.


Rabbits were inoculated with purified antigen preparations of Coxiella burnetii and representative species of the spotted fever and typhus groups of rickettsiae. Their antibody responses were monitored by complement fixation tests; high-titered antisera were fractionated with ammonium sulfate and then labeled with fluorescein isothiocyanate by the dialysis method. The conjugates had homologous 3+ staining titers of 1:256 to 1:2,048 and did not exhibit nonspecific staining. The Rickettsia rickettsii, R. conorii, and R. akari conjugates reacted only with rickettsiae of the spotted fever group; the R. canadá, R. prowazekii, and R. typhi conjugates were specific for the typhus group rickettsiae; and the C. burnetii conjugate stained only homologous organisms. One of these conjugates (R. rickettsii) is currently being used to identify rickettsiae in clinical specimens and has already proven its value as a diagnostic tool.


Twenty-three patients with Q fever who were diagnosed over a 3 year period are described. The majority came from the Madrid urban area and less than half had epidemiological antecedents. Nine patients presented with pulmonary infiltrations, 12 with suppressed fever and in 2 criteria for fever of unknown origin were met. The majority had clinical or analytic data of hepatic disease and liver biopsy practiced in 4
patients showed granulomas. Diagnosis was established through the increment of seric antibodies against antigens of phase II C. burnetii, detected by complement fixation test. Acute Q fever is not a rare disease in our environment and must be taken into account when a differential diagnosis is looked for in processes such as fever of short evolution, fever of unknown origin, pneumonias and granulomatous hepatitis.


Q fever manifests as primary infection or acute Q fever and may become chronic in patients with underlying valvulopathy. Because Coxiella burnetii infection depends on host response, we measured tumor necrosis factor (TNF), interleukin (IL)-6, IL-12, and IL-10 in patients with different clinical presentations of acute Q fever. Compared with control subjects, patients with uncomplicated acute Q fever exhibited increased release of the 4 cytokines. Their amounts were higher in patients with hepatitis than in patients with fever or pneumonia. In patients with valvulopathy, who exhibited the highest risk of chronic evolution, the amounts of TNF and IL-10 were higher than in patients without valvulopathy. TNF production was specifically enhanced in patients who developed Q fever endocarditis. These results show that acute Q fever is associated with cytokine overproduction. Persistent TNF amounts were associated with the occurrence of endocarditis in patients with valvulopathy, and that may be a marker of chronic evolution of Q fever.


Fifteen cases of Q fever endocarditis that occurred in 1999-2000 in southern France are described and compared with 15 cases from the same area reported in 1987. Significant decreases were found in the prevalences of heart failure, hepatomegaly, inflammatory syndrome, anemia, leukopenia, and abnormal liver function test results in patients who had Q fever endocarditis after 1997. This was probably the result of a reduction in the delay before diagnosis of the disease and of the use of novel, effective antibiotic regimens.


A serological survey using an indirect micro-immunofluorescence test among people considered to be at risk of contracting an infection with C. burnetii yielded 75.9% seropositives, whereas controls from three geographical regions in the Netherlands.
showed a mean of 45.5% with considerable differences per region and sex. A comparable retrospective sample from 1968 showed 46% seropositives. Sera from people aged 0 to 19 years yielded 38.3% positives (8). The preliminary data of a survey among cattle using an indirect ELISA showed antibodies against C. burnetii in 21.4% of 1160 animals in 234 dairy herds and lower percentages in other types of herds. Among 3603 sheep from 191 flocks, 3.5% appeared to be seropositive and a limited survey among goats demonstrated specific antibodies in less than 1%. A total of 219 dogs and 26 cats was examined with negative results. The results of a clinical and epidemiological study of 51 cases of human Q fever are summarized. Of these patients, 13 were female and 18 were younger than 3 years of age. In 29 cases the infection could be associated with direct or indirect contact with animals or animal products of different species. Family and other contacts of 29 patients were serologically examined and 61% were positive for specific IgG and 10% also for IgM. In addition, 22 babies from seropositive mothers were serologically examined and none was found positive for specific IgM. The epidemiological implications of these observations are discussed.


Blood specimens were collected over various periods of time from 30 abattoir workers with a clinical diagnosis of Q fever. All specimens were tested for complement-fixing antibodies and for specific immunoglobulin M (IgM) globulins to phase 1 and 2 Coxiella burnetii organisms by an immunofluorescence technique. All 22 patients with increasing levels of complement-fixing antibodies were shown to have generated specific IgM globulins, as did 4 patients with high convalescent titers but from whom "acute" specimens were not collected. Four individuals who did not show increasing levels of complement-fixing antibodies did not produce measurable levels of specific IgM. All patients with Q fever gave positive specific IgM results by 2 weeks after the onset of symptoms. IgM to phase 1 antigen persisted for 27 weeks in one patient, but IgM to phase 2 antigen was not detectable beyond 17 weeks. The estimation of Q fever-specific IgM has proved useful in confirming infection when only a "convalescent" blood specimen is available.


The authors report a case of tricuspid endocarditis complicating a congenital coronary artery fistula to the right ventricle in an eight-year-old female. The patient underwent valve replacement using a cryopreserved mitral homograft. Six months later, clinical and echocardiographic status are excellent. Using a mitral homograft for tricuspid endocarditis is a recognized approach in adults, whereas in pediatric cases it is exceptional. Homografts could prove to be a valid procedure in children when repair is not feasible, although one could expect a more rapid deterioration.
Sera of Brill-Zinsser disease patients (70 samples) Q fever patients (12 samples) and healthy persons from Q fever enzootic areas (99 samples) were studied in indirect solid phase enzyme immunoassay (ELISA), indirect immunofluorescent antibody test (IFA) and indirect passive hemagglutination test. ELISA and IFA have been proved as most sensitive tests for detection of rickettsial antibodies in both clinical and retrospective diagnosis of Rickettsial diseases.

Isada et al. 2003. Infectious diseases handbook. Lexi-Comp. 5th Ed.

The clinical, serological and electron microscopic findings in a 47 year old woman with bioprosthetic valve coxiella endocarditis occurring 15 years after streptococcal endocarditis are described. The patient underwent valvular surgery a total of four times to control symptoms and remains well on medical therapy more than two years after her last operation.

BACKGROUND: All the community acquired pneumonia followed up in an outpatient clinic were prospectively studied in order to determine: etiology, clinical-radiological characteristics and its progression with diagnostic and therapeutic protocols. PATIENTS AND METHOD: We arranged clinical evaluation protocols, etiological diagnosis by means of serology (in the first visit and three weeks later); and when necessary, by means of fiberbronchoscopy (protected microbiological brush), as well as clinical and radiological progression (up to three visits) after empirical treatment. RESULTS: Initially, 240 patients were included, of which 221 were fully followed up. Etiological diagnosis was obtained in 86 patients (39%). The bacteria most frequently isolated was Coxiella burnetii (12.2%), followed up Mycoplasma pneumoniae and Legionella pneumophila. Two cases of Streptococcus pneumoniae were diagnosed. The most frequent radiological onset was alveolar infiltrate (86%). The initial empiric treatment were macrolids (71%) or second generation cephalosporines (22%). Most patients presented a favourable clinical and radiological progression. Only 2 patients needed admission to the hospital (< 1%). CONCLUSIONS: In community acquired pneumonias studied in our outpatient clinic we found a high number of "atypical" agents. Treatment with macrolids or second generation cephalosporines are appropriate for these patients.

Q fever is an important zoonosis that occurs throughout the world. In contrast to most other European countries, there has been no evidence of endemic Q fever in Norway up to now. The disease is caused by Coxiella burnetii, a rickettsia-like bacterium. Humans are infected mainly by inhalation of contaminated aerosols from cattle, sheep and goats. Clinical manifestations are protean, ranging from asymptomatic infection to life-threatening endocarditis. In this article we present the first four cases of serological proven acute Q fever imported into Norway. The patients were Norwegian tourists who had visited Bhutan, the Canary Islands, and Morocco. Two patients had fever with maculopapular exanthema, one had pneumonia, and one had biopsy-proven granulomatous hepatitis. Three were treated with tetracyclines. All four patients recovered well.


**BACKGROUND:** Although the pathogenic role of Coxiella burnetii infection during pregnancy is controversial, some cases of stillbirth and abortion occurring after an acute or chronic infection have been mentioned in the literature. Recently, Q fever has been advocated as a significant cause of morbidity and mortality in pregnancy

**CASE:** We describe an 18-year-old primipara woman admitted to our hospital for high fever and pancytopenia during an acute *C. burnetii* infection. She was successfully treated with clarithromycin, overcoming fever and pancytopenia. Finally, she gave birth to a healthy infant, and 1 year later both remained well. **CONCLUSION:** Q fever is a potentially serious disease in pregnancy owing to the possibility of placenta infection and fetal transmission affecting its outcome. Q fever infection should be suspected in unexplained febrile episodes or abortion during pregnancy, when epidemiologic and clinical data are present. We believe that *C. burnetii* serology should be tested in cases of fever of known origin or unexplained abortions, as the TORCH infections are.


Q fever is a bacterial zoonosis caused by *Coxiella burnetii*, a unique intracellular coccobacillus, adapted to live within the phagolysosomes of macrophages and monocytes. It is highly infectious, with as little as one organism needed to cause clinical infection, making it an attractive organism for use in biowarfare. Despite its high infectivity, it has low virulence, and most patients undergo only asymptomatic seroconversion. Acute clinical manifestations are a nonspecific febrile illness, pneumonia, hepatitis, and neurologic abnormalities ranging from headache to meningoencephalitis. Chronic Q fever can result in endocarditis, hepatitis, or a chronic fatigue syndrome. Diagnosis usually is made by serology because culture of the highly contagious organism is potentially hazardous. Tetracyclines are the antibiotics of choice. When individualized therapy is possible, a 14- to 21-day course of doxycycline usually is...
used. In a mass casualty situation, a 5- to 7-day course of doxycycline is recommended, both for therapy and prophylaxis. For chronic infections such as endocarditis, 18 months of doxycycline supplemented with hydroxychloroquine is currently the best therapy.


The cost and effectiveness of examinations (sputum staining and culturing, antitest determination for Influenza A and B, RSV, Adenovirus, Chlamydia psittaci and pneumoniae, Coxiella burnetii, Mycoplasma pneumoniae and Legionella pneumophila, and determination for Streptococcus pneumoniae antigen) performed to explore the aetiology of community-acquired pneumonia in the case of 258 hospitalised patients were analysed. The aetiology could be determined in 44.2% of the cases. On the basis of prevailing prices in 1986-88 one pneumonia case with determinable aetiology costs 8111 Forint. The authors have come to the conclusion that in the present epidemiological situation in this country it is not worthwhile to look for so-called non-bacterial microorganisms routinely, because of their rarely occurrence (16.7%) the cost per one positive finding is unrealistically high. Comparing the cost and the practical use the examinations applied the rational choice seems to be to culture the sputum with deep airway origin and to determine the Streptococcus pneumoniae antigen routinely. In the case of suspicion of non-bacterial origin to perform complement fixation test for Mycoplasma pneumoniae and in a severe clinical state to culture the blood is recommended.


Sera from 216 ostriches on nine farms around Zimbabwe were examined by indirect fluorescent antibody (IFA) testing for the presence of antibodies reactive with Cowdria ruminantium, Coxiella burnetii, and Rickettsia africae, a spotted fever group rickettsia. Although no reactive antibodies could be detected to C. ruminantium or C. burnetii, 51/216 (35%) sera reacted with R. africae. The seroprevalence in ostriches from the south of Zimbabwe was significantly higher than in birds from the north (P < 0.01).

Immunoblots of four sera positive by IFA (&gt; 1/160) showed antibodies reactive with antigens of R. africae that also were recognized by pooled sera from mice inoculated with the organism. No reactive antibodies could be detected in six sera negative by IFA.


An unusual case of Coxiella burnetii infection is described in which the patient presented with an "acute abdomen" and marked clinical icterus. This case emphasizes that Q-fever may appear as acute hepatitis and illustrates its "characteristic" histopathological lesions which have been recognized only recently.


The protective efficacy of a killed, purified, phase I Coxiella burnetii vaccine was tested in cynomolgus monkeys. Monkeys vaccinated once with 30 micrograms of the antigen were challenged 6 or 12 months later with virulent phase I rickettsiae administered in small-particle aerosols. The vaccine provided only partial protection, since some of the challenged monkeys developed clinical signs of illness. However, the vaccinated animals did not develop pneumonia as determined by radiographic evaluation nor any hematologic or chemical changes except for an increase in fibrinogen. Although rickettsiae were isolated from peripheral blood in vaccinated monkeys, the rickettsemia persisted for only 1-2 days; whereas, organisms were recovered from unvaccinated animals for 6-7 days. All vaccinated animals had circulating microagglutinating antibodies to phase I and phase II antigens 6 and 12 months after vaccination.


BACKGROUND AND PURPOSE: The emergence of infection with Coxiella burnetii, the causative organism of Q fever, has been only recently recognized in Taiwan. Several cases of acute Q fever infection have been described, but the prevalence of antibodies to C. burnetii in the general population in Taiwan has not been reported. Thus, we studied the seroprevalence of C. burnetii infection in southern Taiwan. METHODS: We conducted a retrospective serosurvey to examine the prevalence of C. burnetii infection among subjects admitted to a rural hospital in Taiwan for various reasons, and among presumably healthy attendees of a routine physical examination clinic of an urban public hospital. The diagnosis of C. burnetii infection required the presence of antibodies to both phase I and II antigens (titer ≥ 1:16) or only to phase II antigens (titer ≥ 1:256), as detected by indirect immunofluorescence assay. RESULTS: The prevalence of C. burnetii infection was 4.2% in both the in-patient (15/357) and physical examination participant (11/259) populations. None of these subjects had signs compatible with acute Q fever (febrile illness within the past 3 months). The antibody prevalence rate was higher in males than in females, and peaked in persons aged 61 to 70 years. CONCLUSIONS: These data suggest that C. burnetii infection is not rare in southern Taiwan and does not cause clinical symptoms in all infected patients.
Kovacova et al. 1998. Clinical and serological analysis of a Q fever outbreak in western Slovakia with four-year follow-up. *Eur.J.Clin.Microbiol.Infect.Dis.* 17(12): 867-869. In the spring of 1993, an outbreak of respiratory infection affected 113 persons (103 males) in Jedl'ove Kostol'any, a village located in a hilly area of western Slovakia. Q fever, manifested as a flu-like illness with atypical pneumonia and hepatic involvement, was diagnosed using four serological tests (microimmunofluorescence, microagglutination, complement fixation, and enzyme immunoassay). Aborting goats were proven as a source of infection. During a 4-year follow-up study, no chronic form of Q fever could be demonstrated, either clinically or by tests to detect phase I Coxiella burnetii antibodies.

