5 | **RICKETTSIA PROWAZEKII**

### 5.1 Disease agent

- *Rickettsia prowazekii*

### 5.2 Disease agent characteristics

- **Order:** Rickettsiales; **Family:** Rickettsiaceae.
- *Rickettsiae* are obligate intracellular Gram-negative bacteria that take up Gram stain poorly.
- **Size:** 0.3–1.0 μm diameter by 0.8–2.0 μm length.
- **Nucleic acid:** Rickettsial genomes are among the smallest of bacteria at 1000 to-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 h).
- An extracellular dormant form remains infectious in louse feces for months or longer.

### 5.3 Disease name

- Typhus, epidemic typhus, louse-borne typhus, typhus exanthematicus, jail fever.
- Brill-Zinssser disease is recrudescent human typhus, occurring months or 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.

### 5.4 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

### 5.5 Background

- Can cause devastating human epidemics by louse-borne transmission under appropriate conditions.
- Typhus was studied as an agent of biowarfare before and during World War II.

### 5.6 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 membranes of the mouth or eyes, or inhaled.
- As a bioweapon, the agent can be aerosolized, with the intent of infection through inhalation.
- Sporadic cases occur after exposure to flying squirrels. The exact mechanism of transmission from flying squirrels to humans is not specifically known.

### 5.7 Likelihood of secondary transmission

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

### 5.8 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.

### 5.9 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.
- The primary reservoir for *R. prowazekii* in the Americas is the Southern flying squirrel (*Glaucomys volans*).

* *Rickettsia prowazekii* has been classified as a Category B bioterrorism agent by the CDC due to its mode of transmission via inhalation, low infectious dose, and high morbidity and mortality.*
5.10 | Blood phase

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

5.11 | Survival/persistence in blood products

- No data are available.

5.12 | Transmission by blood transfusion

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

5.13 | Cases/frequency in population

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

5.14 | Incubation period

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

5.15 | 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 is high.

5.16 | 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, recrudescent 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.

5.17 | 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.

5.18 | 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.
5.19 | Chronic carriage

- Up to 40 years or longer.

5.20 | Treatment available/efficacious

- Doxycycline is the first-line treatment for typhus. A 7–10 day course is regarded as curative.
- Critically ill patients may have marked capillary permeability and can easily succumb to pulmonary and cerebral edema. Response to therapy is prompt. Clinical failures with azithromycin therapy have been reported. Macrolides are not recommended therapy for \textit{R. prowazekii} infection.

5.21 | 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.

5.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Serologic tests are used for diagnosis:
  - Antibodies are measurable at 2 weeks.
  - A four-fold rise between acute and convalescent titers is diagnostic.
  - Cross-reactions on antibody tests for \textit{R. prowazekii} occur, especially with \textit{R. typhi} (up to 50%).
  - Cross-absorption studies can differentiate between \textit{R. prowazekii} and \textit{R. typhi} antibodies but are very resource intensive.
  - Immunofluorescence assay remains the standard test for diagnosing infection with \textit{R. prowazekii}; specific IgM can be identified by this method.
  - Microagglutination and latex agglutination assays are available.
  - Enzyme immunoassay tests have been developed and these are sensitive and specific and allow differentiation of IgG and IgM antibodies.
  - 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 polymerase chain reaction with specific primers performed on skin biopsies allows determination of rickettsial species.
  - NAT is the only potentially rapid and specific practical approach to early diagnosis.

5.23 | 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, considering the chronicity of infection (i.e., Brill–Zinsser disease), a permanent deferral should be considered for infected persons without documentation of optimal therapy.

5.24 | 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 applicable.

5.25 | 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

5.26 | Leukoreduction efficacy

- No data are available.

5.27 | 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.
5.28 Other prevention measures

- Measures to maintain hygiene and prevent or control louse infestations are critical.
- Riboflavin and ultraviolet (UV) light (available outside the US) have been effective in inactivating Orienteria tsutsugamushi, a related organism.
- Amotosalen and UV light used to treat platelet concentrates reduced infectivity in mice by a factor of 10^5 in RBCs, platelets and plasma in Orientia tsutsugamushi, a related organism.
- The agent would likely be susceptible to inactivation strategies designed to remove WBCs and kill bacteria.

SUGGESTED READING