Q-Fever

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General

In some textbooks, Q fever is included among the rickettsiosis for historical reasons, but clinically the condition differs fundamentally from “typhus” presentations. In 1937, Derrick described a new and unusual febrile illness affecting abattoir workers in Brisbane, Australia. When the blood of these febrile patients was injected into guinea pigs the animals developed mild fever and splenomegaly. Burnet identified small, filterable rickettsial-like micro-organisms in the spleens of these infected animals. Cox cultured the bacteria in yolk sacs of embryonated hen’s eggs (the bacteria cannot be cultured on cell free media). Davis and Cox isolated the organism from ticks collected near Nile Mile Creek in Montana, USA. The disease is now called Q fever, where the Q refers to query because of the initial mysterious nature of the disease. Cox and Burnet have been honoured for their discoveries in the designation of the causal agent *Coxiella burnetii*.

Coxiella burnetii is a small (0.3-1.0 µm) pleomorphic **strict intracellular Gram-negative bacterium** that originally was classified among the *Rickettsiaceae*. More recent phylogenetic studies show that taxonomically the organism is only distantly related to the *Rickettsiae*. Gene-sequence analysis (16S rDNA) now classifies it in the order of the *Legionella*, family *Coxiellaceae*.

C. burnetii proliferates **intracellularly in an acidic vacuole** (phagolysosome, pH 4.8). Infection with this bacterium inhibits the normal final phagosome maturation step, and therefore the bacterium will survive. Interferon-gamma reverses this and allows intracellular killing of the bacterium. Interferon-gamma also induces the killing of *C. burnetii* through apoptosis of infected macrophages. The organism can survive for a long time as a spore (small-cell) in very unfavourable conditions in the environment. The small-cell and large-cell variants can be distinguished by electron microscopy. The large-cell variants multiply in host cells. These variants should not be confused with antigenic states phase I and II (see further).

Epidemiology

Reservoir

The reservoir is found in animals. Q fever is a **worldwide zoonosis**, although no endemic cases have occurred in New Zealand. Arthropods, fish, birds, rodents, marsupials, horses, dogs, cats, cattle, goats and other animals can be infected. The most important sources of infection for humans are cattle,

sheep and goats. In these animals, the uterus and mammary glands are primary sites in the chronic phase of infection. Infected mammals shed bacteria in urine, faeces, milk and birth products. High concentrations of *C. burnetii* (up to 109 bacteria per gram of tissue) can be found in the **placenta of infected mammals**. Bacterial spores can remain viable in **dust and dried faeces** for a very long time (years).

Transmission

Transmission **between animals often occurs through ticks**. There is often reactivation of an infection in pregnant animals. During parturition, an infectious aerosol can be formed. Inhalation of contaminated aerosols from parturient fluids of infected lifestock is important. Animal-to-human transmission of the infection then occurs **aerogenically**. There is apparently no human-to-human transmission. Very rarely transmission occurs from drinking contaminated milk. Inhalation of stirred up contaminated dust (e.g. sleeping in stables previously occupied by sheep, manure) is another risk factor. Persons most at risk for infection are farmers, people living downwind from farms and contaminated manure, straw or dust, laboratory personnel working with *C. burnetii* and abattoir workers.

The largest outbreak ever recorded started in Herpen, in the south of the Netherlands in 2007. It soon spread to two Dutch provinces Noord Brabant and Gelderland. Before 2007, about 15 cases per year were diagnosed in the country. This increased to 2357 human cases in 2009, luckily with “only” 6 deaths in this year. The epidemic continued in 2010. A considerable number of cases were urban. An official ban to spread manure from goat and sheep farms did not seem to achieve significant results. Other hygienic measures, particularly pregnant women avoiding contact with small ruminants have been applied. Limited vaccination of milking sheep and goats was undertaken in 2008. A massive vaccination program was undertaken in 2009 (see further, under prevention).

Q fever was studied by the military for its **potential as a biological weapon**.

