Q Fever

Q fever is a zoonosis normally acquired directly from farm animals. It is caused by the widely distributed Gram-negative bacteria *Coxiella burnetii*, an obligate intracellular parasite related to the genus *Rickettsia*. The disease was named as Q (for query) fever in 1937 when it was first described, "until fuller knowledge should allow a better name". It can cause acute or chronic disease in humans.

Q fever is important because it
- Has wide global impact.
- Is difficult to diagnose.
- Is extensively present in the animal kingdom.
- Has significant potential for use as a bioterrorism agent.
- Has acute and chronic stages: the acute stage is often unrecognised; the chronic stage is a rare (<5% of acute cases) but potentially serious or even fatal consequence.
- Prompt diagnosis shortens the acute stage and greatly reduces the likelihood of development of the chronic stage.

Pathogenesis

Q fever is a highly infectious zoonosis which globally is widely distributed in animal reservoirs:
- The main reservoirs are arthropods (mainly ticks), farm animals, particularly cattle, sheep and goats, and domestic pets (particularly cats, and particularly when giving birth).[1, 2]
- A recent study in England and Wales suggested that up to 21% of dairy herds are infected.[2]
- The animals rarely become ill, but the bacteria localise in the uterus and mammary glands and become reactivated during pregnancy.
- The bacterium can cause abortion in sheep and reproductive problems in cattle. Very high concentrations of *C. burnetii* are found in the placenta.
- Animals excrete the bacterium in urine, faeces, milk and amniotic fluid. After desiccation the micro-organism is aerosolised.
- Transmission is usually through inhaling the organism, although occasionally by ingesting raw milk.
- There is an incubation period of 1-6 weeks, after which acute Q fever develops, with a variety of clinical presentations which can make early diagnosis challenging.[1]

Epidemiology

- Q fever is considered largely an occupational disease of slaughterhouse, animal husbandry and animal research workers. However, outbreaks have been associated with intensive farming - particularly of goats - and even those visiting the affected farms have been affected.
- Cattle, sheep, and goats are the primary reservoirs, but infection has been confirmed in multiple vertebrate species, including wildlife, marine mammals, domestic mammals, birds, and reptiles, and many species of ticks. Any infected animal has the potential to transmit the pathogen via bacterial shedding. Human outbreaks have been epidemiologically linked to pigeons, dogs, and rabbits, and to exposure to infected parturient cats.[3]
- Infected animals are usually asymptomatic although reproductive disorders such as stillbirth, abortion and endometritis are associated. The highest organism shedding is in birth products.
- Person-to-person transmission of Q fever is possible but rarely reported, although infection of the genital tract has been documented both in animals and humans, and sexual transmission and transplacental transmission of disease have been reported.[3]
- Q fever is endemic in every part of the world except New Zealand. Cases have been reported in 45 countries on 5 continents and it is a significant problem in Australia.
**Incidence**

- Seasonal incidence of acute Q fever is greatest in the spring, presumably correlating with livestock birthing times.
- In the USA where the disease is notifiable 100-200 cases a year are notified in most years, although given the difficulties in diagnosis and the high percentage of asymptomatic, self-limiting cases, this is almost certainly an underestimate.
- In June 2006, the UK experienced its largest outbreak of Q fever with 138 cases associated with a slaughterhouse near Stirling in Scotland. The slaughterhouse had been processing post-parturition ewes which were thought to be the likely source.[4]
- The largest known outbreak of Q fever occurred in the South Netherlands from 2007-2010, with more than 4,000 cases, mainly associated with intensive goat farming. In the most affected areas, up to 15% of the population were affected, and 20% of notified cases were hospitalised. It is likely that there will be significant numbers of cases of chronic Q fever presenting over the next few years following on from this outbreak. Veterinary control measures introduced in the relevant area in 2009 - including mandatory vaccination of dairy goats and sheep and selective culling - probably ended the outbreak.[5]
- The USA had a significant multi-state outbreak in 2011 which seemed to begin with an abortion storm amongst goats on a farm in Washington State.[6]
- In a nationally representative sero-survey of otherwise healthy persons in 2004, 3.1% of the general adult US population had detectable antibodies to *C. burnetii*.[3]

**Importance in bioterrorism**

*C. burnetii* is globally widespread, highly infectious and resistant to physical breakdown, so although the culture process is laborious, large amounts of infectious material could potentially be produced. If used as an aerosolised biological weapon, it could provoke acute disabling non-fatal disease.