La Scola et al. 1996. Serological cross-reactions between Bartonella quintana, Bartonella henselae, and Coxiella burnetii. *J.Clin.Microbiol.* 34(9): 2270-2274. The clinical manifestations of Q fever and bartonelloses can be confused, especially in cases of infectious endocarditis. Differential diagnosis of the diseases is important because the treatments required for Q fever and bartonelloses are different. Laboratory confirmation of a suspected case of either Q fever or bartonelloses is most commonly made by antibody estimation with an indirect immunofluorescence assay. With an indirect immunofluorescence assay, 258 serum samples from patients with Q fever were tested against Bartonella henselae and Bartonella quintana antigens, and 77 serum samples from patients with infection by Bartonella sp. were tested against Coxiella burnetii antigen. Cross-reactivity was observed: more than 50% of the chronic Q fever patients tested had antibodies which reacted against B. henselae antigen to a significant level. This cross-reaction was confirmed by a cross-adsorption study and protein immunoblotting. However, because the levels of specific antibody titers in cases of Bartonella endocarditis are typically extremely high, low-level cross-reaction between C. burnetii antibodies and B. henselae antigen in cases of Q fever endocarditis should not lead to misdiagnosis, provided serology testing for both agents is performed.

Laufer et al. 1986. Chronic Q fever endocarditis with massive splenomegaly in childhood. *J.Pediatr.* 108(4): 535-539. Two children with congenital heart disease developed persistent fever, anemia, and hepatosplenomegaly. Both were shown to have intracardiac vegetations and evidence of infection with Coxiella burnetii. Thus, the same clinical manifestations of Q fever may develop in both children and adults.

Lee et al. 2002. Atypical pathogens in adult patients admitted with community-acquired pneumonia in Korea. *Jpn.J.Infect.Dis.* 55(5): 157-159. This study examined the prevalence of atypical pathogens causing community-acquired pneumonia (CAP) in Korea. We collected sera and clinical data for a period of 1 year for the adult patients consecutively admitted to Chunchon Sacred Heart Hospital with CAP.
The diagnosis was made using serologic methods to detect antibodies for Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella spp., Chlamydia psittaci, and Coxiella burnetii. Among 81 recruited patients, C. pneumoniae (n = 10, 12.3%) was the leading cause of illness, followed by M. pneumoniae (n = 7, 8.6%). One case of C. burnetii pneumonia was detected, but there were no cases of Legionella spp. or C. psittaci. Three cases of C. pneumoniae pneumonia were co-infected with either M. pneumoniae or C. burnetii. There was no significant difference between atypical pneumonia and non-diagnosed pneumonia in terms of clinical manifestations. In conclusion, of the atypical pathogens causing CAP, C. pneumoniae and M. pneumoniae appear to be the important etiologic pathogens in Korea.


Q fever is characterized by its clinical polymorphism, and pericarditis associated with Q fever has occasionally been described. Herein we report 15 cases of Coxiella burnetii pericarditis, 9 from our data bank and 6 encountered within the past 12 months. Three patients presented with life-threatening tamponade. We compare our cases with the 18 previously reported and with 60 Q fever-matched controls at our center. This study showed that Q fever pericarditis can present as acute as well as chronic disease; we describe relapse after 6 months in association with a serological profile compatible with the chronic form of disease (phase I C. burnetii IgG titer of $\geq 800$). Discriminant factors among patients and controls are age of $\geq 52$ years (adjusted odds ratio [OR], 5.66), the occurrence of general symptoms such as arthralgias or myalgias (adjusted OR, 6.54), and a normal erythrocyte sedimentation rate (adjusted OR, 16.37). No specific symptoms or underlying cardiac predispositions are observed.


For PCR detection of Coxiella burnetii in various clinical specimens we developed a sample preparation method in which silica binding of DNA was used. This method was found to be fast, easily performed with large numbers of samples, and equally sensitive for all of the specimens tested (livers, spleens, placentas, heart valves, milk, blood). The DNA preparation method described here can also be used as an initial step in any PCR-based examination of specimens. The procedure was tested with more than 600 milk samples, which were taken from 21 cows that were seropositive for C. burnetii and reportedly had fertility problems (and therefore were suspected of shedding the agent through milk intermittently or continuously). Of the 21 cows tested, 6 were shedding C. burnetii through milk. Altogether, C. burnetii DNA was detected in 6% of the samples. There was no correlation between the shedding pattern and the serological results.

**OBJECTIVES:** To add to the limited information on infective endocarditis (IE) not related to intravenous drug abuse (IVDA) in HIV-1-infected patients. **METHODS:** We have reviewed the characteristics of eight cases of IE in non-IVDA HIV-1 infected patients diagnosed in our institution between 1979 and 1999 as well as cases in the literature. **RESULTS:** All our patients were male, and the mean age was 44 years (range 29-64). HIV-1 risk factors were: homosexuality in five, heterosexuality in two, and the use of blood products in one. HIV stage C was found in six cases, and the median (range) CD4 cell count was 22/μL (4-274 cells/μL). IE was caused by Enterococcus faecalis in three cases, staphylococci in two cases, and Salmonella enteritidis, viridans group streptococci and Coxiella burnetii in one case each. Three patients acquired IE while in the hospital. All IE cases involved a native valve, and underlying valve disease was found in three patients. The aortic valve was the most frequently affected (five cases). Two patients underwent surgery, with a good outcome, and one patient died. Fourteen cases of IE not related to IVDA in HIV-1-infected patients were found in the literature review. The most common causative agents were Salmonella spp. and fungi (four cases each). Two patients had prosthetic valve IE, and the mitral valve was the most frequently affected (10 cases). The remaining clinical characteristics and the outcome were similar to those in the present series. **CONCLUSIONS:** IE not related to IVDA is rare in HIV-1-infected patients. In more than half of the cases, IE develops in patients with advanced HIV-1 disease. A wide etiologic range is found, reflecting different clinical and environmental conditions. None of the patients who underwent surgery died, and the overall mortality rate was not higher than in non-HIV-1-infected patients with IE.


We describe a case of acute symptomatic infection with *Coxiella burnetii* acquired between the 16th and 28th week of pregnancy. Oral ciprofloxacin therapy was started on diagnosis, at the 28th week of pregnancy, but symptoms were unabated after 3 weeks treatment, suggesting persisting infection of the products of conception. Caesarean section was therefore performed at 32 weeks gestation when a healthy infant was delivered, and subsequent investigations showed no evidence of transplacental spread of infection. Infection control measures were applied at the time of delivery to minimize the risk of infection to obstetricians and midwives from potentially infectious products of conception.

**Lukacovicova et al. 1993.** [Clinical and serologic study of Czecho-Slovak citizens working in developing countries from the aspect of risk of infection with *Coxiella burnetii*]. *Bratisl.Lek.Listy.* 94(8): 415-418.

In the years 1984-1988 we observed, besides the routine examinations of history, clinical state, and laboratory tests, also the presence of antibodies to *Coxiella burnetii* antigens by means of microagglutination reaction (MAR). The examinations were performed in our
citizens returning to Czecho-Slovakia from a long termed business stay in the developing
countries. Antibodies to C. burnetii antigen 2 have been detected entirely in 91 serum
samples, out of which 48 cases following their stay in Libya, 42 cases following their
stay in Iraq, and 1 in Syria. Diagnostically significant antibody titres (64) were detected
in 44 serum samples, in which the serological positivity was proved by complement
fixation test (CFT) examination. Clinical symptoms in the history, responding to the
acute form of "Q" fever; fever, occurred in 44 serologically positive cases, 37 of
which developed high antibody titres, which is considered to be a significantly high
incidence. The results imply the necessity to become more concerned by the incidence of
"Q" fever, its diagnostics and therapy, eventually prevention in our citizens
working in a more exacting climate of some developing countries. (Tab. 1, Ref. 15.).

Lumio et al. 1981. Q fever in Finland: clinical, immunological and epidemiological
Clinical, immunological and epidemiological features of 14 human cases of Q fever
diagnosed at Aurora Hospital are presented. All patients had an acute febrile disease and
9 (64%) had respiratory symptoms, 4 (29%) verified pneumonia, and 9 (64%) hepatitis,
which in 4 biopsied cases proved to be granulomatous. Presence of circulating immune
complexes was shown in 10/11 patients investigated by the platelet aggregation test
(PAT) and the platelet iodinated protein A (PIPA) test. Q fever is not known to be
endemic in the Nordic Countries. However, the causative agent, Coxiella burnetii, should
tolerate our climate and there is a rich potential animal reservoir. All patients had visited
some endemic area shortly before they were taken ill. In 3 cases the interval between
arrival in Finland and the onset of symptoms was more than double the reported maximal
incubation period, namely 69, 75 and 88 days. We suggest that these patients acquired the
infection after their return to Finland from their clothing or from souvenirs. If so, Q fever
could be acquired by this mechanism by persons who have never visited an area where
the disease is endemic.

Maartens et al. 1994. 'Atypical' bacteria are a common cause of community-acquired
OBJECTIVES: To assess the proportion of cases of community-acquired pneumonia
causd by 'atypical' bacteria, including the recently discovered Chlamydia pneumoniae,
and to compare the clinical, radiographic and laboratory features of patients with and
without 'atypical' bacteria. METHODS: A prospective serological study was carried out
on consecutive adult pneumonia patients from July 1987 to July 1988. Acute and
convalescent sera were tested in batches for antibodies against Legionella pneumophila
serogroup 1, C. pneumoniae, Chlamydia psittaci, Coxiella burnetii (phase-2 antigen) and
Mycoplasma pneumoniae (IgG and IgM). Records and chest radiographs were examined
retrospectively. RESULTS. Acute and convalescent sera were available from 113
patients. The records of 4 patients could not be traced and 17 patients did not fulfil the
inclusion criteria. Thirty-two of these 92 patients (35.9%) were found to be infected with
'atypical' bacteria. The two most common organisms were C. pneumoniae (20.7%) and L.

Coxiella Burnetii Health Effects
pneumophila (8.7%). There were no differences in the clinical and radiographic features of patients with and without 'atypical' bacteria. Clinicians prescribed erythromycin or tetracyclines with equal frequency in the two groups. CONCLUSIONS. 'Atypical' bacteria, especially C. pneumoniae, are a common cause of community-acquired pneumonia in adults in South Africa. This is the first demonstration of an aetiological role of C. pneumoniae in this country. We confirmed the finding of other studies that there are no clinical, radiographic or laboratory features characteristic of 'atypical' bacterial infection in hospitalised patients. This has major implications for therapy, as these organisms respond to erythromycin and tetracyclines, but not to beta-lactam antibiotics.

Q fever is a zoonosis caused by Coxiella burnetii. Farm animals and pets are the main reservoirs of infection, and transmission to human beings is mainly accomplished through inhalation of contaminated aerosols. This illness is associated with a wide clinical spectrum, from asymptomatic or mildly symptomatic seroconversion to fatal disease. Q fever in children has been rarely reported. We reviewed published work on this topic. Seroepidemiological studies show that children are frequently exposed to C burnetii. However, children are less frequently symptomatic than adults following infection, and may have milder diseases. Using the standard diagnostic criteria, we identified 46 published paediatric cases only. Self-limited febrile illness and pneumonia were the most common manifestations of acute Q fever. Chronic disease manifested as endocarditis and osteomyelitis. A history of exposure to possible sources of infection with C burnetii in a child with a compatible infectious syndrome should prompt testing for Q fever. Studies are required to determine the spectrum of morbidity associated with Q fever during childhood.


The first case of Q fever in Poland in a 5-year girl is presented. A girl is inhabitant of the Lublin region where this disease is of endemic character. Q fever was diagnosed on the base of the clinical examinations and serological tests. The course of the disease was acute. Doxycycline and lincomycin were given. A short time lapse between the treatment and eradication of Coxiella burnetii antigen indicates rather spontaneous recovery.

During the period 1981-8 a clinical trial of a Q fever vaccine (Q-vax; Commonwealth Serum Laboratories, Melbourne) has been conducted in abattoir workers and other at-risk groups in South Australia. Volunteers in four abattoirs and visitors to the abattoirs were given one subcutaneous dose of 30 micrograms of a formalin-inactivated, highly-purified
Coxiella burnetii cells, Henzerling strain, Phase 1 antigenic state, in a volume of 0.5 ml. During the period, over 4000 subjects have been vaccinated and the programme continues in the abattoirs and related groups. 'Common' reactions to the vaccine comprised tenderness and erythema, rarely oedema at the inoculation site and sometimes transient headache. Two more serious 'uncommon' reactions, immune abscess at the inoculation site, were observed in two subjects, and two others developed small subcutaneous lumps which gradually dispersed without intervention. Protective efficacy of the vaccine appeared to be absolute and to last for 5 years at least. Eight Q fever cases were observed in vaccinees, but all were in persons vaccinated during the incubation period of a natural attack of Q fever before vaccine-induced immunity had had time (greater than or equal to 13 days after vaccination) to develop. On the other hand, 97 Q fever cases were detected in persons working in, or visiting the same abattoir environments. Assays for antibody and cellular immunity showed an 80-82% seroconversion after vaccination, mostly IgM antibody to Phase 2 antigen, in the 3 months after vaccination. This fell to about 60%, mostly IgG antibody to Phase 1 antigen, after 20 months. On the other hand, 85-95% of vaccinees developed markers of cell mediated immunity as judged by lymphoproliferative responses with C. burnetii antigens; these rates remained elevated for at least 5 years. The Q fever vaccine, unlike other killed rickettsial vaccines, has the property of stimulating long-lasting T lymphocyte memory and this may account for its unusual protective efficacy as a killed vaccine.

