COXIELLA BURNETII

2.1 | Disease agent

- *Coxiella burnetii*

2.2 | Disease agent characteristics

- **Order:** Legionellales; **Family:** Coxillaceae.
- Small, Gram-negative, pleomorphic coccobacillus; obligate intracellular bacterium that replicates in macrophages and monocytes.
- **Size:** 0.3–0.7 μm in length.
- **Nucleic acid:** *Coxiella* genome is approximately 2000 kb.
- **Physicochemical properties:** Resistant to heat, low or high pH, 0.5% sodium hypochlorite, ultraviolet irradiation, desiccation, and sunlight because of the existence of a spore-like stage. Reported to survive for 7–10 months on wool at 15°–20°C, for more than 1 month on fresh meat in cold storage, and for 40 months in skim milk at room temperature.
- The microorganism has two antigenic forms: phase I and phase II. Phase I is the highly infectious form found in nature and has intact lipopolysaccharide (LPS) on the cell membrane, whereas phase II is laboratory-grown, attenuated, avirulent in animals, and has truncated LPS.
- Infected cells contain two structural forms of the bacterium: large cell variant (LCV) or vegetative forms, and small cell variant (SCV) or condensed forms. SCV released during lysis of infected cells result in the spore-like form found in the environment.

2.3 | Disease name

- Q fever

2.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Very low
- Public perception and/or regulatory concern regarding blood safety: Very low
- Public concern regarding disease agent: Low

2.5 | Background

- Described in 1935 by E. H. Derrick in abattoir workers in Australia as a disease of unknown origin and, therefore, termed “query fever.”

2.6 | Common human exposure routes

- Infection caused by inhalation of aerosols or contaminated dust containing air-borne bacteria derived from infected ruminants or their products. As few as a single inhaled organism may produce clinical illness.
- Bacteria are shed in milk, urine, and feces of infected animals. High numbers of organisms in the amniotic fluids and placenta during birthing (e.g., 10⁹ bacteria/g placenta).
- **Contact with contaminated wool or other fomites.**
- **Ingestion of unpasteurized contaminated dairy products (rare).**
- **Sexual transmission is possible.**

2.7 | Likelihood of secondary transmission

- Extremely rare but has occurred during postmortem examination to autopsy attendants.
- An obstetrician developed Q fever following delivery of an infant from a woman infected with *C. burnetii* during pregnancy. The index patient, hospitalized with an acute Q fever, is believed to have transmitted to another patient during their time in the same hospital room.
- **There was a single report of human-to-human transmission of Q fever within a household.**
- **Three health care providers involved with removal of an infected breast implant seroconverted.**
- **Sexual transmission has been reported.**

2.8 | At-risk populations

- Farmers, veterinarians, or those who handle potentially infected livestock, especially animals giving birth.
- During the 2007–2010 outbreak in the Netherlands the relative risk of infection if residing within 2 km versus >5 km of infected farms was 31. Abortion waves in

isolated in 1937 by Burnet and Freeman who identified the organism as a rickettsial species.
- Cox and Davis isolated the pathogen from ticks in Montana in 1938 and described its transmission. The agent was officially named *Coxiella burnetii* in 1948.
- No longer regarded as closely related to *Rickettsia* species.
- Classified as Category B bioterrorism agent by the CDC.
goats were confirmed as the primary source of human infection; nondairy sheep farms were involved to a lesser extent.

- Since a 2008 change in the case definition, up to 225 cases per year have been reported in the United States, most associated with ranching and other livestock-related activities.

### 2.9 Vector and reservoir involved

- Reservoirs for human infection include domestic ruminants, primarily cattle, sheep, and goats.
- Wildlife can also be infected, as well as domestic animals such as cats and dogs.
- Ticks may be involved in transmission among animals but are rarely involved in transmission to humans.

### 2.10 Blood phase

- Bacteremia has been documented during both acute and chronic infections, with and without symptoms.
- The organism replicates in macrophages. This could result in eventual cell lysis and the dissemination of free bacteria in plasma.

