

## *Rickettsia rickettsii*

### Disease Agent:

- *Rickettsia rickettsii*

### Disease Agent Characteristics:

- Rickettsia are obligate intracellular Gram-negative bacteria.
- Order: Rickettsiales; Family: Rickettsiaceae
- Size:  $0.3 \times 1.0 \mu\text{m}$  intracellular bacteria that stain poorly
- Nucleic acid: Rickettsial genomes are among the smallest of bacteria at 1000-1600 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:

- Rocky Mountain spotted fever (RMSF)
- Brazilian spotted fever or São Paulo fever (Brazil), Tobia fever (Colombia), Fiebre manchada (Mexico)

### 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: Absent/Low, but higher in selected areas

### Background:

- First described in the Snake River Valley (Idaho) in 1896
- First available test was the Weil-Felix test (agglutination of certain *Proteus vulgaris* strains), described in 1921
- Endemic in the US and in several other parts of the Western hemisphere: Canada, Mexico, Costa Rica, Panama, Colombia, Brazil, and Argentina; in the US, *Rickettsia rickettsii* has become more common in the central southwest and south Atlantic states than in the Rocky Mountains.
- In many parts of the world, it is considered as an emergent or re-emergent disease.
- Classified (Category B) as bioterrorism agent by the CDC.

### Common Human Exposure Routes:

- Adult stage of ticks feed on humans, to whom they transmit the agent during a prolonged period of feeding (usually for 1 to 2 weeks).
- Rickettsiae are injected from salivary glands of an infected tick into the human bloodstream only after 6 to 10 hours that the tick is feeding (the so-called *grace period*).
- A few cases describing infection by aerosols in the laboratory exist.
- Only one case reported by blood transfusion

### Likelihood of Secondary Transmission:

- Low

### At-Risk Populations:

- Initially restricted to rural residents
- More recently, urban populations exposed to open spaces (parks, open sports areas, fishing ponds) surrounded by bushes, domestic animals, and large rodents
- Animal care workers (dogs, horses, cattle), agricultural workers in open fields, and ecological tourists
- A threat as a bioterrorist weapon for susceptible populations

### Vector and Reservoir Involved:

- Ticks (primarily *Dermacentor* species) are the main vectors in the US.
- Ticks also are the agent reservoir, given that there are tick-to-tick mechanisms of transmission, allowing infection to all four tick life-cycle stages (eggs, larvae, nymphs, and adults).
- Usually, only 1-5% of ticks are infected by *Rickettsia rickettsii*, even in high incidence areas.
- The main tick species involved in transmission are:
  - *Dermacentor variabilis* (American dog tick)—eastern and far west US. Dogs and medium-sized mammals are preferred hosts.
  - *Dermacentor andersoni* (Rocky mountain wood tick)—western US states and southwestern Canada. Small rodents and large mammals are preferred hosts.
  - *Rhipicephalus sanguineus* (Brown dog tick)—Mexico, US (Arizona) and Europe. This is a newly recognized vector in the US.
  - *Amblyomma cajennense*—South America
- Other reservoirs include wild rodents (e.g., capybaras), dogs, horses and donkeys
- Humans are not considered as reservoirs, only accidental hosts.

**Blood Phase:**

- Bacteremia is present for up to 9 days, including several days during the incubation period prior to the onset of symptoms.

**Survival/Persistence in Blood Products:**

- Viability in blood at 4°C for at least 9 days is demonstrated by transmission of RMSF in the single reported case. A fraction of this unit kept refrigerated to 21 days did not transmit to three male guinea pigs.

**Transmission by Blood Transfusion:**

- The only known case was from a donor who donated blood 3 days before the clinical onset of RMSE
  - The donor reported tick removal 18 hours after a whole blood donation and subsequently died after 7 days. *Rickettsia rickettsii* was identified in several tissues by IFA.
  - The recipient became mildly ill 6 days after transfusion and fully recovered after appropriate antibiotic treatment (starting at the fourth day of illness).
- In 1997, an investigation of 377 National Guard blood donors at Fort Chaffee, AR, identified 10 recipients of units from donors later identified as probable RMSF cases. No recipient was infected, although the infection status of the donors at the time they were bled is unknown.

**Cases/Frequency in Population:**

- Between 1996 and 2000, the number of cases of RMSF reported in the US was between 400 and 600 cases per year. The number of recognized cases increased to over 1000 in 2002.
- More than 90% of cases in the US are reported during April through September
- Despite the name “Rocky Mountain Spotted Fever,” during recent decades cases have predominated in the southern Atlantic states (especially N. and S. Carolina) and lower Midwest (especially Missouri, Arkansas, and Oklahoma).

