

Rickettsia prowazekii

Disease Agent:

- *Rickettsia prowazekii*

Disease Agent Characteristics:

- Rickettsiae are obligate intracellular Gram-negative bacteria.
- Order: Rickettsiales; Family: Rickettsiaceae
- Size: 0.3 × 1.0 µm intracellular bacteria that take up Gram stain poorly
- Nucleic acid: Rickettsial genomes are among the smallest of bacteria at 1000-1600 kb. The *R. prowazekii* genome is 1100 kb.
- Physicochemical properties: Susceptible to 1% sodium hypochlorite, 70% ethanol, glutaraldehyde, formaldehyde and quaternary ammonium disinfectants. Sensitive to moist heat (121°C for at least 15 min) and dry heat (160-170°C for at least 1 hour). The organism is stable in tick tissues or blood under ambient environmental conditions, surviving up to 1 year; sensitive to drying (feces of infected ticks quickly lose their infectivity on drying).

Disease Name:

- Typhus, epidemic typhus, louse-borne typhus, typhus exanthematicus
- Brill-Zinsser disease is recrudescence of human typhus, occurring up to many years after initial infection as a result of chronic subclinical infection.
- A related disease, murine typhus occurs worldwide and is milder than epidemic typhus and is caused by *R. typhi*. It is a zoonosis maintained in rodents and transmitted via fleas.

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical
- Public perception and/or regulatory concern regarding blood safety: Absent
- Public concern regarding disease agent: Absent

Background:

- Can cause devastating human epidemics by louse-borne transmission under appropriate conditions.
- Typhus rickettsiae were studied as agents of biowarfare before and during World War II.
- Classified (Category B) as bioterrorism agent by the CDC.

Common Human Exposure Routes:

- Exposure to the feces of infected body lice. The lice are infected by a human blood meal. The rickettsiae reproduce in the louse gut epithelium. Infection occurs when louse feces are scratched into the skin, inoculated onto mucous membrane or inhaled.
- As a bioweapon, the agent can be aerosolized, with intent of infection through inhalation.
- Sporadic cases occur after exposure to flying squirrels, most likely as a result of exposure to squirrel flea feces. The organism has also been identified in ticks feeding on livestock in Africa.

Likelihood of Secondary Transmission:

- No evidence of direct person-to-person transmission
- Under crowded conditions, where bathing and washing clothes are difficult, and where lice are present, typhus can spread explosively.
- Recent outbreaks have occurred in a number of areas in the world under conditions of war and population displacement.

At-Risk Populations:

- Any population in which weather and living conditions favor the presence and activity of infected body lice
- A threat as a bioterrorist weapon for susceptible populations

Vector and Reservoir Involved:

- The body louse, *Pediculus humanus corporis*, is the vector and chronically infected humans are the most important reservoir.
- Lice live in clothing take multiple blood meals per day, acquire infection from their blood meal, excrete *R. prowazekii* in feces, and abandon febrile hosts for other hosts. Infected body lice eventually succumb to their *R. prowazekii* infections so do not function as a major reservoir.
- Other reservoirs for *R. prowazekii* include Southern flying squirrels (*Glaucomys volans*) in the Americas and ticks feeding on livestock in Africa.

Blood Phase:

- *R. prowazekii* infects endothelial cells releasing progeny into the blood, from which they can be isolated. Data are lacking regarding bacteremia during the incubation period of acute infection.
- The blood phase is the source of infection of the lice and subsequent transmission to other humans.
- Acute disease is symptomatic, but clinically recovered individuals may have persistent infection for years.

- *R. prowazekii* has been isolated from otherwise healthy individuals whose infection could only have been remote.

Survival/Persistence in Blood Products:

- No data are available.

Transmission by Blood Transfusion:

- Theoretical; experimentally transmitted to non-human primates and other animals

Cases/Frequency in Population:

- Rare in the US
- Occasional cases arising from exposure to flying squirrels, usually during the colder months
- Outbreaks in Africa and the republics of the former USSR
- Active foci in South and Central America
- Potential occurrence in jails, refugee camps, and anywhere people are crowded under poor sanitary and hygienic conditions
- Used as a biologic weapon, a focal outbreak with narrow epidemic curve would be expected.

Incubation Period:

- Range of 5-23 days, usually 10-14 days
- Onset often sudden, but may vary
- Incubation period for recrudescence Brill-Zinsser disease can be decades after apparent recovery from acute infection.