### 2.11 Survival/persistence in blood products

- Spiking experiments using whole blood and blood components (leukoreduced blood, plasma, and packed RBCs) indicate that C. burnetii remains viable and infectious at 1°C–6°C for at least 42 days of storage.

### 2.12 Transmission by blood transfusion

- A single case of transmission from blood transfusion was described in 1977. The donor and the recipient both showed serological evidence of C. burnetii infection, and the clinical symptoms and their time courses were compatible with the diagnosis of Q fever transmitted from the donor.
- Transfusion risk assessments have been published by the European CDC using the Dutch outbreak and data from 2008 to 2009 as the model.
- No cases of transfusion transmission during the epidemic in the Netherlands were recognized even in the face of extensive airborne transmission. Donor screening interventions including single unit NAT were developed and implemented.
- Testing data estimated that between 2 and 3 infections might have occurred during the epidemic peak years.
- Also reported to have been transmitted by bone marrow transplantation.
- Increased antibody prevalence in drug users, HIV-infected patients and those on dialysis further supports the possibility of parenteral transmission.
- The organism can be isolated from blood and DNA amplified by PCR during chronic endocarditis.
- During acute infection, C. burnetii can be detected by PCR in blood and serum up to 17 days after symptom onset.

### 2.13 Cases/frequency in population

- Q fever was made a nationally notifiable disease in the United States in 1999.
- In 2008, the Q fever case definition was changed to allow for the reporting of chronic and acute Q fever separately, and since the change, up to 225 cases per year have been reported in the United States, most associated with ranching and other livestock-related activities.
- In 2003–2004, the CDC estimated 3.1% seropositivity in the United States among healthy persons. Up to 20% of people in high-risk professions (e.g., veterinarians, ranchers) had elevated antibody titers from presumed past infection.
- Between 2000 and 2019, the CDC reported a total of 1756 confirmed human cases with peak months of April through June.
- In the Netherlands, the confirmed human case counts for 2007, 2008, 2009 and 2010, respectively were: 168, 1,000, 2,357 and 492 (to November 1, 2010). Cases were confirmed by both clinical and laboratory findings. Most of these cases occurred in the southern part of the country.
- Worldwide distribution except Antarctica and New Zealand.

### 2.14 Incubation period

- Dependent on dose; usually 2–3 weeks

### 2.15 Likelihood of clinical disease

- About 50% of acute infections are symptomatic.
2.16 | **Primary disease symptoms**

- Acute disease is characterized by fever (usually >40°C) and headache (usually retroorbital). The fever lasts approximately 2–14 days.
- Pneumonia or hepatitis is seen in more severe acute infections. Infrequently causes pericarditis, myocarditis. Neurological manifestations can occur in acute or chronic infection, but their frequency is debated.
- Endocarditis is the most important manifestation of chronic infection.
- Infections of vascular prostheses and aneurysms, osteomyelitis, hepatitis, interstitial pulmonary fibrosis, prolonged fever, and purpuric eruptions are also seen in chronic infection.

2.17 | **Severity of clinical disease**

- May progress to chronicity in approximately 2% of those infected if untreated, in which case the frequency of mortality increases. Chronic Q fever is defined as lasting >6 months.
- Chronic Q fever predominantly occurs in individuals with underlying valvular heart disease, vascular aneurysms, or vascular grafts manifesting primarily as culture-negative endocarditis.
- In 2009 in the Netherlands, the mortality rate was 0.25% (6 deaths in 2357 acute cases, all occurring in patients with underlying medical conditions). The hospitalization rate was 20%. The cumulative number of deaths due to Q fever in the Netherlands continued to increase through 2010, again in patients with underlying medical conditions.

2.18 | **Mortality**

- Less than 2% in acute infection
- Ranges from 5% to 60% in untreated chronic infection

2.19 | **Chronic carriage**

- A small percentage of those infected (<5%) develop chronic Q fever months or years following initial infection often leading to endocarditis.