**Incubation Period:**

- Median of 7 days (range: 2-14 days), Partially related to the inoculum size

**Likelihood of Clinical Disease:**

- Seroprevalence studies demonstrate that there are many asymptomatic cases (up to 95% in some areas).
- Mild symptoms are also frequent, but not recognized as RMSE.

**Primary Disease Symptoms:**

- Classical triad includes fever, severe headache, and rash.
- The main targets for infection are vascular endothelial cells, responsible for the typical maculopapular rash.
- Rash is fully present up to 5 days after the onset of fever, though cases without rash can be observed in elderly or African-American patients, and usually associated with more severe cases, probably because of the late diagnosis in the absence of typical rash.

**Severity of Clinical Disease:**

- High, especially when recognition and appropriate treatment are delayed
- Because of endothelial injury with increased vascular permeability, the resulting outcome is edema, hypovolemia, hypotension, and hypoalbuminemia
- Main target organs for serious disease are:
  - Lungs (leading to noncardiogenic pulmonary edema, interstitial pneumonia, pleural infusion, and adult respiratory distress)
  - Heart (myocarditis)
  - Central nervous system (focal neurologic deficits, transient deafness, meningismus, and photophobia)
  - Gastrointestinal tract (nausea, vomiting, abdominal pain, diarrhea, sometimes resembling an acute gastroenteritis or acute surgical abdomen)
  - Pancreas
  - Liver (hepatomegaly and jaundice)
  - Kidneys (prerenal kidney failure and acute tubular necrosis)
  - Thrombocytopenia is observed in approximately 50% of cases.
  - Activation of coagulant cascade due to endothelial damage is also observed in the most severe cases, usually after a long period between onset of symptoms and diagnosis.
  - Damage to the microcirculation may evolve to necrosis and gangrene of digits or limbs.

**Mortality:**

- Approximately 65% in untreated patients
- Decreased since the advent of chloramphenicol and tetracyclines (especially doxycycline), but still remains around 5% in the US
- Usually occurs after 8-15 days, especially when there is a late diagnosis with delay of appropriate therapy
- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more susceptible to fulminant disease.

- A recent outbreak in Brazil, with absence or late onset of rash in most cases and other classical symptoms led to late diagnosis and treatment with a mortality rate up to 42%.
- Other predictive factors for poor outcome include older age, and failure to recognize tick bites.

**Chronic Carriage:**

- No

**Treatment Available/Efficacious:**

- Tetracyclines (e.g., doxycycline) and chloramphenicol have reduced the mortality from 65% to 5% in the US.

**Agent-Specific Screening Question(s):**

- No specific question is in use.
- Not indicated because transfusion transmission is limited to a single reported case.
- No sensitive or specific question is feasible. In endemic areas, a question on exposure to tick bites has been shown to be ineffective in distinguishing *Babesia*-infected from *Babesia*-uninfected donors. This question probably also lacks sensitivity and specificity for *Rickettsia rickettsii*.
- 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.
- Antibodies are detected only after the second week of illness. All available tests show a considerable cross-reactivity among different rickettsiae and different bacteria (e.g., *Proteus* species, *Brucella* species).
- Available tests include the following:
  - Complement fixation
  - IFA
  - Latex agglutination
  - EIA
  - Western blot
  - NAT—both for whole blood samples (limit of detection: 50-500 organism/mL) or fresh skin biopsies (higher sensitivity)
- Given that antibodies develop only after the onset of disease, asymptomatic infected donors will not be detected by serology.
- Should a screening procedure be required, molecular methods (NAT) will be the strongest candidates, however, sensitivity is still inadequate.
- Direct identification of the agent includes isolation of *R. rickettsii* in embryonic hen's eggs, cell culture, and by the shell vial culture technique. These methods take days or weeks to detect organisms.

**Currently Recommended Donor Deferral Period:**

- No FDA Guidance or AABB Standard exists.
- Prudent practice would be to defer the donor until signs and symptoms are gone and a course of treatment is completed.
- In focal outbreaks a different policy may be appropriate. At the time of the recognition of the events at Fort Chaffee, AR, in 1997, a recall of components collected during the deployment was undertaken, and FDA recommended that exposed individuals not donate blood for 4 weeks after departure from the area.

**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): Not applicable

**Leukoreduction Efficacy:**

- Unknown, but may be useful as leukoreduction has been shown to have some efficacy in vitro in the case of *Orientia tsutsugamushi*.

**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 bacteria

**Other Prevention Measures:**

- Tick avoidance measures (e.g., long pants, long sleeves, insect repellent)
- Riboflavin/light has been effective in vitro in inactivating *Orientia tsutsugamushi*, a related organism.

**Suggested Reading:**

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5. Leiby DA, Gill JE. Transfusion-transmitted tick-borne infections: a cornucopia of threats. *Transf Med Rev* 2004;8:293-306.
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