Likelihood of Clinical Disease:

- Experimental infections in humans suggest clinical illness is nearly universal following infection.
- If bacteremia is present during an asymptomatic prodrome (before the onset of acute disease), the likelihood of clinical disease in a nonimmune recipient seems high.

Primary Disease Symptoms:

- Fever, chills, headache, and severe myalgia are prominent.
- Macular rash, with onset at 4-6 days, starting on the trunk and spreading centrifugally, but usually sparing the palms and soles. Not recognized in 30-70% of cases
- Conjunctival injection and conjunctivitis common
- Primary symptoms often accompanied by dry mouth, nausea and vomiting, and constipation
- Patient may appear toxic, with apathy, delirium, cough, and hemorrhagic rash (microvascular injury), leading to coma and death in the untreated.
- Complications include pneumonitis and myocarditis. Cough is frequent, and chest x-ray may demonstrate infiltrates.

- Spontaneous recovery is associated with rapid defervescence at 2 weeks, with similar but earlier response with antibiotic treatment.
- Brill-Zinsser disease, recrudescence typhus, is usually a milder disease with similar symptoms.
- Naturally acquired disease from the flying squirrel reservoir is milder, and the rash may be more maculopapular.

Severity of Disease:

- Acute infection appears to be uniformly symptomatic, but seroconversion without definite history of typhus is recognized in endemic areas.
- Chronic infection generally asymptomatic, except for development of Brill-Zinsser syndrome

Mortality:

- Untreated mortality ranges between 10 and 40% and correlates with age. With treatment, case mortality ranges from 2 to 4%.
- Mortality from Brill-Zinsser disease and typhus of flying squirrel origin is rare.

Chronic Carriage:

- Up to 40 years or longer

Treatment Available/Efficacious:

- Antibiotic treatment with a tetracycline, such as doxycycline, is effective at lowering acute mortality from 10-40% to <5%. Chloramphenicol is an alternative agent. A 7-10 day course of appropriate antibiotic therapy is curative. Relapses or chronic disease may occur with shorter courses of treatment.

Agent-Specific Screening Question(s):

- No specific question is in use.
- Not indicated because transfusion transmission has not been demonstrated.
- No sensitive or specific question is feasible.
- Under specific circumstances of exposure in an epidemic environment, 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.
- Serologic tests are used for diagnosis:
 - Antibodies are measurable at 2 weeks.
 - Cross-reactions on antibody tests for *R. prowazekii* occur, especially with *R. typhi* (up to 50%).
 - Cross-absorption studies can differentiate between *R. prowazekii* and *R. typhi* antibodies, but are very resource intensive.

- IFA remains the standard test for diagnosing infection with *R. prowazekii*; specific IgM can be identified by this method.
- Latex fixation assays are also available.
- EIA tests have been developed and these are sensitive and specific and allow differentiation of IgG and IgM antibodies.
- Serologic tests utilizing specific monoclonal antibodies for epitope saturation are under development.
- Direct detection:
 - Isolation in cell culture, animals, and embryonated chicken eggs
 - Immunofluorescence and immunoperoxidase staining can demonstrate organisms in tissue.
 - Shell vial culture techniques have been proposed. However, utilization of culture techniques is limited by the requirement for biosafety level 3 conditions.
- NAT for whole blood, blood clots and serum
 - Nested PCR with specific primers performed on skin biopsies has allowed determination of rickettsial species.
 - NAT is the only potentially rapid and specific practical approach to early diagnosis.

Currently Recommended Donor Deferral Period:

- No FDA Guidance or AABB Standard exists.
- If optimal therapy was administered, prudent practice would be to defer the donor until signs and symptoms are gone, and the treatment course is completed. However, in light of the chronicity of infection (i.e., Brill-Zinsser disease), a permanent deferral should be considered for infected persons without documentation of optimal therapy.

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 applicable

Impact on Blood Safety:

- Agent-specific screening question(s): Not applicable; unknown impact in response to a bioterrorism threat
- Laboratory test(s) available: Not applicable

Leukoreduction Efficacy:

- No data are available.

Pathogen Reduction Efficacy for Plasma Derivatives:

- No data available for this organism, but fractionation and inactivation techniques in use for plasma derivatives should be robust against an intracellular bacterium.

Other Prevention Measures:

- Measures to maintain hygiene and prevent or control louse infestations are critical.
- Riboflavin/light has been effective in inactivating *Orientia tsutsugamushi*, a related organism.
- The agent would likely be susceptible to inactivation strategies designed to remove WBCs and kill bacteria.

Suggested Reading:

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