Clinical aspects

Primary infection with *C. burnetii* is commonly asymptomatic. HIV patients appear to have a higher risk for symptomatic disease. The **incubation period is rather long** (14-26 days with an average of 15 days). Q fever does not cause direct vasculitis and the infection manifests itself differently from typhus. However, circulating immune complexes may occur which can lead to glomerulonephritis and leukocytoclastic vasculitis. There is no such thing as “classic Q fever”. Most symptomatic patients have a **self-limiting, febrile syndrome**, possibly with headache, nausea and losing weight ±

atypical pneumonia; similar to *Mycoplasma pneumoniae*, *Chlamydiae pneumoniae*, legionellosis or viral pneumonia. With pulmonary involvement, there is often no cough (cough occurs in only 25%), but in general the chest X-ray will be abnormal. **Hepatitis and endocarditis** also occur, as well as -albeit rarely- thyroiditis, orchitis, pancreatitis, myocarditis, pericarditis, SIADH, haemophagocytosis or erythema nodosum. Various **neurological** problems can occur, including optic neuritis and aseptic lymphocytic meningitis. In Q fever cerebrospinal fluid is often normal even though *C. burnetii* can be isolated from patient's cerebrospinal fluid. Encephalitis and/or cerebellitis can occur (often with ataxia). Severe headache and chronic tiredness are also frequently present. There is rarely rash and there is no chancre. Sometimes slight leukocytosis is present, but in most cases (75-90%) the white blood cell count is normal. Thrombocytopenia is present in approximately 1/3 of patients. Liver enzymes and creatine kinase levels can be elevated.

Cases of Q fever have been reported in pregnancy. Intrauterine transmission has been documented. The placenta can develop necrotic foci (vasculitis) and fetal infection is known. There is an increased risk of oligamnios, fetal miscarriage, abortion, prematurity, low birth weight and neonatal death. There is also a risk to the obstetrician delivering the baby. Long-term treatment with cotrimoxazole protects against maternal chronic Q fever, although it is only bacteriostatic and carries the risk of neonatal hyperbilirubinemia if used just before delivery.

Chronic Q fever develops in a minority (1-5%) and is defined as infection lasting for 6 months or more. The organs most commonly affected are heart, arteries (vascular aneurysm), bones (beware prothesis, osteomyelitis) and liver. In rare cases mixed cryoglobulinemia can occur. Chronic disease may develop insidiously months or years after the acute disease. In chronic Q fever with cardiac valve involvement, vegetations are only rarely found on echocardiography. Q fever endocarditis carries a high mortality and tends to occur in patients with pre-existing valvulopathy. Chronic Q fever is most likely to develop in those who are pregnant, immunocompromised (eg, patients receiving prolonged or high-dose corticosteroid therapy or tumour necrosis factor-alpha inhibitors), have underlying valvular or vascular disease or a prosthetic joint. In such patients, C. burnetii multiplies in macrophages and produces a prolonged bacteraemia; the resulting high levels of antibodies and immune complexes directed at the organism contribute to many of the symptoms.

Diagnosis

The diagnosis is extremely difficult and based on **specific serology**. The best approach is to look for **seroconversion**. IgM can remain positive for a very long time, even longer than one year in this infection (low titres). The serological response in acute infections is mainly IgM against phase II antigens, followed by IgG antibody to phase II antigen. In chronic infection there is a serological

response (IgG and to a lesser extent IgA) to phase I and II antigens. Phase I antigens are less immunogenic than phase II antigens. In patients convalescing from acute disease, phase I antibodies decrease rapidly. In patients with chronic disease, antiphase I titres remain raised as a consequence of constant antigenic stimulation. Immunofluorescence titres to phase I antigen of 1/800 or more are very suggestive of endocarditis, but the cut-off titres used in different labs are variable. As such a positive serology is a major criterion in the "modified Duke criteria" for endocarditis. Because of cross-reactivity between *Coxiella* and *Bartonella* antibodies, a positive *Bartonella*-serology in a patient in whom Q-fever endocarditis is suspected, paradoxically favours the diagnosis of Q-fever.
Remember: cats are sources of both *C. burnetii* and *B. henselae*. PCR can be performed on excised heart valve tissue or serum in the initial stage of the infection when serology reveals no or low level antibodies.