PURPOSE OF REVIEW: In this era of emerging infectious diseases and bioterrorism it is important to be up to date with the diagnosis and management of Q fever pneumonia.
RECENT FINDINGS: A considerable amount of new information has emerged regarding the pathogenesis of Coxiella burnetii infection. The complete genome of this microorganism has now been sequenced and there are several unique features. The spectrum of manifestations of infection due to C. burnetii continues to expand. Some of the more recently described findings are acalculous cholecystitis, rhabdomyolysis, long-term persistence of Coxiella, post Q fever fatigue syndrome, and hemolytic uremic syndrome. Pneumonia as a manifestation of acute Q fever shows tremendous geographic variation, being common in one area of a country such as Spain but not in another area.
SUMMARY: Pneumonia continues to be an important manifestation of infection with C. burnetii. It responds to treatment with doxycycline, quinolones or macrolides.

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.


**Marrie et al. 1996.** Ambulatory patients with community-acquired pneumonia: the frequency of atypical agents and clinical course. *Am. J. Med.* 101(5): 508-515. OBJECTIVES: To determine the etiology of community-acquired pneumonia in patients treated in an ambulatory setting, using serological methods, and to compare presenting symptoms, radiographic manifestations, and clinical outcomes of patients with pneumonia of "atypical" and undetermined etiology. PATIENTS AND METHODS: This prospective cohort study was conducted in emergency room and outpatient facilities of Victoria General Hospital, Halifax, Nova Scotia, and in offices of participating family doctors based in Halifax. One hundred forty-nine adults with acute onset of one or more symptoms or signs suggestive of pneumonia and radiographic evidence of pneumonia who provided informed consent were enrolled. Patients known to be HIV positive or who had been discharged from a hospital within the previous 10 days were ineligible for enrollment. Demographic features and clinical data were collected by direct patient interview and chart review by trained research nurses. Outcome measures included quantitative evaluation of pneumonia-specific symptoms, and responses to the Short Form 36 Health Survey at presentation and at 30 days after presentation. Information was also collected on each patient's health prior to pneumonia, as well as the time until each patient's self-reported return to work and to usual activities. The etiology of pneumonia was determined by testing acute and convalescent serum samples for antibodies to Legionella pneumophila serogroup 1, Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia psittaci, Coxiella burnetii, adenovirus, respiratory syncytia virus, influenza viruses A and B, and parainfluenza viruses 1, 2, 3. RESULTS: The study population consisted of 149 patients, 54 (36%) of whom were men, with a mean age (+/- SD) of 41 +/- 15 years. An etiological diagnosis was made in 74 (49.7%) patients using serological methods. Etiological agents included M pneumoniae 34 (22.8%); C pneumoniae 16 (10.7%); M pneumoniae and C pneumoniae 5 (3.4%); C burnetii 4 (2.7%); influenza A virus 4 (2.7%); and other agents 6% (7.4%). Three patients (2%) had a conventional bacterial etiology, and 72 patients (48.3%) had pneumonia of undetermined etiology. Patients with pneumonia of known (atypical) and undetermined etiology were similar in terms of age, gender, race, education, employment, and comorbidity. Despite a higher proportion of patients with pneumonia of known etiology reporting sweats, chills, and headache at presentation, the two groups were similar for symptom severity and bother. The patients with pneumonia of undetermined etiology were more likely to have multilobar pneumonia (P < 0.02). Both patients with atypical pneumonia and those with pneumonia of undetermined etiology suffered severe deterioration of physical functioning with a marked but incomplete recovery at 30 days. Those with atypical pneumonia had higher physical functioning and general mental health scores at 30 days. CONCLUSIONS: Nearly half the cases of ambulatory
community-acquired pneumonia are due to "atypical" agents. It is not possible to reliably distinguish patients with atypical pneumonia from those with pneumonia of undetermined etiology by clinical features at baseline. The outcomes in terms of resolution of symptoms, functional status, return to work, and return to usual activities are essentially similar in the two groups.

In Nova Scotia the main manifestation of acute Q fever is pneumonia, while in France it is granulomatous hepatitis. To test the hypothesis that the route of infection is the major determinant of the manifestations of acute Q fever, 10 groups of 10- to 12-g female BALB/c mice (4 animals/group) were used. Five groups were inoculated intraperitoneally (ip) and 5 intranasally (inl) with *Coxiella burnetii*. Both routes of infection resulted in pneumonia. However, the inl route resulted in greater airway changes (on a numeric scale with 0 being no changes): 2.05 +/- 2.20 versus 0.60 +/- 0.83 (P < .002). The ip route resulted only in hepatosplenomegaly. It was concluded that the route of infection is one determinant of the manifestations of acute Q fever.

Pneumonia is one manifestation of acute Q fever following infection with *Coxiella burnetii*. Fever, headache, and myalgia dominate the clinical picture of Q fever pneumonia. Cough is nonproductive and may be absent despite the presence of pneumonia. While in most instances pneumonia results in an illness of mild-to-moderate severity, on occasion it is rapidly progressive and results in respiratory failure. Infection occurs as a result of inhalation of contaminated aerosols. Infected cattle, sheep, and goats are the usual reservoirs for this zoonosis. In some areas, infected parturient cats serve as the reservoir, and in such instances, rounded opacities are seen on the chest radiograph. The diagnosis of *C. burnetii* pneumonia is usually confirmed by demonstration of a fourfold or greater rise in antibody titer. Treatment is usually with a tetracycline or rifampin for 7 to 10 days.

Pneumonia is one of several clinical syndromes that results from inhalation of *Coxiella burnetii*. This microorganism, the etiologic agent of "query" fever, infects a wide range of animals and insects. Cattle, sheep, goats, and cats are the reservoirs whereby this agent is spread to humans. High concentrations of *C. burnetii* are present in the placenta and at parturition, the organism is shed into the environment to be inhaled by humans. Following an incubation period that ranges from four to 30 days (mean 14 days),
fever, headache, malaise, and cough ensue. The clinical presentation of pneumonia may range from a mild to a severe illness—the latter with the clinical picture of rapidly progressive pneumonia. There are no characteristic features of Q fever pneumonia but the severe headache and the epidemiological history should serve as clues. Treatment with tetracycline or rifampin for two weeks usually results in cure. Many cases of Q fever pneumonia remit without antibiotic therapy. The diagnosis is usually confirmed serologically using a complement fixation or microimmunofluorescence test.


There were 858 (37.7 percent) Q fever-infected dairy herds among the 2,277 tested in Illinois in 1963. The percentage decreased to 19.2 percent (380 of 1,975) in 1967. Reaction rates (complement-fixation test titer of 1:8 or greater) in serum samples from veterinarians decreased from 13.3 percent in 1956 to 3.9 percent in 1964 and from 3.6 percent in 1966 to 0 percent in 1968, 1970, 1972. There were 14 (2.7 percent) reactive serum samples among 526 abattoir workers tested in 1966; reaction rates were higher among workers having contact with swine (8.2 percent) than among workers having contact with cattle (1.8 percent). Two (0.1 percent) of 1,432 serum samples collected from 1967 to 1971 during preemployment examinations at another abattoir were reactive. Only two clinical cases of Q fever were reported to the Illinois Department of Public Health in the period 1963-80. All evidence evidence points to a decreasing prevalence of Q fever in Illinois.


The aim of the present investigation is the complex study of experimental infection in pregnant ewes by means of clinical, serological, biological, histological and Electron microscopy methods. Four ewes, pregnant from the 2nd to 5th month, were infected by intravenous (in one case by intraperitoneal) routes with a C. burnetii strain at 10^6 ID 50/ml. The clinical illness in all of the animals was characterized by fever and two-phase temperature reaction on the 5th and 12th days. The clinical symptoms were as follows: torpidity, reduced appetite, thirst, conjunctivitis, rhinitis, rapid breathing. As a result of the developed latent infection, after the acute stage, the animals gave birth to three unviable lambs who died within 24 h. Another lamb was still-born. The lambs showed cachexia, arthritis, ataxia, wrinkled skin. The highest CF-titers (1:256-1:512) were reached on the 40th day, but serum antibodies (1:8-1:32) first appeared on the 8th day. The titers began to decrease on the 60th day. The pathomorphological changes testify to a latent infection characterized by placentitis, lymphocellular proliferation of the lamb's parenchymal organs and lymph nodes, multiple thromboses, interstitial pneumonia and plural proliferative changes. The EM exam showed rickettsiae in placentas mainly in the form of inclusions in cytoplasm of leukocytes and epithelial cells.

Q fever is a zoonosis found worldwide and is produced by Coxiella burnetii. It may be acute or chronic with neurological manifestations being infrequent. Several cases of acute encephalitis or meningoencephalitis have been described, generally with an evolution towards cure regardless of the use of selective antibiotic treatment. Recently the authors had the opportunity to study a 33 year old male presenting acute meningoencephalitis in which the clinical manifestations, CSF findings (increase in cellularity with lymphocytic predominance and excess proteins) and neurophysiological findings (appearance of periodic bilateral complexes in the EEG) suggested the diagnosis of herpetic meningoencephalitis. Treatment with acyclovir was initiated. However, serologic studies demonstrated, a posteriori, that the germ responsible had been Coxiella burnetii. The patient evolved satisfactorily with no specific treatment and the EEG anomalies disappeared within a few days. The authors insist on the need to include Q Fever in the diagnostic differential of acute meningoencephalitis and emphasize the possibility that germs of a non viral nature may produce periodic EEG complexes in all that similar to those found in herpetic encephalitis.

Q fever is a zoonosis with a worldwide distribution with the exception of New Zealand. The disease is caused by Coxiella burnetii, a strictly intracellular, gram-negative bacterium. Many species of mammals, birds, and ticks are reservoirs of C. burnetii in nature. C. burnetii infection is most often latent in animals, with persistent shedding of bacteria into the environment. However, in females intermittent high-level shedding occurs at the time of parturition, with millions of bacteria being released per gram of placenta. Humans are usually infected by contaminated aerosols from domestic animals, particularly after contact with parturient females and their birth products. Although often asymptomatic, Q fever may manifest in humans as an acute disease (mainly as a self-limited febrile illness, pneumonia, or hepatitis) or as a chronic disease (mainly endocarditis), especially in patients with previous valvulopathy and to a lesser extent in immunocompromised hosts and in pregnant women. Specific diagnosis of Q fever remains based upon serology. Immunoglobulin M (IgM) and IgG antiphase II antibodies are detected 2 to 3 weeks after infection with C. burnetii, whereas the presence of IgG antiphase I C. burnetii antibodies at titers of $\geq 1:800$ by microimmunofluorescence is indicative of chronic Q fever. The tetracyclines are still considered the mainstay of antibiotic therapy of acute Q fever, whereas antibiotic combinations administered over prolonged periods are necessary to prevent relapses in Q fever endocarditis patients. Although the protective role of Q fever vaccination with whole-cell extracts has been established, the population which should be primarily vaccinated remains to be clearly identified. Vaccination should probably be considered in the population at high risk for Q fever endocarditis.


We studied the causes of community-acquired pneumonia (CAP) in 184 patients. Microbiologic evaluation included sputum examination, blood culture, assessment of acute and convalescent antibody titers for *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Coxiella psitacci*, *Coxiella burnetii* and respiratory viruses, polymerase chain reaction (PCR) assays for *M. pneumoniae* and *C. pneumoniae* in throat swab, and PCR assay based on the amplification of pneumolysin gene fragment in sera. The causative pathogen was identified in 78 patients (*Streptococcus pneumoniae*, 44; *M. pneumoniae*, 26; *C. pneumoniae*, 1; others, 7). *S. pneumoniae* was detected in serum by the PCR assay in 41 patients, five of whom also had a positive blood culture. PCR assay was negative in two patients with positive blood culture for *S. pneumoniae*. *C. pneumoniae* was detected by PCR in nine patients, but only one showed seroconversion. *M. pneumoniae* was detected by PCR in only three patients (two without seroconversion). The diagnosis of pneumonia caused by *S. pneumoniae* was five times greater using PCR in serum than with blood culture. Detection of *C. pneumoniae* by PCR without fulfilling criteria for acute infection may be considered a prior infection. The PCR assay for the diagnosis of *M. pneumoniae* has a lower sensitivity than serologic methods.

Miljak et al. 1998. [Fever, negative blood culture findings and absence of response to antibiotic therapy in a patient after a second aortic valve prosthesis].

HISTORY AND CLINICAL FINDINGS: A 53-year-old patient had a prosthetic valve (St. Jude Medical 25) 9 years ago because of a *Staphylococcus aureus* endocarditis with severe aortic regurgitation. An initially mild, progressively more severe, aortic regurgitation then developed as a result of an empty paravalvular abscess cavity, requiring another valve replacement. Fever started on the 3rd postoperative day and persisted despite combined treatment with beta-lactam antibiotics and aminoglycoside. INVESTIGATIONS: At first no infectious focus could be identified radiologically or by echocardiography. But transeosophageal echocardiography revealed vegetations in the old abscess cavity. Several blood cultures were negative, while serological tests gave markedly raised antibody titers against *Coxiella burnetii*. DIAGNOSIS, TREATMENT AND COURSE: Assuming *Coxiella burnetii* endocarditis the patient was given doxycycline, 2 x 100 mg daily and cotrimoxazole, 1 x 960 mg daily. The fever subsided and the vegetations had disappeared after four weeks. Because of the high risk of recurrence the antibiotic treatment was to be continued for two years. CONCLUSION: *Coxiella burnetii* should be considered as a possible cause of fever of unknown origin, especially in patients with existing or operated cardiac valvar defects, when endocarditic vegetations have been demonstrated and several blood cultures have been negative.


