Coxiella burnetii

Disease Agent:

- *Coxiella burnetii*

Disease Agent Characteristics:

- Small, Gram-negative, pleomorphic coccobacillus; obligate intracellular bacterium that replicates in macrophages and monocytes.
- Order: Legionellales; Family: *Coxiellaceae*
- Size: 0.4-1.2 μm in length and 0.2-0.4 μm in width
- Nucleic acid: *Coxiella* genome is approximately 2000 kb.
- Physicochemical properties: Resistant to heat, low or high pH, 0.5% sodium hypochlorite, UV irradiation, and environmental conditions, such as desiccation, extreme temperatures, and sunlight, because of the presence 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 2 structural forms of the bacteria: 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.

Disease Name:

- Q fever

Priority Level:

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

Background:

- Described in 1935 by E. H. Derrick in abattoir workers in Australia as a disease of unknown origin and, therefore, termed "query fever."
- Isolated in 1937 by Burnet and Freeman who identified the organism as a *Rickettsia* 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.

Common Human Exposure Routes:

- Infection caused by inhalation of aerosols or contaminated dusts containing air-borne bacteria derived from infected ruminants or their products. 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., 10^9 bacteria/g placenta)
- Contact with contaminated wool or other fomites
- Ingestion of unpasteurized contaminated dairy products (rare)
- Sexual transmission is possible

Likelihood of Secondary Transmission:

- Extremely rare, but has occurred during autopsy and to autopsy attendants; very rarely occurred with care of infected patients. An obstetrician developed Q fever following delivery of a woman infected with *C. burnetii* during pregnancy and there is a single apparent human-to-human transmission of Q fever to members of a household.

At-Risk Populations:

- Farmers, veterinarians, or those who handle potentially infected livestock, especially animals giving birth
- During the 2007-2010 outbreak in the Netherlands, persons living within 5 km of dairy goat farms
    - Abortion waves in goats have been confirmed as the primary source of human infection; non-dairy sheep farms have been involved to a lesser extent. Living within 5 km of infected farms has accounted for 59% of cases although only 12% of the Dutch population live in these areas; the relative risk of infection if residing within 2 km vs >5 km of infected farms is 31.

Vector and Reservoir Involved:

- Reservoirs for human infection include domesticated 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.

Blood Phase:

- Bacteremia 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.

Survival/Persistence in Blood Products:

- No available information on storage stability under blood bank conditions.

Transmission by Blood Transfusion:

- A single case of transmission from blood transfusion has been 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 Centre for Disease Prevention and Control (ECDC) using the Dutch outbreak in 2008-2009 as the model.
- 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.

Cases/Frequency in Population:

- Fewer than 200 cases reported annually in the US from 1978-2009
- In 2003-2004, the CDC documented 3.1% seropositivity in the US.
- In the Netherlands, the confirmed human case counts for 2007, 2008, 2009 and 2010, respectively were: 168, 1000, 2,357 and 492 (to November 1, 2010). Cases are confirmed by both clinical and laboratory findings. Most of these cases have occurred, and continue to occur, in the southern part of the country.
- Worldwide distribution except Antarctica and New Zealand

Incubation Period:

- Very dependent on dose; estimated at 20 days (range: 14-39 days)

Likelihood of Clinical Disease:

- <50% of acute infections are symptomatic.

Primary Disease Symptoms:

- Acute disease is characterized by high fever (usually >40°C) and headache (usually retro-orbital). The fever lasts approximately 7-14 days. Other signs and symptoms may include hallucinations, diarrhea, weight loss, facial pain, and speech impairment. A rash is rarely observed in Q fever.
- 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.

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 disease is defined as Q fever 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 continues to increase through 2010, again all in patients with underlying medical conditions.

Mortality:

- Less than 1% in acute infection
- Ranges from 5-50% in untreated chronic infection

Chronic Carriage:

- Overall estimated rate of 1.86% following acute infection based on analysis of several studies

Treatment Available/Efficacious:

- Doxycycline for 2 weeks (acute illness) and doxycycline in combination with hydroxychloroquine (preferred for chronic infection). Rifampin and fluoroquinolones have been used with doxycycline for chronic infections but are less effective than hydroxychloroquine. Antibiotic treatment for 18 months to several years is required for chronic infection, depending on the regimen used.

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.

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening test exists.
- Available diagnostic tests include antibody testing (IgM/IgG) by complement fixation, indirect immunofluorescence, EIA, and immunohistochemical staining. 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. However, antibody levels differ significantly from person to person and some individuals may never produce antibodies to phase I antigen.
- PCR-based NAT 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.

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.

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

Impact on Blood Safety:

- Agent-specific screening question(s): Not applicable; 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. No confirmed positives were identified as a result of this measure after the peak of the epidemic. 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 exists in the Netherlands with respect to chronic carriage following the 2007-2010 epidemic in which thousands of individuals became infected; asymptomatic infected individuals, who may not have cleared infection, may carry high concentrations of the organism and may pose a risk to blood, tissue and organ donors. Such donors would be antibody positive and thus antibody screening may prove to be more efficacious than NAT screening but the impact of this measure on donor loss is unknown but likely to be appreciable.

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.

Pathogen Reduction Efficacy for Plasma Derivatives:

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

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. In 2010, the control measures have reduced the outbreak to mild, but clinical cases continue to be reported and are 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.
- 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:

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