

## 6 | *RICKETTSIA RICKETTSII*

### 6.1 | Disease agent

- *Rickettsia rickettsii*

### 6.2 | Disease agent characteristics

- Order: Rickettsiales; Family: *Rickettsiaceae*
- *Rickettsia* are obligate intracellular Gram-negative bacteria that take up Gram stain poorly.
- Size: 0.3–1.0 μm × 0.8–2.0 μm
- Nucleic acid: Rickettsial genomes are among the smallest of bacteria, most at 1000–1600 kb; however, *R. rickettsia* is 2100 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). 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.

### 6.3 | Disease name

- Rocky Mountain spotted fever (RMSF)
- Other spotted fever Rickettsioses (SFR) are clinically very similar to RMSF. They are caused by closely related *rickettsiae*; for example, Tidewater spotted fever (*R. parkeri*) and Brazilian spotted fever or São Paulo fever (Brazil), Tobia fever (Colombia), fiebre manchada (Mexico) and Pacific Coast tick fever.

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

### 6.5 | Background

- *R. rickettsia* is one of the most pathogenic *rickettsia* strains, first described in the Snake River Valley (Idaho) in 1896 with the first clinical description reported in 1899. Wolbach is credited for the first

detailed description of the pathogen recognizing it as an intracellular bacterium most frequently seen in endothelial cells.

- First available test was the Weil-Felix test (agglutination of certain *Proteus vulgaris* strains), described in 1921.
- Endemic in the United States and a large majority of the Western hemisphere: Canada, Mexico, Costa Rica, Panama, Colombia, Brazil, and Argentina; in the United States, *R. rickettsii* has become more common in the central southwest and south Atlantic states than in the Rocky Mountains. It is also present in small areas of the Eastern hemisphere.
- In many parts of the world, it is considered as an emergent or re-emergent disease.
- Classified (Category B) as a bioterrorism agent by the CDC.

### 6.6 | Common human exposure routes

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

### 6.7 | Likelihood of secondary transmission

- Low

### 6.8 | 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
- People over 40 years account for the highest number of reported cases; however, children under 10 represent the highest number of reported deaths.
- Persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency

- A threat as a bioterrorist weapon for susceptible populations

## 6.9 | Vector and reservoir involved

- Hard-bodied ticks (primarily *Dermacentor* species) are the main vectors in the United States.
- 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 ixodid tick species involved in transmission are:
  - *Dermacentor variabilis* (American dog tick)—eastern and far west US. Dogs and medium-sized mammals are the preferred hosts.
  - *Dermacentor andersoni* (Rocky Mountain wood tick)—western US states and southwestern Canada. Small rodents and large mammals are the preferred hosts.
  - *Rhipicephalus sanguineus* (Brown dog tick)—Mexico, US (Arizona) and Europe. This is a newly recognized vector in the United States.
  - *Amblyomma cajennense*—South America
- Other reservoirs include wild rodents (e.g., capybaras), dogs, horses, and donkeys.
- Humans are not considered reservoirs, only accidental hosts.

## 6.10 | Blood phase

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

## 6.11 | 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.

## 6.12 | Transmission by blood transfusion

- The only known case was from a donor who donated blood 3 days before the clinical onset of RMSF.

- The donor reported tick removal 18 h after a whole blood donation and subsequently died after 6 days. *R. 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 on the fourth day of illness).
- In 1997, an investigation of 377 National Guard blood donors at Fort Chaffee, Arkansas, 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. The outbreak was subsequently attributed to HME.

## 6.13 | Cases/frequency in population

- As of January 1, 2010, cases of RMSF reported in the United States are now categorized under SFR that include RMSF, *R. parkeri* rickettsiosis, Pacific Coast tick fever, and *rickettsia* pox.
- Because most commonly available serologic tests lack the ability to differentiate the spotted fever group *Rickettsia* species, SFR reports may include less severe spotted fevers. The number of SFR cases has risen in the past two decades, from 495 cases in 2000–6248 in 2017.
- More than 90% of cases in the United States are reported from May through August.
- Despite the name “Rocky Mountain spotted fever,” cases occur throughout the US, but are most commonly reported from Arkansas, Missouri, North Carolina, Oklahoma, and Tennessee. These five states account for more than 60% of the reported SFR cases. Over the last few years, RMSF has become increasingly common in certain areas of Arizona, where the number of cases peaks from April through October.

## 6.14 | Incubation period

- Median of 7 days (range 2–14 days), partially related to the inoculum size.

## 6.15 | 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 RMSF.

## 6.16 | Primary disease symptoms

- Classical triad includes high 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.