We present 35 patients diagnosed as suffering from Q fever during 1986, 1987, 1988. We establish a diagnosis criteria of complement titres greater than or equal to 1/64 or indirect immunofluorescent titres (IIT) 4 or more times higher than the initial, or a maintained title greater than or equal to 1/640 with specific IgM detected by positive IIT. 80% were male with a median age of 40.3 years. 85% had had contact with goats. 77% lived on the west side of the island 88.5% had increased GOT and GPT and only 5.7% had pneumonia. One patient previously healthy had ARDS, needing prolonged mechanical ventilation, and one patient had A-V blockade grade III which was treated successfully. We comment on the high incidence observed, which showed and endemic situation, and the epidemiological and clinical features of the disease.

Despite various pointers to an infectious aetiology, the cause of Bell's palsy remains obscure. We examined paired sera from 62 patients with facial palsy and 50 age and sex matched contemporaneus controls. Significantly more patients than controls had IgM antibodies by ELISA to varicella zoster virus (56.5% vs. 20%, P = 0.0001) and herpes simplex virus (41.9% vs. 18%, P = 0.006). Additionally, significantly more patients than controls were positive for CF antibody to varicella zoster virus (14.5% vs. 0%, P = 0.004) but not to herpes simplex or cytomegalovirus. Significantly more controls than patients (54% vs. 25.8%, P = 0.002) had no evidence of antigenic stimulation by any of the herpesvirus group. No significant difference between patients and controls in seropositivity by IgM ELISA to cytomegalovirus. Epstein-Barr virus and IFA for human herpes virus 6 was found. Furthermore, there was no significant difference between the two groups as to evidence of recent infection by the following agents: rubella virus and Borrelia burgdorferi by IgM ELISA, influenza A, influenza B, adenovirus, respiratory syncytial virus, mumps and measles. Mycoplasma pneumoniae, Coxiella burnetii and chlamydia spp. by complement fixation test. The first reported case of clinically and serologically proven Mycoplasma pneumoniae pneumonia associated with Bell's palsy is described. The rate of complete recovery at 6-8 weeks after onset was not significantly different in patients who were given steroids compared to those who were not. Ear related symptoms were the most common, occurring in 12 of 65 cases, but only three (4.6%) had clinical shingles (vesicles in ear).(ABSTRACT TRUNCATED AT 250 WORDS)

Coxiella burnetii myocarditis is a rare but severe clinical form of acute Q fever. We report the case of a 40-year-old man hospitalized for acute febrile syndrome. Forty-eight hours later, he presented dyspnea, orthopnea, and paroxysmal nocturnal dyspnea; cardiac auscultation revealed a third sound and echocardiography showed a diffusely hypokinetic and dilated left ventricle (30% ejection fraction). Serological studies showed antibodies against phase-II C. burnetii antigens (IgG titer 1:320 and IgM 1:50). The patient was treated with losartan, furosemide, and clarithromycin, resulting in rapid improvement. Six months after admission, the echocardiographic changes had completely disappeared.

Q fever, a worldwide zoonosis caused by Coxiella burnetii, may present as either an acute or a chronic disease. We correlated the results of 844 C. burnetii blood cultures with serological, clinical, and therapeutic data. C. burnetii was isolated from 17% of untreated patients with acute Q fever and from 53% of untreated patients with chronic Q fever. C. burnetii was not isolated from patients who were receiving antibiotics active against C. burnetii. For seven culture-positive patients with acute Q fever, serology was negative when C. burnetii was isolated. One patient with acute Q fever had a positive blood culture 25 days after the discontinuation of specific antibiotic therapy, and another had a positive blood culture after the resolution of symptoms. In one case of chronic Q fever, a positive blood culture resulted from noncompliance with treatment. The culture method described in this report is suitable for all laboratories with cell culture facilities. Our findings suggest that blood samples must be collected prior to the initiation of an antibiotic regimen if C. burnetii is to be successfully isolated.


**BACKGROUND:** The aim of this study was to describe an outbreak of acute fever in a rural town from Soria (Spain) in the spring of 1998 and to know the prevalence of IgG antibodies to Coxiella burnetii in this population. **METHODS:** 1. Outbreak of Q fever: epidemiological, clinical and analytical data were obtained by standardised questionnaire and the clinical records from all clinical cases. These cases were confirmed by complement fixation test. 2. Seroprevalence: 253 sera were chosen by not probabilistic sampling of convenience of sera samples collected between 1 September 1996 and 28 February 1999. Were regarded as positive anti-phase II C. burnetii IgG titles by indirect immunofluorescence assay equal or higher to 1/80. **RESULTS:** 1. A total of 14 cases of Q fever with a mean age of 21.5 +/-3.1 years were confirmed. 64% presented pneumonia and in 36% the symptoms were nonspecific. No patient had direct contact with animals but near to the town there were 4 flocks with 2,614 sheeps overall. 2. The seroprevalence was 60% (95% confidence interval: 54-66). The seroprevalence was not increased with the outbreak (p &gt; 0.05). **CONCLUSION:** The high prevalence of antibodies to C. burnetii in this population shows that this area is hyperendemic for such infection, but generally is asymptomatic or clinical signs are extremely mild because no cases of Q fever had been reported in the years before. Probably indirect exposure to flocks of sheep was the source of infection and transmission mechanism airborne.


The clinical difference between a lobar pneumonia caused by pneumococci or other...
bacterial agents and lower respiratory tract infections presenting with atypical symptoms is important. Mycoplasma pneumonieae, chlamydia species, Coxiella burnetii and several viruses amongst others are micro-organisms which cause atypical symptoms. All the time new types of micro-organisms like Ureaplasma urealyticum are found as a cause of pneumonia with atypical symptoms. Special diagnostic tools like cultures, serological or antigen detection are often needed to determine the exact causative agent. Clinical data are important to suspect a specific micro-organism.


The citrate synthase gene (gltA) of Bartonella henselae was cloned and sequenced to compare genetic divergence among alpha and gamma branches of the class Proteobacteria and to develop enhanced genotypic reagents for B. henselae identification. B. henselae gltA is 1,293 nucleotides in length and 63 to 66% homologous with corresponding gene sequences of Rickettsia prowazekii, Escherichia coli, and Coxiella burnetii. The observed genetic variability suggests that gltA sequences can provide a useful means for studying moderate divergence among related bacteria. Oligonucleotides specific for B. henselae gltA were evaluated for the ability to prime PCR amplification within the alpha and gamma branches of the proteobacteria. Under the conditions used, only B. henselae, Bartonella quintana, and R. prowazekii template DNAs yielded amplification products (approximately 380 bp). DNAs from 28 Bartonella-like isolates of feline origin were amplified by B. henselae primers and analyzed for restriction fragment length polymorphism. The resulting patterns for all 28 isolates were similar or identical to that of the recognized B. henselae strain. Current studies are aimed at optimization of PCR conditions for specificity and sensitivity of amplification of Bartonella sequences from clinical isolates.


The most common cause for persistently negative blood cultures is the previous administration of antibiotics, but other causes include fastidious organisms (such as Brucella and Legionella), cell-dependent organisms (such as Chlamydia and Coxiella), fungi and a major immune reaction. Fastidious organisms may take up to 3 weeks to grow in optimal media. Abscess formation may take the organisms inaccessible. If the diagnosis is in doubt, echocardiography, and more specifically transoesophageal echocardiography, is invaluable. If the clinical diagnosis is made but cultures are unavailable or negative, treatment should be started without delay. The choice of antibiotic depends on the clinical setting. In general, penicillin and gentamicin are indicated for a subacute onset: flucloxacillin and gentamicin if the onset is acute. Intravenous drug abusers should receive vancomycin; those who have recently had a prosthetic valve inserted should receive vancomycin, together with rifampicin and gentamicin.
We report four cases of Q fever pneumonia diagnosed using PanBio Coxilla burnetii ELISA. The patients, a 21-year-old woman, a 53-year-old man, a 74-year-old man and a 87-year-old man, were among 284 with community-acquired pneumonia who were treated as inpatients from March 2001 till March 2003. The frequency of Q fever pneumonia in community-acquired pneumonia was 1.4%. The 21-year-old woman was a typical case of Q fever pneumonia, since her clinical features showed 1. the breeding of cats, 2. development from a fever and non-productive caught in March, 3. multiple soft consolidations in the chest radiograph, 4. normal WBC count, 5. cure by administration of clarithromycin. The pneumonias of the other 3 cases were considered to be mixed infections, with bacteria such as Streptococcus pneumoniae and Haemophilus influenzae. Their clinical features were 1. elderly male patients with underlying diseases, 2. development from fever and cough with purulent sputum in winter, 3. coarse crackle on auscultation, 4. consolidation with pleural effusion in chest radiograph, 5. leukocytosis, elevation of BUN, hyponatremia, 6. a few cases with unfavorable prognoses despite medication with carbapenem and minocycline. These findings suggested that two types of pneumonia exist; one with the usual features of atypical pneumonia, and the other presenting the clinical features of bacterial pneumonia of the elderly due to a mixed infection including C. burnetti.

A cross-sectional study of the prevalence, significance, and specificity of antibodies to phospholipids (aPL) in patients with Q fever was undertaken in a university-based tertiary care medical center. The results of the lupus anticoagulant (LA) test, VDRL test, fluorescent treponemal antibody absorption test, and ELISA with different phospholipid antigens were determined for 26 patients with Q fever diagnosed by clinical and serological criteria. Plasma from four patients with Q fever and antibodies to cardiolipin (aCL) was purified by affinity chromatography in a cardiolipin column and tested against all phospholipids. For 17 patients with high levels of aCL, a modified ELISA without fetal calf serum was performed to determine if the serum cofactor was needed for a CL activity. Fisher's exact test was used for the statistical analysis. From the results of our study we conclude the following: patients with Q fever have a high incidence of aPL, with techniques with aCL or LA being the most sensitive to determine aPL (these antibodies can help diagnose Q fever presenting only as a fever); antibodies (phase II) to Coxiella burnetii and aCL are different antibodies; and the aCL activity in patients with Q fever is cofactor-independent.
During the period June 1967 to May 1972, viral tests were performed upon 1195 inpatients aged 12 and over in the Brompton Hospital. The overall diagnostic rate was 21.5%, comparing 9.3% by isolation and 14.9% by complement fixation (6.5% by fourfold rises in titre in paired sera, 8.4% by titres larger than or equal to 160 in single sera). Only 42% of all patients had an acute respiratory illness within one week prior to admission, which seriously curtailed the chances of isolating viruses and of obtaining early serological specimens. The value of complement fixation tests on single specimens in the clinical management of patients is discussed. The profound effect of infections by influenza A on respiratory morbidity and hospital admission is stressed.

In the United Kingdom, the infection of people with *Coxiella burnetii*, the causative agent of Q fever, is of significant public health importance and is associated with contact with dairy cattle. An ELISA was developed for the detection of IgG antibodies against *C. burnetii* in bulk tank milk, and in a survey of randomly selected samples from dairy herds in England and Wales, 21 per cent showed serological evidence of *C. burnetii* infection.

Endocarditis was recorded in 92 (11%) of 839 confirmed Q-fever infections reported for the Communicable Disease Report by laboratories between 1975 and 1981; Q-fever endocarditis accounted for approximately 3% of all cases of endocarditis reported. Two-thirds of the 92 reports were of men, and in both men and women endocarditis affected mainly young and middle-aged adults. Only one-third of Q-fever endocarditis patients were noted to have an underlying heart-valve lesion. There were also 30 reports of chronic Q-fever infection, and in 10 the primary clinical feature was liver disease. The laboratory data do not support the view that Q-fever endocarditis is a rare compilation of *Coxiella burnetii* infection, and the condition may be considerably underdiagnosed. Joint veterinary and medical investigations should be undertaken to establish the natural history of *Coxiella burnetii* infection in the U.K. in order to formulate policies for prevention of acute and chronic infection.

Serological parameters were compared in 15 cases of *Coxiella burnetii* infection comprising 5 cases each of primary Q fever, chronic granulomatous hepatitis, and endocarditis. The diagnosis was made on the basis of clinical history and serology and on
the isolation of C. burnetii phase I from biopsy specimens of liver and bone marrow from two patients with granulomatous hepatitis and from the aortic valve vegetations of five patients with endocarditis. The temporal sequences of immunoglobulin levels, rheumatoid factor, and specific antibody responses to phase II and phase I antigens of C. burnetii were evaluated as predictive correlates of the three Q fever entities. Serum levels of immunoglobulin classes G, M, and A were variable in all the entities of Q fever. Increased mean levels (in milligrams per deciliter) of immunoglobulin G (IgG) and IgA were noted with chronic disease in the sera of some patients, whereas IgM levels were not significantly different from normal values. Rheumatoid factor was significantly elevated in chronic disease but not in primary Q fever. The temporal sequence of C. burnetii phase II and phase I antibodies were compared by microagglutination, complement fixation, and indirect microimmunofluorescence tests. All of these serological tests were useful in distinguishing primary from chronic disease. Thus, the ratio of anti-phase II to anti-phase I antibodies was greater than 1, greater than or equal to 1, and less than or equal to 1 for primary Q fever, granulomatous hepatitis, and Q fever endocarditis, respectively. Moreover, the high phase-specific IgA antibody titers in the indirect microimmunofluorescence test were diagnostic for endocarditis.


We report the case of a 62-year-old man who developed bronchiolitis obliterans with organizing pneumonia (BOOP) associated with acute Coxiella burnetii infection. The diagnosis of BOOP was made by fiber-optic transbronchial biopsy. Treatment with corticosteroids resulted in rapid clinical improvement and complete resolution of airspace opacities. To the best of our knowledge, this is the first well-documented case of BOOP associated with C. burnetii infection. This case suggests that this infection might trigger the development of BOOP.