2.20 | **Treatment available/efficacious**

- Doxycycline is preferred for acute infection. Fluoroquinolones, macrolides, and beta-lactams also have some activity.
- Prolonged courses of doxycycline with hydroxychloroquine are preferred for chronic infection.

2.21 | **Agent-specific screening question(s)**

- No specific question is in use.
- Not indicated because transfusion transmission is very infrequent, and incidence of infection in the population is low.
- No sensitive or specific question is feasible.
- Under circumstances of a bioterrorism threat, the need for and potential effectiveness of specific donor screening questions would need to be addressed.

2.22 | **Laboratory test(s) available**

- No FDA-licensed blood donor screening test exists.
  - Indirect immunofluorescence is sensitive and specific and is the method of choice.
  - The antibody titer is higher to phase II antigen than to phase I antigen in acute infection, whereas chronic Q fever is generally characterized by an elevated and continually rising IgG titer to phase I antigen.
  - Antibody levels differ significantly from person to person and some individuals may never produce antibodies to phase I antigen.
  - PCR is rapid, sensitive, and useful early in acute infections to evaluate whole blood or serum samples.
  - Isolation of bacteria is available but only in secure high containment facilities.

2.23 | **Currently recommended donor deferral period**

- No FDA Guidance or AABB Standard exists.
  - Prudent practice would be to defer donor until signs and symptoms are gone and a course of treatment is completed.

2.24 | **Impact on blood availability**

- Agent-specific screening question(s): Not applicable; in response to a bioterrorism threat, impact of a local deferral would be significant.
- Laboratory test(s) available: Not widely available.
2.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable but an unknown impact in response to a bioterrorism threat.
- Laboratory test(s) available: Not widely available
  - From March 15–November 1, 2010, Sanquin (the blood collector in the Netherlands) screened 5000 blood donations by an in-house, individual unit PCR assay in high-incidence areas after the peak of the epidemic. No confirmed positives were identified. However, 3 PCR-confirmed positive donors, who subsequently seroconverted, were identified during the trial of the PCR method in 2009 when 1000 donations were screened.
- Concern existed in the Netherlands with respect to chronic carriage following the 2007–2010 epidemic in which thousands of individuals became infected; asymptomatic infected individuals, who would not have cleared infection, may have carried high concentrations of the organism and posed a potential risk to blood, tissue, and organ recipients.

2.26 | Leukoreduction efficacy

- May have some efficacy because organism is an obligate intracellular bacterium in monocytes/macrophages, although cell-free organisms can survive for extended periods.

2.27 | Pathogen reduction efficacy for plasma derivatives

- Unknown, but the bacterium is resistant to heat and chemical/physical disinfection.

2.28 | Other prevention measures

- Control measures taken in the Netherlands during the 2007–2010 outbreak included mandatory small ruminant vaccination, animal movement restrictions, culling and hygiene measures.
- Bulk milk monitoring by PCR remains mandatory on farms with more than 50 dairy animals and notification of residents in affected areas occurs to enable those persons with risk factors to avoid infected farms.
- By 2010, the control measures reduced the outbreak to mild, but clinical cases continued to be reported at a level about that observed prior to 2007. So called “abortus storms” on goat farms no longer occur; however, a more diffuse spread of Q fever exists probably due to aerosol dissemination of the spore-like form of the organism from the soil of previously infected/currently infected farms. A human vaccine is available only in Australia (formalin-inactivated phase I organisms), and its use is recommended for exposed or high-risk individuals (livestock handlers, abattoir workers, veterinarians, and laboratory workers) who do not have immunity. Adverse effects may occur when vaccine is administered to previously infected individuals; requires pre-vaccination skin test.

SUGGESTED READING

6. CDC. Diagnosis and Management of Q Fever—United States. Recommendations from CDC and the Q Fever Working Group. 2013 Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/r6203a1.htm