This is significant for populations, as Q fever can have fatal or debilitating consequences. Effective antibiotic treatment is available for the acute form of disease but not for the chronic complications. Vaccination and chemoprophylaxis in selected individuals may be used in the event of bioterrorism.[7]

It has been designated a category B bioterrorism agent, as an incapacitating agent:

- The incubation period depends on the dose.
- Incubation is usually 2-3 weeks, but ranges from 1-6 weeks.
- Although it has a low case fatality rate, it meets criteria such as ease of manufacture, stability in the environment, and ability to cause disease.
- *C. burnetii* is extremely resistant to physical stresses, including heat and desiccation and can survive in the environment for months to years. The bacteria can become airborne, travelling on wind currents for miles, resulting in distant outbreaks.

**Presentation**[3]

**Acute Q fever in adults**

Symptomatic Q fever is characterised by a wide variety of signs and symptoms, many of which are nonspecific. The most common are:[8]

- Onset of symptoms can be gradual or abrupt and severity varies.
- Mortality of acute Q fever is <2% but hospitalisation is commonly required.
- Most commonly, a nonspecific febrile illness with fever, fatigue, chills and myalgia the most common complaints.
- Fever lasts a median of 10 days (range 5-57 days): the duration increases with age.
- Severe debilitating headaches are common, often retro-orbital and associated with photophobia.
- Up to 20% develop a rash which may be maculopapular or purpuric.[5,9]
- Pneumonia is commonly associated and this may be a more common cause of community-acquired atypical pneumonia than is realised.
- Q fever pneumonia can range from mild to severe, and extrapulmonary manifestations of severe headache, myalgia, and arthralgia are common. Cough is dry. Upper respiratory signs are less likely. CXR changes are nonspecific.
- Hepatitis can be associated and may be clinically asymptomatic or present with hepatomegaly and (rarely) jaundice.
- Less frequently described clinical symptoms include pericarditis, myocarditis, aseptic meningitis, encephalitis, and cholecystitis.[10]
- The clinician suspecting Q fever must check for heart valve disease and immunosuppression because these conditions predispose to the development of endocarditis.

Rarer features include:

- Erythema nodosum.
- Guillain-Barre syndrome, neuritis (including optic, brachial, and mononeuritis multiplex), myelitis and peripheral neuropathy, polyradiculopathy, and extrapyramidal neurological disease.

**Q fever in pregnancy**[3]

- Q fever in pregnancy can cause miscarriage, premature deliveries, and stillbirths.
- Antibiotic treatment can reduce miscarriage rate. Transplacental transmission has been reported.
- Women of childbearing age who receive a diagnosis of acute Q fever should be advised to avoid pregnancy for at least one month after diagnosis and treatment.
Women infected with Q fever during pregnancy are at high risk for developing chronic Q fever. The earlier during pregnancy a woman is infected, the greater her risk for development of chronic disease. After a diagnosis of new-onset acute Q fever, treatment throughout pregnancy is recommended to decrease the risk of miscarriage, stillbirth or prematurity, as well as the risk for future development of chronic Q fever.

Q fever in children[3]
- Children with Q fever are less likely than adults to have symptoms.
- Symptomatic children have a flu-like illness, often with headache, weakness and cough, which is usually self-limiting but can relapse over several months.
- Gastrointestinal symptoms of abdominal pain, diarrhoea and vomiting and anorexia are common in children with acute Q fever.
- Severe manifestations in children are rare but, if they occur, include hepatitis, haemolytic uraemic syndrome, myocarditis, pericarditis, encephalitis, meningitis, haemophagocytosis, lymphadenitis, acalculous cholecystitis, and rhabdomyolysis.