## 6.17 | 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, photophobia, and cerebral edema)
  - Gastrointestinal tract (nausea, vomiting, abdominal pain, and diarrhea, sometimes resembling an acute gastroenteritis or acute surgical abdomen)
  - Pancreas
  - Liver (hepatomegaly and jaundice; elevated hepatic transaminases)
  - 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.

## 6.18 | Mortality

- Approximately 65% in untreated patients
- Decreased since the advent of chloramphenicol and tetracyclines (especially doxycycline), but remains around 5%–10% in the United States. The inclusion of

less severe spotted fevers likely leads to the underestimation of case fatality rates in recent decades.

- Usually occurs after 8–15 days, especially when there is a late diagnosis with a delay of appropriate therapy
- Patients with G6PD deficiency are more susceptible to fulminant disease.
- A recent outbreak in Brazil, with the 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 outcomes include older age, and failure to recognize tick bites.

## 6.19 | Chronic carriage

- No

## 6.20 | Treatment available/efficacious

- Doxycycline is the first line treatment for all suspected RMSF in patients of all ages. Treatment should start within the first 5 days of illness as delay in treatment may result in severe illness or death and should continue for at least 3 days after fever subsides and until there is evidence of clinical improvement. Minimum course of treatment is 5–7 days.

## 6.21 | 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 *R. rickettsii* and other tickborne diseases.
- Under circumstances of a bioterrorism threat, the need for, and potential effectiveness of, specific donor screening questions would need to be addressed.

## 6.22 | Laboratory test(s) available

- The CDC states that the diagnosis of RMSF must be made based on clinical signs and symptoms and then later confirmed using specialized laboratory tests.

- 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:
  - Immunofluorescence assay—considered the reference standard by the CDC
  - Complement fixation
  - Latex agglutination
  - Enzyme immunoassay
  - Western blot
  - Nucleic acid test (NAT)—both for whole blood samples (limit of detection: 50–500 organism/mL) or fresh skin biopsies (higher sensitivity)
  - Pan-rickettsial and *R. rickettsii*-specific polymerase chain reaction assays are available at some local and state health departments.
- 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 may be 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.

### 6.23 | 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, Arkansas, 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.

### 6.24 | 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

### 6.25 | Impact on blood safety

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

### 6.26 | Leukoreduction efficacy

- No data are available

### 6.27 | 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.

### 6.28 | Other prevention measures

- Tick avoidance measures (e.g., long pants, long sleeves, insect repellent)

### SUGGESTED READING

1. Arguin PM, Singleton J, Rotz LD, Marston E, Treadwell TA, Slater K. An investigation into the possibility of transmission of tick-borne pathogens via blood transfusion. Transfusion-associated tick-borne illness task force. *Transfusion*. 1999;39:828–33.
2. Centers for Disease Control and Prevention. Rocky mountain spotted fever (RMSF). 2021 Available from: <http://www.cdc.gov/rmsf/index.html>
3. Centers for Disease Control and Prevention. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States: a practical guide for health care and public health professionals. *MMWR*. 2016;65:(No. RR-2).
4. Dumler JS, Walker DH. Rocky Mountain spotted fever—changing ecology and persisting virulence. *N Eng J Med*. 2005;353:551–3.
5. Herbert FL, Thangam M, Aisenberg GM. Pathogens transmitted in red blood cell transfusions: an up-to-date table. *Proc (Bayl Univ Med Cent)*. 2018;31(3):307–9.
6. Leiby DA, Chung AP, Cable RG, Trouern-Trend J, McCullough J, Homer MJ, et al. Relationship between tick bites and the seroprevalence of *Babesia microti* and *Anaplasma phagocytophila* (previously *Ehrlichia* sp.) in blood donors. *Transfusion*. 2002;42:1585–91.
7. Leiby DA, Gill JE. Transfusion-transmitted tick-borne infections: a cornucopia of threats. *Transf Med Rev*. 2004;8:293–306.
8. McQuiston JH, Childs JE, Chamberland ME, Tabor E. Transmission of tick-borne agents of disease by blood transfusion: a

- review of known and potential risks in the United States. *Transfusion*. 2000;40:274–84.
9. Rotz LD, Khan AS, Lillibridge SR, Ostroff SM, Hughes JM. Public health assessment of potential biological terrorism agents report summary. *Emerg Infect Dis*. 2002;8:225–30.
  10. Walker DH, Raoult D. *Rickettsia rickettsii* and other spotted fever group *rickettsiae* (Rocky mountain spotted fever and other spotted fevers). In: Mandell GL, Bennet JE, Dolin R, editors. *Principles and practice of infectious diseases*. 5th ed. Philadelphia: Churchill Livingstone; 2000. p. 2035–43.
  11. Wells GM, Woodward TE, Fiset P, Hornick RB. Rocky Mountain spotted fever caused by blood transfusion. *JAMA*. 1978; 239:2763–5.