A case of a 25-year-old female characterized by febrile osteoarthritis and arthromyalgias as the only clinical manifestation of a Q fever is discussed. Analytical data were compatible with those of an acute inflammation and serologic findings reached diagnostic levels. Response to Doxycycline treatment was totally satisfactory. Even though associated arthromyalgias are described in some cases of Q fever as well as sporadic cases of osteoarthral infection due to Coxiella burnetii, there are no oligosymptomatic cases published as the one discussed. Some physiopathologic considerations referred to this peculiar onset are suggested.


Of three patients with Coxiella burnetii endocarditis, two developed focal segmental
proliferative glomerulonephritis (GN), and the third developed diffuse intracapillary proliferative glomerulonephritis. In one case, a good therapeutic response was followed by partial remission of the renal alterations, but 10 months later there were clinical and histological signs of active glomerular nephropathy, suggesting that the antigenic stimulus persisted. In another case, poor evolution of the infection was accompanied by clinically and histologically aggressive glomerular nephropathy, and advanced renal failure. The third patient, who had diffuse proliferative glomerulonephritis, underwent renal biopsy earlier than the other two cases, and the behavior of the nephropathy has not been aggressive to date. Immunohistopathologic study revealed a diffuse granular deposit of IgM and C3 in all three cases; the first two also presented a discrete linear IgG deposit in the capillary loops. Attempts to identify C. burnetii antigen at the glomerular level by immunohistologic techniques failed in two patients. The literature on the association of chronic Q fever with glomerulonephritis is briefly reviewed.


From 1982 through 1987 we diagnosed 13 chronic Q fever cases. Clinically these patients presented a culture-negative endocarditis, and all but two had high complement-fixing antibody titers to *Coxiella burnetii* phase I (reciprocal titer above 200). With the enzyme-linked immunosorbent assay (ELISA), titers of immunoglobulin G (IgG) to phases I and II of *C. burnetii* averaged 158,000 and 69,900, respectively, whereas they reached 300 and 3,200 in acute Q fever cases. Similarly, IgA to both phases of *C. burnetii* and IgM to phase I were consistently higher during chronic than acute Q fever. The serological follow-up of one patient with chronic Q fever over a 4-year period showed a good correlation between the titers of IgG and IgM antibody titers detected by ELISA and indirect fluorescent-antibody test (IFA) to both phases of *C. burnetii*. Few discrepancies appeared with IgA. Shortly after initiation of antibiotic treatment, a slow and steady decrease of the antibody titers to *C. burnetii* phases I and II was observed. The complement fixation, IFA, and ELISA tests showed the same type of antibody response. The ELISA proved to be an excellent diagnostic test for chronic Q fever. It distinguished negative from positive reactions clearly, and results were highly reproducible. The reading is objective, and the test is simple to perform and more sensitive than the IFA and complement fixation tests. The ELISA is recommended for serologic evaluation of patients with chronic Q fever.


The scope of current diagnostic methods for Q fever endocarditis includes serology, direct demonstration of *Coxiella burnetii* in the resected heart valve tissue, and animal inoculation studies. Illustrated by a clinical case report, the different methods are presented and discussed. Serology represents the primary method, using the techniques of complement fixation, indirect immunofluorescence, and enzyme-linked immunosorbent assay (ELISA). The latter two techniques allow the detection of immunoglobulins G, M,
and A to the phase I and II antigens of C. burnetii. After cardiac surgery, we visualized C. burnetii on smears and specifically stained it on histologic sections of the resected heart valve by light and electron microscopic immunohistochemistry. In addition, seroconversion in animals after inoculation with valve specimens confirmed the presence of C. burnetii in the heart valve. The antibody titers determined by ELISA correlated well with the patient's clinical course during the treatment period. Therefore it is suggested that its usefulness for monitoring the efficacy of antimicrobial agents in patients with Q fever endocarditis should be further evaluated.

We present two cases of infection by Coxiella burnetii which developed with sustained fever symptoms. During its evolution, the first case presented granulomatous hepatitis, whereas the second case presented left Cosofemoral Arthritis. We describe the clinical-evolutive characteristics of these clinical forms and within the evolution of the chronic forms of Q fever.

Methods have been worked out for the electron-microscopic diagnosis of Q-fever. A characteristic feature with them is the use of clinical, pathological, and experimental material that is investigated through negative contrast and ultra thin sections for the detection of rickettsial cells and inclusions. It is underlined that the methods referred to are readily applicable, economic, highly effective, and hazardless. They are described for the first time and could be adopted into the diagnostic and epizootiologic practice as well as in experimental investigations.

In a previous prospective study, Streptococcus pneumoniae was identified as the causative agent in 148 (42.8%) of 346 adult patients hospitalized over the course of one year with community-acquired pneumonia (CAP) in the Soroka Medical Center, Beer-Sheva, Israel. The present study characterizes those cases in which Streptococcus pneumoniae was the only pathogen and those in which additional etiological agents were identified. Pneumococcal CAP was diagnosed by standard blood cultures or positive serological tests by one of two laboratory methods. In 100 (67.6%) patients, at least one other etiological agent of CAP was identified in addition to Streptococcus pneumoniae. Compared with patients who were not infected by Streptococcus pneumoniae, patients with Streptococcus pneumoniae CAP were older and had a higher rate of comorbidity (39.5% vs. 29.8%). Streptococcus pneumoniae CAP had a more severe clinical course
and a higher mortality rate, especially when Streptococcus pneumoniae was the only pathogen. Community-acquired pneumonia due to Streptococcus pneumoniae only was more similar in its clinical manifestations to classic typical pneumococcal pneumonia. When an additional etiological agent was identified, the clinical characteristics could not be distinguished from those of atypical pneumonia. It is concluded that Streptococcus pneumoniae remains the principal cause of CAP in this region. The frequency of additional etiological agents of CAP and the difficulty in differentiating clinically between cases due to Streptococcus pneumoniae only and those due to Streptococcus pneumoniae plus other organisms necessitates initial empirical treatment that covers Streptococcus pneumoniae as well as other causative agents of atypical pneumonia.

OBJECTIVE: To study the frequency of Q fever in HIV-infected individuals. DESIGN: A seroprevalence study. SETTING: French National Reference Centre for Rickettsial Agents, Marseille, France. PATIENTS AND METHODS: Five out of the 68 hospitalized cases of Q fever diagnosed in 1987-1989 were also HIV-infected and are described here. Sera from a blood-donor bank (n = 925) and from HIV-positive individuals selected at random, irrespective of clinical or immunological status (n = 500) were tested for Q fever. RESULTS: Comparisons of the two groups showed a statistically significant difference (2.4 versus 0.8%; Fisher's exact test) at the diagnostic dilution 1:200 and at the dilution considered positive for seroprevalence study (1:1000). CONCLUSIONS: Using the estimated incidence of HIV infection in Marseille, the number of Q fever cases in 1987-1989 was 13 times higher and the clinical expression more frequently symptomatic in the HIV-positive population than in the general one. The prevalence:seroprevalence ratio for Q fever was 1.37% in the HIV-positive group and 0.36% in the blood-donor group. Sera positive for Q fever were confirmed by Western blot analysis in order to minimize cross-reaction. Transmission of Q fever appears to be more frequent in HIV-positive individuals than in the general population; this is not surprising, since Coxiella burnetii lives in the phagolysosome, like other micro-organisms described in immunocompromised hosts. Q fever should be added to the spectrum of diseases that occur more frequently during HIV infection.

Sera from 40 patients (25 men, and 15 women) with clinical features compatible with the diagnosis of chronic Q fever were received. Total or partial clinical data were available. All of them had serological evidence of chronic Q fever (IgG class anti-phase I titer greater than 800). The final diagnosis was vascular infection in four cases (with two positive cultures for Coxiella burnetii), bone infection in two patients (one positive culture), chronic hepatitis in one patient, and endocarditis in 32. The last patient had an isolated fever with a chronic Q fever serologic profile. Among the 32 with endocarditis, valve replacement was performed in 59%, and valve cultures were positive in 14/18 patients. Twenty-nine of these patients had previously known valvulopathy; 23 were
exposed to cattle, sheep or goats; and four had an immunocompromised situation. Ten patients died; two before any treatment, five of cardiac failure during or a few weeks after surgery, and three during the medical treatment. For antibiotic treatment, tetracycline alone was employed in seven cases. For the other patients, combined therapy including tetracycline and another drug (rifampin, fluoroquinolones, cotrimoxazole, or erythromycin) was initiated. Three patients were considered to be completely cured.


In order to describe the clinical features and the epidemiologic findings of 1,383 patients hospitalized in France for acute or chronic Q fever, we conducted a retrospective analysis based on 74,702 sera tested in our diagnostic center, National Reference Center and World Health Organization Collaborative Center for Rickettsial Diseases. The physicians in charge of all patients with evidence of acute Q fever (seroconversion and/or presence of IgM) or chronic Q fever (prolonged disease and/or IgG antibody titer to phase I of Coxiella burnetii &gt; or = 800) were asked to complete a questionnaire, which was computerized. A total of 1,070 cases of acute Q fever was recorded. Males were more frequently diagnosed, and most cases were identified in the spring. Cases were observed more frequently in patients between the ages of 30 and 69 years. We classified patients according to the different clinical forms of acute Q fever, hepatitis (40%), pneumonia and hepatitis (20%), pneumonia (17%), isolated fever (17%), meningoencephalitis (1%), myocarditis (1%), pericarditis (1%), and meningitis (0.7%). We showed for the first time, to our knowledge, that different clinical forms of acute Q fever are associated with significantly different patient status. Hepatitis occurred in younger patients, pneumonia in older and more immunocompromised patients, and isolated fever was more common in female patients. Risk factors were not specifically associated with a clinical form except meningoencephalitis and contact with animals. The prognosis was usually good except for those with myocarditis or meningoencephalitis as 13 patients died who were significantly older than others. For chronic Q fever, antibody titers to C. burnetii phase I above 800 and IgA above 50 were predictive in 94% of cases. Among 313 patients with chronic Q fever, 259 had endocarditis, mainly patients with previous valvulopathy; 25 had an infection of vascular aneurysm or prosthesis. Patients with endocarditis or vascular infection were more frequently immunocompromised and older than those with acute Q fever. Fifteen women were infected during pregnancy; they were significantly more exposed to animals and gave birth to only 5 babies, only 2 with a normal birth weight. More rare manifestations observed were chronic hepatitis (8 cases), osteoarticular infection (7 cases), and chronic pericarditis (3 cases). Nineteen patients were observed who experienced first a documented acute infection, then, due to underlying conditions, a chronic infection. To our knowledge, we report the largest series of Q fever to date. Our results indicate that Q fever is a protean disease, grossly underestimated, with some of the clinical manifestations being only recently reported, such as Q fever during pregnancy, chronic vascular infection, osteomyelitis, pericarditis, and myocarditis. Our data confirm that chronic Q fever is mainly determined by host factors and demonstrate for the first time that host factors may also play a role in the clinical expression of acute Q fever.

Human granulocytic ehrlichiosis (HGE) is an emerging infection caused by an *Ehrlichia* species closely related to *Ehrlichia equi* and *Ehrlichia phagocytophila*. Recent advances in the isolation and cultivation of this organism have allowed us to develop an immunofluorescence assay (IFA), enzyme immunoassay (EIA), and Western immunoblotting (WB) using HL-60 cell culture-derived human isolates. Antibody was detected in sera from culture-confirmed HGE patients by IFA and EIA, and these samples were reactive when analyzed by immunoblot analysis. HGE patient sera had high antibody titers and did not react with uninfected HL-60 cells. When IFA, EIA, and WB were used to analyze sera from healthy donors or those with a range of other disorders, including infections caused by *Ehrlichia chaffeensis*, *Rickettsia rickettsii*, and *Coxiella burnetti*, no significant cross-reactivity could be detected by EIA or immunoblot analysis with the exception of two of four serum samples from *R. rickettsii*-infected patients that were reactive by IFA only. Sera from HGE patients did not significantly cross-react in serologic tests for *Borrelia burgdorferi*. Using sera from patients previously enrolled in two clinical trials of treatment for early Lyme disease, we evaluated a two-step approach for estimation of the seroprevalence of antibodies reactive with the etiologic agent of HGE. On the basis of the immunoblot assay results for sera from culture-confirmed HGE patients, WB was used to confirm the specificity of the antibody detected by EIA and IFA. EIA was found to be superior to IFA in the ability to detect WB-confirmed antibodies to the HGE agent. When EIA and WB were used, 56 (19.9%) patients with early Lyme disease (n = 281) had either specific immunoglobulin M (IgM) or IgG antibodies; 38 patients (13.5%) had IgM only, 6 (2.1%) had IgG only, and 12 (4.3%) had both IgM and IgG. Therefore, Lyme disease patients are at high potential risk for exposure to *Ehrlichia*. Analysis by immunoblotting of serial samples from persons with culture-confirmed HGE or patients with Lyme disease and antibodies to the agent of HGE revealed a reproducible pattern of the immune response to specific antigens. These samples confirmed the importance of the 42- to 45-kDa antigens as early, persistent, and specific markers of HGE infection. Other significant immunogenic proteins appear at 20, 21, 28, 30, and 60 kDa. Use of the two-test method of screening by EIA and confirming the specificity by WB appears to offer a sound approach to the clinical immunodiagnosis of HGE.


Between 1972 and 1988 we have serologically confirmed 103 *Coxiella burnetii* infections: 46 were acute, 5 were chronic, 52 represented past infections. Details of 61 cases are presented. Of acute cases 80% had respiratory involvement; at least 63% had pneumonias. The incidence (22%) of neurological complications was of particular interest; 40% of these patients had prolonged sequelae. One acutely ill patient died of fulminating hepatitis. Patients with pre-existing pathology or immunosuppression were
especially susceptible to C. burnetii. In the absence of acute sera, the complement fixation test alone provided inadequate differentiation between recent and past Q fever: phase II titres persisted at greater than or equal to 80 for more than 1 year after the acute infection in 15 cases; maximum duration of persistence was 14 years. Three patients acquired high phase I titres. Only 5% of cases had chronic Q fever, but in view of the diverse sequelae observed in this series, we suggest that long-term serological and clinical follow-up of all cases of Q fever is fully justified.