Chronic Q fever[3]
- Chronic Q fever is rare, occurring in <5% of people with acute infection.
- It can occur months, years or even decades after the acute infection.
- It can occur after asymptomatic infection as well as after symptomatic infection.
- Endocarditis is the most common manifestation:
  - If untreated this leads to heart failure. It is invariably fatal if untreated.
  - Most affected patients have prosthetic heart valves or valvular abnormalities, particularly aortic bicuspis valves, mitral valve prolapse, and moderate mitral insufficiency.
  - Approximately 40% of persons with a known valvulopathy with an acute Q fever diagnosis subsequently develop infective endocarditis.
- The second most common form of chronic Q fever is infection of aneurysms or vascular prostheses:
  - Most affected patients are those with a prosthetic vascular graft or an arterial aneurysm.
  - This was the most common manifestation following the Netherlands outbreak of 2007-2010.
- The third most common manifestation is chronic Q fever infection after pregnancy.
- Other potential manifestations include chronic hepatitis, chronic vascular infections, osteomyelitis, osteoarthritis, and chronic pulmonary infections.

Clinical presentation of chronic Q fever endocarditis, as for any endocarditis, can be nonspecific and variable.[3] However, included are:
- Fever (70%).
- Hepatomegaly ± splenomegaly (50%).
- Clubbing (30%).
- Purpuric rash (vasculitic) in 20% of cases.
- Abdominal pain.
- Chest pain.
- Night sweats.
- Hepatosplenomegaly.
- Chronic Q fever is rarely reported in children, although when it does occur, osteomyelitis is one of the most common findings.

Investigations
Because of the nonspecific symptoms, healthcare providers typically do not suspect Q fever during the acute stage of the disease and diagnosis is often retrospective. However, in the acute phase, investigations may show:

Blood tests
- WCC raised in 1/3 of cases.
- Liver enzymes raised at 2-3 x normal; alkaline phosphatase raised in 70% of cases.
- Plasma sodium reduced in 28% of cases.
- Reactive thrombocytosis and microscopic haematuria are common.
- Hyperglobulinaemia of up to 60 g/L is commonly found and a useful diagnostic sign.

Serology
- The most commonly used means of confirming the diagnosis of acute Q fever is demonstration of a fourfold rise in phase II IgG by indirect immunofluorescence assay (IFA) between serum samples from the acute and convalescent phases taken 3-6 weeks apart.[3]
- This requirement - with often undetectable initial levels - forces definitive diagnosis to be retrospective.
- The IFA is commercially available and is the most commonly used method for serologic diagnosis of Q fever. Other methods such as PCR have proved disappointing.[3]
- Ideally, the first serum specimen should be taken during the first week of illness.
- Although this can be tested immediately, results often are negative or too low for detection.[11]
- Seroconversion typically occurs 7-15 days after symptoms appear: 90% of patients seroconvert by the third week of illness.[3]
- C. burnetii detection involves two antigens: phase I or phase II. Phase II antigen levels are higher than phase I in acute Q fever; the converse occurs in chronic Q fever.
After infection, antibodies may remain detectable for many years or even for life.

Other investigations
- Plain X-ray shows typical signs of bacterial pneumonia but rounded opacities are suggestive of Q fever.
- Chronic Q fever cases may test positive for rheumatoid factor, anti-smooth muscle, antinuclear or antimitochondrial antibodies, or circulating anticoagulant antibodies.

Management

Acute Q fever
- Most acute cases resolve in 2-3 weeks with or without treatment.
- Doxycycline 100 mg twice-daily for 14 days is recommended for acute illness.\[9\]
- Treatment is most effective if given within the first three days of symptoms. It shortens the illness, and reduces the risk of severe complications.
- Antibiotic treatment also hastens recovery from pneumonia.\[12\]
- In studies, doxycycline outperforms other antibiotics, including erythromycin.\[12, 13\]
- Starting antibiotic therapy after the third day of fever might not change the clinical outcome.
- Co-trimoxazole is recommended for children younger than 8 years (although even in these patients doxycycline is recommended for severe infections), and the newer macrolides might also prove useful.
- Other antibiotics which may be helpful in adults or children if doxycycline is contra-indicated are moxifloxacin, clarithromycin, trimethoprim/sulfamethoxazole, and rifampin.
- Anti-inflammatory agents could be useful when symptoms do not respond to antibiotics.
- Empirical treatment should be based on the presence of a clinically compatible syndrome but not in asymptomatic patients with positive titres alone.
- Treatment for acute Q fever is not routinely recommended for asymptomatic persons or for those whose symptoms have resolved, although it might be considered in those at high risk for developing chronic Q fever.
- However, because antibodies might remain detectable for months to years after infection, treatment should not be provided based solely on elevated titres without clinical manifestation of acute illness.\[3\]