Diagnosis chronic Q fever:

1.Phase I IgG larger than or equal to 1/4096, or

2.Phase I IgG larger than phase II IgG, or

3.PCR *Coxiella burnetii* positive after one month of illness

Antigenic variation

Coxiella burnetii displays antigenic phase variation, similarly to the smooth and rough colonies of certain bacteria when they are cultured in Petri dishes. In animal or human infection, *C. burnetii* exhibits phase I and is very infectious, but after repeated passage in cells or embryonated eggs, it converts to the non-infectious phase II. This transition is associated with a chromosomal deletion. Phase I antigen is a polysaccharide component of lipopolysaccharide. When some carbohydrates are lost, phase II antigen appears. In acute Q fever antibodies against phase II predominate, but in chronic fever the highest titres are found against phase I antigens.

Suggestive but transient **"doughnut"-shaped granulomas** (fibrinoid ring formation) are sometimes detected by liver biopsy. In practice, most cases of Q fever are missed unless serology (IgG and IgM) is available. Culture is possible in embryonated hen's eggs and in various cell lines (human embryo fibroblast cells, green monkey kidney cells and others). However, in view of the infectious and dangerous nature of the organism, in vitro isolation is rarely performed. People who work (e.g. research) with *Coxiella burnetii* have an increased risk of becoming infected.

Treatment

The aim of treatment is **different in acute and chronic Q fever**.

In acute infection, bacteriostatic treatment will usually suffice for a clinical cure. Doxycycline is a good choice here (200 mg/day x 2-3 weeks). Clarithromycin or azithromycin are alternatives.

In chronic Q fever, a bacteriostatic treatment will probably control the disease but not cure it. Bactericidal therapy is preferable. Since the organism lives in a very acidic environment (pH of the phagolysosome = 4.8), an attempt may be made to alkalinise the vacuole, for example by the simultaneous administration of hydroxychloroquine. This will raise the pH from 4.8 to 5.7. In this way it is possible to render doxycycline bactericidal. The preferred treatment for chronic Q fever is hydroxychloroquine combined with doxycycline for at least 18 months (longer if antibody titre IgG remains > 1/800). QTc-time prolongations should be monitored.

In case of Q fever endocarditis, cardiac surgery will often be required. In pregnancy, treatment with cotrimoxazole will prevent fetal death and miscarriage, but this treatment will not prevent the development of chronic infection in the mother. Once the child is delivered, treatment with doxycycline plus hydroxychloroquine for one year will enable normal subsequent pregnancies.

Prevention

When an outbreak is identified, transport of manure in the area will be prohibited.

A formalin-inactivated whole cell vaccine from the Henzerling strain (Q vax) has been used in Australia. In November 2005, CSL Ltd in Australia (Commonwealth Serum Laboratories, the only producer in the world) announced to stop production of the vaccine for economic reasons, but the Australian government subsequently prevented this. In the Soviet Union, an avirulant variant of the Grita strain has been studied as a vaccine. However, the general public does not need to be vaccinated. Vaccination of people at risk (e.g. lab personnel) is useful. Prevaccination testing is advised, and includes history, serology and a skin test with dilute vaccine. In order to stem the large Dutch outbreak of 2007-2011, the Dutch government provided 400,000 vaccine doses in 2009 (Coxevac, a killed vaccine based on the Nile Miles strain).

Vaccination for humans are reserved for high risk professions (e.g. slaughterhouse workers) and patients with

1. previous endocarditis (non-Coxiella)
2. heart valve prothesis
3. congenital hear disease
4. aortic or mitral valve problem
5. aortic aneurysm
6. aortic prothesis

Contraindications for vaccination with Q-vax include pregnancy and previous Q-fever.

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