Serum antibody titres to Adenovirus, Chlamydia Group B, Coxiella burnetii, Cytomegalovirus, Herpes simplex virus, Influenza A, Influenza B, Measles and Mycoplasma pneumoniae were measured in 33 patients with a clinical diagnosis of Alzheimer's disease, and in 28 non-demented controls suffering from functional psychiatric disorders. No statistically significant differences were found between the patients and controls, and it is concluded that these agents play no role in the aetiology of Alzheimer's disease.

Sera obtained from 274 dairy cows in commercial dairies around Zimbabwe examined by indirect immunofluorescence for antibodies reactive with phase II Coxiella burnetii antigens. Overall, 41 pc of the cows were reactive at a titre of 1/40 or greater with the seroprevalence in dairies varying from 33-75 pc. The implications for human and animal health are discussed.

Infection with Coxiella burnetti (Q fever) was diagnosed in 18 children younger than 3 years of age in The Netherlands during a 16-month period. The diagnosis was confirmed serologically by means of a complement-fixation test and immunofluorescence for IgM determination. A summary of the clinical, hematologic, serologic and epidemiologic features is given. Four children had relapsing episodes of fever during several months. The problem of childhood infection with C. burnetti, particularly in relation to the possibility of intrauterine infection or infection during birth and in the neonatal period, is discussed. In at least one child of this series, an infection by means of breast feeding was considered likely. Q fever is possibly underdiagnosed in children; it should be considered in children with fever of unknown origin.
Case of an 48 year old man who has presented from 1968 to 1973 a lot of diseases such as: --mitral incompletence discovered in 1968 in Madagascar island in spite of many previous clinical examinations; --acute pneumonia and heart failure in January 1973. Serological reactions of Ricketsia were quite positive; --acute thrombosis of right humeral artery in May 1973. It has been treated by surgical way, bay "desobstruction" and by pass and medical treatment chloramphenicol. Pathologic endartery has been inoculated to an hamster, cobaye. These animal became feverish, and presented an inflammation of testis. A least serological reaction of Ricketsia became positive for all of them; --few weeks, thrombosis of left femoral and posterior tibial arteries treated by surgical and medical ways. Some commens are exposed about evolution of Coxiella Burneti infections, about the frequency of arterial and cardiac lesions, and about the effect of tifomycine which seems to be decreasing and the action of cycline (doxicycline).

An immunoenzymatic test using as antigen purified suspensions of Coxiella burnetti coated by methylglyoxal on microtiter plates was developed. Multiple testing of the same sera gave similar results: two dilutions of serum (1:400 and 1:1600) were used in routine tests. Good agreement between the immunoenzymatic and the indirect immunofluorescent antibody tests was obtained for 41 of 50 sera examined. Five sera negative by the immunofluorescent antibody test were positive by the immunoenzymatic test; this result may be due to the higher sensitivity of the latter test. On the other hand, three sera with higher titers by the indirect immunofluorescent antibody test showed a rather feeble positivity by the immunoenzymatic test. This is probably due to the different specificity of the reacting antibodies in the two methods. The indirect immunofluorescent antibody test permits better distinction of the very high titers (greater than 1:5120) than the immunoenzymatic test. The immunoenzymatic test seems to be the method of choice for seroepidemiology surveys of Q-fever; however, its use for clinical serodiagnosis needs further confirmation.

Q fever is a worldwide-occurring zoonosis caused by Coxiella burnetii. There are various clinical manifestations of acute Q fever, of which acute cholecystitis is a very rare clinical presentation. This study reports seven cases of acute cholecystitis associated with Coxiella burnetii and reviews two other cases from the literature. All patients were admitted to hospital for fever and abdominal pain in the right upper quadrant. Abdominal echography showed a distended gallbladder with biliary sludge without concrements in eight cases and with a single stone in one case. Diagnosis was made by specific serological investigation (microimmunofluorescence assay) for Coxiella burnetii. All
nine patients were cured, six after laparoscopic cholecystectomy and three with antibiotics only. Histological examination of the gallbladders showed inflammation in five cases, although Coxiella burnetii was not detected by immunohistochemistry. The results show that laboratory investigations in patients admitted to hospital for symptoms consistent with acute acalculous cholecystitis should include a systematic search for Coxiella burnetii.

INTRODUCTION: To describe the clinical and epidemiologic characteristics of hepatic involvement in a cohort of 109 patients with Q fever. RESULTS: Involvement of the liver alone was documented in 55% of cases. In 96% it was manifested as a febrile process without focal symptoms and hepatic cytolysis. There were no differences in epidemiologic characteristics between patients with hepatitis and those and without. CONCLUSION: Q fever should be included in the differential diagnosis of community-acquired febrile syndromes.

Five cases of acute Q fever diagnosed in the same family are reported. The epidemiological and clinical features, the therapy and evolution of the infections by Coxiella burnetti are discussed. Q fever is a condition to be considered in febrile illnesses or atypical pneumonia, particularly when developing in outbreaks. It is concluded that Q fever should be considered as endemic in some areas of this country (Basque Country, Catalonia...). Finally, we think that antibiotic therapy (tetracyclines) should be given, as it can shorten the duration of the disease and prevent the development of severe chronic forms.

PURPOSE: To determine the role of Bartonella henselae in intraocular inflammatory disease and identify its clinical features. METHODS: We retrospectively determined the serum immunoglobulin (Ig)G and IgM antibodies against B. henselae and Bartonella quintana by enzyme immunoassays in stored sera of 138 consecutive newly referred patients with uveitis who, during the acute stage of their ocular disease, underwent a standardized screening protocol to determine the cause of uveitis. RESULTS: For the entire series, the frequency of high positive levels of IgG (above 1:900) or IgM (above 1:300) antibody against B. henselae was 6% (8/138) and 3% (4/138), respectively. Except for cross-reactions between B. henselae and B. quintana, we did not find additional evidence for cross-reactions among the various bacteria tested (Coxiella burnetii and
All patients with proven infectious uveitis (n = 21) and those with established uveitic entities (n = 37) had negative B. henselae serology. High positive IgG levels were observed in 9% of patients (5/54) with unknown cause of uveitis, in two subjects with human leukocyte antigen (HLA)-B27 positive uveitis, and in one with sarcoidosis. Five patients with uveitis of unknown origin and highly elevated IgG levels against B. henselae exhibited clinical features characterized by papillitis with surrounding retinal focal lesions or edema. CONCLUSIONS: The serologic and clinical data indicate that uveitis in seropositive cases may be caused by B. henselae. We do not recommend including testing for B. henselae in initial screening of patients with uveitis, but consider it worthwhile for those with papillitis and screening results within normal limits.


The first case of Q fever endocarditis that has been diagnosed in Mexico is presented. A 10-year-old girl with discrete subaortic stenosis (SAS) and patent ductus arteriosus (PDA) was seen in December of 1996 with fever, hepatomegaly and splenomegaly. She presented also anemia, leukopenia, hypergammaglobulinemia, positive rheumatoid factor, cryoglobulinemia, antinuclear and anticytoplasmic antibodies (anti-RNA-proteins and anti-DNA). An aortic valve vegetation was seen by echocardiogram. Blood-cultures were negative. Antibody test for Coxiella burnetii was positive. Treatment with doxycyclin was initiated as soon the diagnosis was done. PDA was closed, SAS was liberated and two aortic vegetations were resected. Endocarditis in Q fever occurs when there is predisposing heart disease and/or immunodeficiency. Effective therapy has not yet been established. The diagnosis of Q fever endocarditis is difficult; it should be considered, in case of clinical suspicion of endocarditis with negative blood-cultures.


BACKGROUND AND AIM OF THE STUDY: Q fever endocarditis caused by Coxiella burnetii is the most important etiology of negative blood culture endocarditis. Without specific clinical findings, diagnosis is difficult and prevalence of this life-threatening disease is underestimated. METHODS: Q fever endocarditis was assessed in 19 patients (15 men, four women; age range: 36-79 years) by evaluating clinical and echocardiographic criteria and specific serology. All patients had evidence of pre-existing valvular disease, and 10 had a valvular prosthesis. Diagnosis was assessed in: the presence of unexplained fever (n = 5), heart failure with valvular dysfunction (n = 10), hemolysis (n = 1), glomerulonephritis (n = 1) and stroke (n = 2). A late diagnosis was made in eight patients, either during or after surgery. RESULTS: In all cases, usual blood cultures remained negative, despite specific serology being positive. Transthoracic and transesophageal echocardiography were conclusive in only six cases (four vegetations, two periannular abscesses). Surgery was indicated in 15 patients for heart failure or valvular dysfunction (n = 12), hemolysis (n = 1) and periannular abscess (n = 2).
Intraoperative findings were suggestive of endocarditis in seven cases; valvular cultures were positive in 92% of cases. All patients were treated with combined doxycycline/hydrochloroquine or quinolone, for a mean of 24 months (range: 6-60 months). Mean follow up was 40 months (range: 6-144 months). Two patients died from heart failure, one patient was lost to follow up, and 16 patients had no late relapses. CONCLUSION: Q fever is an underestimated cause of endocarditis, and early diagnosis is the key to good prognosis. The need for systematic serologic examination in case of valvular dysfunction, with or without endocarditis symptoms, is emphasized.

INTRODUCTION AND OBJECTIVES: Coxiella burnetii is a causative agent of increasingly frequent subacute infective endocarditis, and is associated with elevated morbimortality. Our aim in the present study was to assess the clinical, serological and therapeutic long-term evolution of 20 patients with Coxiella burnetii endocarditis. METHODS: Twenty patients (13 male and 7 female, age 42 +/- 10 years) admitted between 1982 and 1996 were retrospectively studied. All of them fulfilled the Duke criteria modified by Raoult for Q fever endocarditis. RESULTS: Endocarditis involved prosthetic and native valves in 14 and 6 patients, respectively. All patients except one received antibiotic treatment. Patients treated with doxycycline in monotherapy showed worse evolution than those treated with doxycycline in combination with other antibiotics. Valve replacement was performed in 15 patients, due to prosthetic dysfunction in most of them. The overall mortality was 40% (8 patients). At follow-up of 74 months (range 19-156) (mean 74 +/- 47) all patients showed persistent high levels of phase I antibodies. At follow-up of 15 to 65 months (32 +/- 30) antibiotic treatment was suspended in five patients because they were asymptomatic and without microbiologic findings of valvular endocarditis. CONCLUSIONS: Q fever endocarditis was associated with severe complications, which often required valve replacement. All patients showed persistent high serological titers of Coxiella burnetii endocarditis without other signs of active infection. This finding raises the issue of suspending antibiotic treatment in patients with negative microbiologic findings and questions the persistence of abnormal serology as a monitor of treatment efficacy.

We report a childhood case of severe acute cerebellitis caused by Coxiella burnetii. After 10 days of fever and headache, the patient fell into a drowsy state. Examination of the cerebrospinal fluid (CSF) revealed pleocytosis, an increased level of protein, and negative results in bacterial and viral studies. Magnetic resonance imaging demonstrated a herniated tonsil compressed by the swollen vermis. Administration of minocycline relieved the patient's clinical symptoms. C. burnetii was isolated from the CSF obtained during convalescence.
The application of an indirect ELISA for detection of IgM and IgG antibodies against Coxiella burnetii in five Q fever patients--among them one with endocarditis and one with hepatitis--is described. In the acute phase of infection, within a few days after onset of clinical symptoms, a significant rise of IgM antibodies could be detected. It was followed by a rise of IgG in the second and third week. In chronic Q fever endocarditis, IgM antibodies persisted over a period of nine months. High IgM and low IgG values indicated acute infection, while in convalescent sera the IgM/IgG relationship was vice versa. In a comparative investigation with complement fixation (CF) test it could be shown that CF antibodies were associated exclusively with immunoglobulin G. IgM separated from IgG by gel chromatography did not fix complement. So, the CF test does not appear to be suitable for detection of antibodies against Coxiella in the early stages of the disease. Because of the persistence of IgG antibodies over a longer period of time, sole detection of a titer against the agent is insufficient for diagnosis of current disease, if not a rise or fall in titer can be detected in a second serum sample. Using the sensitive ELISA technique, a diagnosis is usually possible with one serum sample--in connection with history and clinical investigation--by differentiation of IgM and IgG antibodies.


In the period 1947-1985, 601 patients with infective endocarditis were seen at the University Hospital Zurich and the Kantonsspital Lucerne. Streptococci, enterococci and staphylococci were the predominant causative organisms in two-thirds of all cases. In more than 25% of the patients blood cultures remained negative. In 6 patients endocarditis was caused by very rare organisms, viz. Coxiella burnetii (2 cases), Hemophilus parainfluenzae, Corynebacterium bovis (diphtheroids), Brucella melitensis and Aspergillus terreus. The clinical and microbiological characteristics of these cases are described and compared with the results in the literature. Diagnostic and therapeutic problems are discussed. Only with special awareness of the role of these unusual organisms in causing infective endocarditis, especially Q fever endocarditis with its notoriously atypical course, can the number of culture negative cases be diminished and the prognosis thereby improved.


Antisera from rabbits immunized with formalin inactivated Coxiella burnetii isolates associated with either acute (Nine Mile, phase I or phase II) or chronic (Priscilla) Q fever showed reactivity to a C. burnetii macrophage infectivity potentiator protein (Cb-Mip) cloned in Escherichia coli. Further, antisera generated in BALB/c mice after infection with live Nine Mile phase I or Priscilla isolates also showed reactivity to Cb-Mip by immunoblot analysis. In addition, human serum from an individual with previous serological and clinical evidence of Q fever showed reactivity to Cb-Mip. This study indicates that Cb-Mip is immunogenic in both experimental and natural infections, and is the first report on the presence of antibodies to Mip/Mip-like proteins of intracellular bacteria in human sera. Cb-Mip may serve as a potential target antigen for developing recombinant vaccines or diagnostic assays for Q fever.