Chronic Q fever\[3\]
- Healthy patients without identified risk factors for chronic illness should receive clinical and serologic evaluation approximately six months after diagnosis of acute infection, to look for potential progression to chronic disease.
- Patients with identified risk factors should be regularly monitored for at least two years and then advised to seek help should symptoms occur at any time, as they remain at high risk for chronic Q fever for life.
- Antibiotic treatment with doxycycline and hydroxychloroquine (100 mg of doxycycline twice daily with 200 mg of hydroxychloroquine three times daily) is recommended.
- Lifelong treatment has been recommended in the past but most guidance now recommends treatment for at least 18 months in patients with cardiac disease, but it may be shorter in other patients, dependent on serological response.
- Concomitant treatment with chloroquine increases the efficacy of doxycycline.
- Most patients treated with this regimen have photosensitivity, and regular heart and eye examinations are needed.
- Patients may take doxycycline with food to avoid stomach upset but should have no dairy products within two hours (before or after) of taking medication.
- Doxycycline should not be taken with antacids or bismuth-containing products, and patients should avoid taking it immediately before going to bed or lying down.
- Doxycycline can decrease the efficacy of hormonal contraceptives.
- Antibody titres should be measured every six months for first two years, with progressive decline (anti-phase I IgG) showing successful treatment.

Q fever during pregnancy
- This is treated with co-trimoxazole until delivery.
- Serology to detect recrudescence is needed in subsequent pregnancies.
- A year of doxycycline and chloroquine after delivery may prevent recrudescence.\[8\]
- Mothers should be advised that both C. burnetii and doxycycline are excreted in breast milk.

Prognosis
- Follow-up for life may be needed, particularly in patients with pre-existing heart valve abnormalities.
- Haemodynamic problems could require valve replacement, and pericarditis can cause cardiac tamponade and require urgent intervention.
- Post-Q fever fatigue syndrome has been reported in up to 20% of patients with acute Q fever and is the most common chronic outcome after acute infection.\[14\]
- In contrast to chronic Q fever, most patients with post-Q fever fatigue syndrome are previously healthy persons.
- Post-Q fever fatigue syndrome is a complex of symptoms dominated by a debilitating fatigue after symptomatic acute Q fever. It lasts beyond a year and may last for many years.
- Management strategies for post-Q fever fatigue syndrome might reflect those used for chronic fatigue syndrome, such as graded exercise therapy and cognitive behavioral therapy.\[3\]
- Mortality is <2% for the acute form, but much higher for the chronic form, at about 25%.

Prevention
Prevention involves implementation of safety standards and surveillance in high-risk situations

- Education about sources of infection - e.g., appropriate hygiene measures and disposal of sheep/goat birth products when farming.
- Vaccination of those whose occupation places them at high risk.
- Only those who are skin test negative are vaccinated to avoid side-effects. Side-effects include local reactions, and sterile abscesses with draining sinuses.
- Notification of cases through local reporting mechanisms.

Further reading & references

- Q fever deliberate release guidelines; Health Protection Agency (2010)
- Q Fever; Centers for Disease Control & Prevention
  2. Q Fever; Background Information; Public Health England, 14 June 2013
  3. Diagnosis and Management of Q Fever --- United States, 2013: Recommendations from CDC and the Q Fever Working Group
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Document ID: 2692 (v22)
Last Checked: 23/06/2014
Next Review: 22/06/2019

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