Young laying hens were infected with Coxiella burnetii to study egg transmission, clinical and serologic responses, excretion of the agent in feces, and its persistence in internal organs. No clinical symptoms were noticed. The birds developed good titers in a capillary agglutination test by 13 days postinfection (DPI), which peaked at 30 DPI and thereafter declined gradually, becoming negative in some birds around 90 DPI. In vivo and in vitro egg transmission of the agent could not be demonstrated. C. burnetii was recovered at 90 DPI from spleen and liver but not from kidney and ovary.

Myocarditis and pericarditis are uncommon complications of human rickettsial, ehrlichial and Bartonella infections. Myocardial inflammation usually occurs in the setting of acute disseminated infection. Organisms associated with myocarditis include: Rickettsia rickettsii, R. conorii, Orientia tsutsugamushi, Coxiella burnetii, Anaplasma phagocytophila (the causative agent of Human Granulocytic Ehrlichiosis) and Bartonella henselae. Pericarditis has been described in the setting of R. conorii and Coxiella burnetii infections. This article reviews the epidemiology, pathologic characteristics, clinical manifestations, diagnosis and treatment of myocarditis and pericarditis caused by these organisms.
**Shaked et al. 1989.** Q fever meningoencephalitis associated with bilateral abducens nerve paralysis, bilateral optic neuritis and abnormal cerebrospinal fluid findings. *Infection.* 17(6): 394-395.

Q fever is a zoonosis caused by Coxiella burnetti, the clinical features of which are often nonspecific and self-limited. Involvement of the central nervous system is rare and is usually seen as a complication of endocarditis caused by this rickettsial organism in the chronic disease. Specific neurological manifestations in the course of the acute illness aseptic meningitis, encephalitis, toxic confusional states, extrapyramidal signs, dementia and behavioral disturbances. We describe a patient who developed reversible bilateral abducens nerve paralysis and bilateral optic neuritis in the course of acute Q fever meningoencephalitis.


A limited, randomized, blind, placebo-controlled trial of Q fever and influenza vaccines has been conducted in three Queensland abattoirs on a sequential analysis design. Ninety-eight subjects were given Q fever vaccine and 102 influenza vaccine. Q fever cases were observed in unvaccinated workers in all three abattoirs during the period of observation. A total of seven Q fever cases in one group, one more than the number required to achieve statistical significance between the two vaccine groups, was reached after 15 months with the cases coming from two of the abattoirs. These Q fever cases were in the group which had been given influenza vaccine and none in that given Q fever vaccine. Symptomless seroconversion rates of 24% were found in the remaining influenza virus vaccinees, and those without immunity were given Q fever vaccine.


A vast literary review on Q-rickettsial endocarditis is presented--spread, frequency, predilection, clinical course, laboratory findings, diagnosis, treatment, prognosis. The first case of Q-rickettsial endocarditis in Bulgaria is reported. The case was proved by the high titre of the specific antibodies while the patient was still alive and post mortem by visualizing the causative agent in the aortic valve and by its isolation through inoculation of material from the aortic valve. The infection was not influenced by high doses of penicillin, gentamycin and brulamycin but was suppressed by vibramycin in combination with lincomycin and biseptol. The lethal outcome was due to severe heart failure. It is suggested that other cases of Q-rickettsial endocarditis should be expected since Q-fever is widely spread in Bulgaria and the characteristics of the disease, its diagnosis and treatment ought to be well known.
The worldwide epidemiology and population-based incidence of Q fever endocarditis (QFE) have been less well studied than those for uncomplicated Q fever. An exhaustive literature review revealed 408 patients with QFE reported between 1949 and 1994, mostly from 3 large geographic areas. Underlying valvular heart disease was almost invariably present, and 38% had prosthetic valves. The most common clinical manifestations were fever and congestive heart failure. The mortality rate dropped over the years from 65% to 25%, but a meta-analysis of published data showed the death rate to be significantly lower among patients receiving combination therapy (12/65, 18%), as compared to patients treated with tetracycline alone (18/41, 44%, p = 0.005). A 10-year (1983-1992) retrospective nationwide survey of QFE in Israel revealed 35 patients with QFE, representing an annual incidence of 0.75 cases per 1 million population. Underlying heart disease, clinical manifestations and outcome in the Israeli group were not substantially different from those described in the world literature. The current state-of-the-art clinical approach includes early diagnosis, prompt initiation of combination therapy for at least 3 years, and long-term clinical and serologic follow-up. Adherence to these rules might have contributed to the improved prognosis in recent years.


We report a case of *Coxiella burnetii* endocarditis in a 42-year old man presenting with a long-known cardiac murmur and an infectious syndrome of several months duration. The aetiological diagnosis, delayed by the lack of knowledge of a primary Q fever, was established by serology. The infection responded to tetracycline combined with cotrimoxazole, but a valve replacement performed for haemodynamic reasons was followed by serious complications. We remind the readers that Q fever endocarditis must be considered as a possible diagnosis in all cases of endocarditis with negative blood cultures and that specific serological examinations in search of anti-phase I antibodies of the IgA type should be performed as soon as possible, using the indirect immunofluorescence technique. Attention is drawn to the different serological responses of the three clinical types of Q fever infection and to the cellular immunity associated with that disease.


Over a period of 6 years (1989 to 1995), serum samples from 3,300 patients suspected to be infected by *Coxiella burnetii* were assayed for the presence of antibodies against antigen phase II of the microorganism by the indirect immunofluorescence antibody technique (IFAT). One hundred fifty-two cases were recorded, and blood samples from 17 patients were cultured for the isolation of the pathogen. By a centrifugation shell vial
technique, eight strains were isolated from patients suffering from acute Q fever. The microorganism was detected in the cultures by IFAT, by Gimenez staining, and by the cytopathogenic effect on Vero and human embryonic lung (HEL) cells. PCR followed by restriction fragment length polymorphism analysis was used to confirm the diagnosis and identify the Coxiella burnetii strains within the cell cultures as well as to compare them with reference strains. In order to avoid time-consuming cultures, to achieve direct detection of Coxiella burnetii in clinical samples (blood, buffy coat, etc.), and to increase the specificity and sensitivity of the detection, nested PCR was performed. The first step of DNA extraction was performed with the QIAamp blood kit 250. For the second step of the PCR assays, the conditions of temperature and times of recycling were properly modified, and the microorganism was detected within 4 h. Our study demonstrates that Q fever is an endemic disease in Crete and that the diagnosis of Coxiella burnetii infection can be rapidly achieved by the detection of the microorganism in buffy coat samples by nested PCR. Although the presenting symptoms of the disease in this study differed from those in other studies, the Cretan strains do not differ genotypically from the reference strains (Nine Mile and Q212).

The polymerase chain reaction (PCR) was used for the detection of Coxiella burnetii, an obligate intracellular bacterium and the etiologic agent of Q fever. A pair of primers derived from the C. burnetii superoxide dismutase gene served to amplify a targeted 257-bp fragment of genomic DNA. These primers were chosen on the basis of GenBank analysis, G + C ratio, and absence of secondary structure. This technique allowed the detection of as few as 10 C. burnetii organisms. C. burnetii was detected in tissue culture and in specimens from patients (heart valves). In all, 8 reference isolates and 22 new isolates of C. burnetii from France were successfully amplified. No amplification products were found when PCR was performed with 25 bacterial species that had been isolated in a clinical laboratory from patients with clinically similar infections. Amplification products of C. burnetii were confirmed by restriction enzyme digestion and dot blot hybridization. The method used here, a combination of PCR and restriction analysis, is a faster and more sensitive assay for C. burnetii than standard culture techniques.

We report an acute Q fever case, a febrile syndrome, in the 14th week of pregnancy. Placental infection was documented by Coxiella burnetii culture. Newborn infection was ruled out on the basis of the absence of serological evidence after 2 years and on clinical normality. Serological diagnosis is reviewed here, as maternal serology was suggestive of chronic Q fever. The clinical progress, following extended observation, was consistent with acute infection. A QpDV plasmid, already described as being common to acute and chronic European cases, was detected.
Thiele et al. 1992. Monoclonal antibody based capture ELISA/ELIFA for detection of Coxiella burnetii in clinical specimens. *Eur.J.Epidemiol.* 8(4): 568-574. A CAPTURE ELISA/ELIFA system based on monoclonal capture and biotinylated monoclonal detection antibody is described. The assay is fast, highly specific and detects a minimum dose of 2500 Coxiella (C.) burnetii particles. In contrast to the sophisticated and cumbersome isolation procedures, even non-specialized laboratories could use this assay system for investigating clinical samples of different origin for C. burnetii within a short period of time.


PURPOSE: To contribute to the knowledge of epidemiologic and clinical features of patients hospitalized with Q fever in France. METHODS: We conducted a retrospective analysis of 22,496 sera submitted between 1982 and 1990 to the French National Reference Center for Rickettsial Diseases (NRC). The diagnosis of acute Q fever was based on an IgG titer greater than or equal to 1:200 and an IgM titer greater than or equal to 1:25 against phase II Coxiella burnetii antigen on an indirect immunofluorescence test (IFA). Fifteen cases prior to 1985 were diagnosed on the basis of a complement fixation titer greater than or equal to 1:8. A serosurvey of blood donors from Marseille was also conducted in 1988 on 924 sera, using IFA with a cutoff titer of 1:25. RESULTS: The serosurvey conducted in 1988 showed a seroprevalence of 4.03%, without age or sex prediction. The incidence rate of acute Q fever detection at the NRC was 0.58 per 100,000 inhabitants over the 9-year period. Three hundred twenty-three clinical cases were diagnosed, rising from 1 in 1982 to 107 in 1990. In patients hospitalized for acute Q fever, there was a significantly higher sex ratio of males to females (2.3), which, coupled with the age distribution, indicated that elder males, who are overrepresented due to our recruitment bias, are more susceptible to C. burnetii infections. The mean age of the patients was 45.5 years, while the risk was increased in the 30 to 39 age group as well as in the 60 to 69 age group. Usual epidemiologic risk factors were found in 20.1% of the cases. Hepatitis (61.9%) was a more common clinical presentation in our patients with Q fever than pneumonia (45.8%). This might reflect differences in strains of C. burnetii or the biology of the host. However, French farmers and stock breeders commonly drink unpasteurized raw milk from their cattle, which might indicate a relationship between hepatitis and infection via the digestive tract. CONCLUSION: Our results indicate that many cases of acute Q fever are undiagnosed. A greater awareness of the disease and more extensive serologic testing of patients with symptoms compatible with Q fever may improve the situation.

Lipopolysaccharides (LPSs) of 8 isolates of Coxiella burnetii from a variety of clinical and geographical sources could be divided into four groups based on molecular heterogeneity in silver-stained sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) profiles in the region of the 10 to 17 kDa. The lipopolysaccharide of group 1 was identified on isolates from acute Q fever patient, milk and tick. The three remaining groups were primarily found on isolates from human cases of chronic Q fever. These LPSs shared many antigenic epitopes, as determined by immunoblotting with mouse anti-C. burnetii antisera.

Torres et al. 1996. Community-acquired pneumonia in chronic obstructive pulmonary disease: a Spanish multicenter study. Am. J. Respir. Crit. Care Med. 154(5): 1456-1461. Community-acquired pneumonia (CAP) is an infectious illness that frequently motivates hospital admission when comorbid conditions are present. However, the epidemiology of CAP in relation to the underlying disease of the patients is not well known. We performed a prospective multicenter study with the aim of assessing the clinical characteristics, etiology, and outcome of chronic obstructive pulmonary disease (COPD) patients with CAP. Between October 1992 and December 1994 we studied 124 COPD patients (mean FEV1 40 +/- 11% of predicted, mean FVC/FEV1 49 +/- 10) admitted because of CAP to one of the participating centers. An attempt to obtain an etiologic diagnosis was performed by means of blood cultures (n = 123), sputum cultures (n = 97), pleural fluid cultures (n = 17), protected specimen brush samples (n = 41), percutaneous transthoracic needle aspiration (n = 41), and serology (n = 106). Etiologic diagnosis was achieved in 80 (64%) of cases, however, diagnosis based upon valid techniques was only possible in 73 (59%) cases. The main causal microorganisms were the following: Streptococcus pneumoniae in 32 (43%), Chlamydia pneumoniae in 9 (12%), Hemophilus influenzae in 7 (9%), Legionella pneumophila in 7 (9%), Streptococcus viridans in 3 (4%), Coxiella burnetii in 3 (4%), Mycoplasma pneumoniae in 2 (3%), Nocordia asteroides 2, Aspergillus ssp. 1, and others 10. In three of these cases the etiology was polymicrobial. Bacteremia was present in 19 (15%) cases; S. pneumoniae was the most frequent isolate (13 cases). Antibiotic treatment was modified in 22 cases due to etiologic findings, and in 9 due to therapeutic failure. Ten patients died (8%), and 22 needed mechanical ventilation, the mortality rate in the latter population being 23%. Total or partial resistance of S. pneumoniae to penicillin was observed in 10 of 32 (31%) isolations, and to erythromycin in 2 (6%). The results of this study are important for the standardization of empiric antibiotic strategies in COPD patients with pneumonia.


The history of Q fever in Italy may be divided into three periods: epidemic in character after the Second World War, endemic occurrence from 1960 to 1980, and sporadic occurrence at present. Clinical symptoms are unspecific, and diagnosis must be confirmed by serology and isolation of the causative agent. The reported incidence is consequently underestimated. Results are reported of a seroepidemiologic survey in
animals and humans in the Italian region and western Sicily. In the Mediterranean area several epidemic foci are still present. The need of further studies to evaluate the incidence of Q fever and to shed more light upon the epidemiology of Coxiella burnetii infections is stressed.

We studied the serological cross-reactions among Bartonella henselae, Chlamydia pneumoniae and Coxiella burnetii by indirect fluorescence antibody (IFA) method, using sera from 8 patients with cat scratch disease (CSD), 13 patients with C. pneumoniae infection and 12 patients with acute Q fever. B. henselae IgG antibody was negative in 13 patients with C. pneumoniae infection, and was positive in 3 (titers being 1:64) of 12 patients with Q fever, whereas B. henselae IgM antibody was negative in all the patients with C. pneumoniae infection or Q fever. C. burnetii IgG antibody was removed by absorption of these 3 sera with C. burnetii antigens, whereas B. henselae IgG antibody did not change. C. pneumoniae IgG antibody was positive in 3 (titers being 1:125 in two, 1:32 in one) of 8 patients with CSD. Both C. pneumoniae and B. henselae IgG antibody titers were significantly reduced by absorption of these 3 sera with B. henselae antigens. C. burnetii IgG or IgM antibodies were negative in all patients with CSD. In conclusion, no serological cross-reaction between B. henselae and C. burnetii was observed. On the other hand. B. henselae IgG antibody cross-reacted to C. pneumoniae antigens, whereas C. pneumoniae IgG antibody did not cross-react to B. henselae antigens. Our findings suggest that determination of B. henselae IgG or IgM antibodies were not influenced by C. pneumoniae and C. burnetii antigens.


Sixteen cases of chronic Q fever are described. In eight there was a history of exposure to infection from farms or farm products. All had valvular heart disease, involving the mitral valve in nine and the aortic valve in seven. Infection occurred on a prosthetic valve in two patients. Arterial embolism was common. Venous thrombosis occurred in three patients, and pulmonary embolism occurred in three other patients. Complement fixing antibodies to phase 1 antigen were found in a titre of 1:200 or greater in all except two patients. In one of these post-mortem examination revealed rickettsial bodies in mitral valve vegetations, and in the other Coxiella burnetii was isolated from heart valve tissue. The majority presented with infective endocarditis but two presented primarily with liver
disease. All patients had evidence of liver involvement and in one this led to death from cirrhosis. Abnormal tests of liver function, particularly hyperglobulinaemia, raised alkaline phosphatase and abnormal bromsulphthalein retention were found in all patients. Hepatic histology was abnormal in all eight patients in whom it was studied. The commonest features were mononuclear cell infiltration of the portal tracts and prominence of the sinusoidal Kupffer cells. Patchy focal necrosis of parenchymal cells, granulomata, fatty change, and eosinophilia of the sinusoidal walls were also noted in several patients and cirrhosis developed in one. Six patients had a purpuric rash, and in 12 there was thrombocytopenia. It is suggested that the presence of hepatomegaly and liver involvement and thrombocytopenia may help to differentiate Q fever endocarditis from bacterial endocarditis. Raised serum IgM and IgA levels occurred frequently, but with only a moderate dominance of IgM. Sheep cell agglutination and latex fixation tests for rheumatoid factor were occasionally positive. Several features of the disease suggest the possibility that immune-complex mechanisms may play a role in chronic Q fever. Treatment was with prolonged courses of tetracycline usually combined with lincomycin. Seven patients underwent valve replacement surgery for haemodynamic reasons. Five patients died; two from heart failure, one from cirrhosis, one seven days after valve replacement and one from intraperitoneal haemorrhage following percutaneous liver biopsy. Three patients have survived for more than five years, and another six for more than three and a half years after diagnosis. Of these nine patients, three received medical therapy alone and six required valve replacement as well. Antibiotics have been discontinued in four patients who have had valve surgery and three others. Six patients had received antibiotics for continuous periods varying from 29-62 months. In the period after stopping therapy varying from 15-21 months, no relapse has occurred. A seventh patient, who had received antibiotics for four months prior to valve replacement, has survived 43 months after the withdrawal of antibiotics...


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Ninety-five acute- and convalescent-phase serum specimens from 48 patients suspected of having rickettsial or Legionella infections were assayed for antibodies to *Coxiella burnetii*, the causative agent of Q fever. To evaluate the specificity of the indirect enzyme-linked immunosorbent assay (ELISA) for human Q fever, we compared the ELISA results with those of the indirect immunofluorescence antibody (IFA) test. The ELISA data were analyzed by two different criteria for a positive test. The first criterion for positive results by ELISA was based upon diagnostic titers established in a study of 150 subjects who had no demonstrable cellular or humoral immune responses to *C. burnetii* phase I or phase II whole cells or phase I lipopolysaccharide. The second criterion was based upon diagnostic antibody titers in a study of 51 subjects who had been diagnosed as having clinical Q fever and had fourfold or greater rises in humoral immune responses to *C. burnetii* phase I and phase II whole-cell antigens. A comparison
of the ELISA and IFA test results of the 95 serum specimens indicated excellent agreement between the tests (Kappa = 92.9%; P < 0.05). None of the 38 patients whose etiologies were confirmed serologically as Legionnaires' disease or rickettsial diseases other than Q fever were classified as positive for C. burnetii by the ELISA. Only one patient identified by the IFA test as having Q fever was not scored positive by the ELISA. These results suggest that the ELISA is useful for epidemiologic screening and as a diagnostic test for human Q fever.

The authors describe a case of chronic endocarditis by Q fever, in a patient who had been operated for coarctation of the aorta twelve years previously and at the same time was carrier of a congenital bivalve aorta. The clinical picture was suggestive of subacute endocarditis, but the blood culture was negative repeatedly. There was also a prolonged and relapsing febrile syndrome over a period of one-year-and-a-half. The following data are also worthy of note: the coexistence of a liver disorder and a focal and segmentary glomerulonephritis. Based on some recent publications (one by the same group) the authors feel that Coxiellosis burnetti must be more frequent in their environment than is suspected.

The authors report the first two cases of legionnaires' disease from Catalonia. Both patients were chronic bronchitic males, and the cases were sporadic. The onset of the disease was characterized by a febrile illness with muscle and joint pains, respiratory symptoms (cough and mucous sputum production), and mental changes. There were no digestive complaints. Pulmonary consolidation occurred in both patients in the left upper lobe. Blood chemistries disclosed the existence of an absolute lymphopenia, altered liver function tests, and elevated CPK levels. Bacterial cultures of blood and sputum, respiratory virus screening (influenza A and B, parainfluenza 1, 2 and 3, and adenoviruses), and tests for Mycoplasma pneumoniae, Coxiella burnetti and Chlamydia psittaci were all negative. Antibody titers against Legionella pneumophila by indirect immunofluorescence were 1/1024 (positive) for serotype I and 1/1024 (positive) for serotype II in one patient, and 1/1024 (positive) for serotype I and 1/128 (negative) for serotype II in the other patient. The authors review the epidemiological, clinical, biochemical and diagnostic aspects of legionnaires' disease, which knowledge will undoubtedly allow to detect an increasing number of cases.

We describe the case of a 69-year-old male with a year-long history of renal failure.
Investigation revealed proliferative glomerulonephritis, cryoglobulinemia, and Q fever endocarditis. Renal tissue examination for the presence of Coxiella burnetii was positive. The patient was treated by doxycycline and chloroquine; his clinical status, renal failure, and chronic Q fever have dramatically improved.


Q fever is a zoonosis related to the existence of Coxiella burnetii infected animals. The authors studied the seroprevalence and risk factors associated to *C. burnetii* infection in veterinary students in Zaragoza (Spain). Sera were collected at the beginning and the end of the academic year (1994-1995) and were tested by Complement fixation test to detect antibodies against *C. burnetii*. 10.02 and 11.02% seroprevalences were observed at the beginning and the end of the study respectively. The cumulative incidence through the period of study was 0.0157. Risk factors associated to *C. burnetii* were multiple: students coursing the speciality in Food Inspection and Technology or the speciality of Animal Production; to practise with living animals in general and particularly with ruminants and to contact frequently with persons who worked with animals, particularly with veterinarians, farmers and animal traders. In parallel, the students coursing the first course showed a significant lower seroprevalence. Male students from the fifth course were significantly more seroprevalent than females, where sex was a protection factor. Concerning the clinical signs asked in the questionnaire, cardiovascular disturbances, flu and/or pneumonia, sweating, transient hyperthermia or spondylitis were associated factors. Conversely, a good response after treatment of symptoms was a protection factor. The only risk factor associated with incidence along the year of study was practising in farms. The authors recommend a revision of hygiene measures to control risk factors and the diagnostic of *C. burnetii* infection when populations at risk show the associated symptoms.


BACKGROUND AND PURPOSE: Q fever is a disease of humans. Vaccines to prevent this disease have demonstrated efficacy in rodents and must also be evaluated for efficacy in a nonhuman primate model. Preliminary to vaccine efficacy experiments, cynomolgus and rhesus monkeys were evaluated as suitable experimental models of acute Q fever.

METHODS: Both species of monkeys were challenged with aerosolized 10(5) virulent phase-I Coxiella burnetii Henzerling strain, and clinical and serologic responses were determined. RESULTS: Radiographic changes were observed in seven of eight monkeys of both species; however, changes in cynomolgus monkeys tended to be more significant. Between 7 and 10 days after challenge, all rhesus monkeys and 88% of cynomolgus monkeys were bacteremic. Sequential increases in antibody responses to *C. burnetii* phase-I and phase-II whole cells and phase-I lipopolysaccharide were observed in both species. Although the maximal rectal temperature increase was similar in both species, duration of fever was slightly longer in rhesus monkeys. Clinical features were similar to...
those described in human acute Q fever patients. CONCLUSIONS: On the basis of the more pronounced radiographic changes in cynomolgus monkeys, we favor use of this species for future studies of vaccine efficacy.


Antibiotic susceptibility testing of two isolates of the Q-fever agent, *Coxiella burnetii*, was performed with recently and persistently infected L929 fibroblast cells. The two genetically distinct isolates, Nine Mile and Priscilla, are implicated in two different clinical disease syndromes, acute and chronic Q fever, respectively. We compared the efficacies of rifampin, doxycycline, and five 4-quinolone compounds (ciprofloxacin, diflloxacin, ofloxacin, norfloxacin, and pefloxacin) in reducing persistent *C. burnetii* infection of L929 fibroblasts. In persistently infected cells, the Priscilla isolate was less susceptible to all antibiotics tested when compared with the Nine Mile isolate. The most effective antibiotics against the Priscilla isolate were ofloxacin, pefloxacin, and ciprofloxacin (50% inhibitory concentrations of 0.5, 2.2, and 2.5 micrograms/ml, respectively). In persistently infected cells, the Nine Mile isolate was highly susceptible to all antibiotics tested except doxycycline. In contrast, the Priscilla and Nine Mile isolates in recently infected cells were somewhat susceptible to doxycycline; the Priscilla isolate was significantly more susceptible to ofloxacin and rifampin in recently infected host cells than in persistently infected cells. Persistently infected L929 cells were also treated with antibiotic combinations. Although ciprofloxacin and doxycycline had no synergistic effect on the Priscilla isolate, ciprofloxacin and rifampin acted synergistically. Collectively, these in vitro results are in accord with the fact that chronic Q fever in humans is generally not successfully managed with antibiotics. They also indicate that early diagnosis may be essential and that combination antibiotic therapy that includes quinolones may be effective in treating chronic Q fever.


BACKGROUND: The identification of etiologic agents of pneumonias acquired in the community (PAC) with risk factors is difficult. The classical diagnostic methods are not profitable and thus invasive techniques are used. In this study the diagnostic use of an invasive technique such as aspirative transthoracic puncture (ATP) was evaluated in this type of pneumonias. METHODS: In 94 patients of high risk suspect of PAC the ATP was carried out. This was performed with an ultrafine needle (25G) without radioscopic control. In all cases blood cultures, serology (Legionella, Mycoplasma pneumonias,
Coxiella burnetti, Chlamydia psittaci) were performed when atypical clinical manifestations were presented and sputum examination (Gram, Ziehl, culture) was undertaken when possible. RESULTS: The sensitivity of ATP was 36% and increased to 54.6% in cases previously untreated with antibiotics. Specificity was 96.4%. The sensitivity of blood culture was 8% and sputum 13.6%. ATP was well tolerated in 97.9% with complication in only 4 (4.3%). The results of ATP led to changes in treatment in 23.1% of the cases with definitive diagnosis of pneumonia. CONCLUSIONS: Aspirative transthoracic puncture with ultrafine needle without fluoroscopic control was a very well tolerated technique with a minimum number of complications, easy to perform at the patients bedside and was used to modify treatment in 23.1% of the cases.


A nested PCR method was developed for the detection of Coxiella burnetii in human serum samples. Two pairs of oligonucleotide primers were designed to amplify a 438-bp fragment of the com1 gene encoding a 27-kDa outer membrane protein of C. burnetii. The primers amplified the predicted fragments of 21 various strains of C. burnetii but did not react with DNA samples from other microorganisms. The 438-bp amplification products could be digested with restriction enzymes SspI and SalI. The utility of the nested PCR was evaluated by testing human serum samples. The com1 gene fragment was amplified from 135 (87%) of 155 indirect immunofluorescence test (IF)-positive serum samples and from 11 (11%) of 100 IF-negative serum samples. The nested PCR with primers targeted to the com1 gene appeared to be a sensitive, specific, and useful method for the detection of C. burnetii in serum samples.

The gene (com1) encoding a 27-kDa outer membrane protein in 21 strains of Coxiella burnetii from a variety of clinical and geographical sources was sequenced for strain differentiation. The com1 gene was highly conserved among all the strains tested but there were several differences in nucleotide and deduced amino acid sequences. Based on the com1 gene-specific nucleotides and deduced amino acids, the 21 strains were divided into four groups. Group 1 contained 14 strains originating from ticks, cattle and human cases of acute Q fever. Groups 2 and 3 included 2 and 3 strains, respectively, originating from human cases of chronic Q fever. Group 4 contained 2 strains originating from a human case of acute Q fever and a goat with abortion. The results indicated that the strains originating from ticks, cattle and human cases of acute Q fever differed at the molecular level from those of human chronic Q fever. This study suggests that a sequence analysis of the com1 gene can be used for strain differentiation of C. burnetii.