4 | *BORRELIA* SPECIES (OTHER THAN *BORRELIA BURGDORFERI*)

4.1 | Disease agent

- *Borrelia recurrentis*—Louse-borne relapsing fever (LBRF).
- *Borrelia hermsii*—Tick-borne relapsing fever (TBRF).
- *Borrelia turicatae*—TBRF.
- *Borrelia miyamotoi*—Hard tick relapsing fever (HTRF).
- More than 20 species may be associated with human disease.

4.2 | Disease agent characteristics

- Order: Spirochaetales; Family: *Spirochaetaceae*; Genus: *Borrelia* [The genus *Borrelia* was recently split into two genera: the Lyme Disease (LD) group into the genus *Borreliella* and the Relapsing Fever (RF) group into the genus *Borrelia*]
- *Borrelia* spp. are pleomorphic and gram-negative but are most readily identified by Giemsa Wright staining of blood smears. They are helical, with 3 to 10 loose spirals, motile, facultatively anaerobic bacteria.
- Size: 9–30 μm long × 0.2–0.5 μm wide.
- Nucleic acid: 1–1.6 Mb DNA.
- Physicochemical properties: Remains viable in natural tick vector up to 12 years, promptly killed by desiccation and ultraviolet rays, survives and retains virulence when frozen at −73°C

4.3 | Disease name

- Relapsing fever

4.4 | Priority level

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

4.5 | Background

- Relapsing fevers occur throughout the world, except for a few areas in the Southwest Pacific.
- The distribution and occurrence of endemic TBRF are governed by the presence of enzootic cycles of the transmitting tick vector.
- TBRF is caused by a number of *Borrelia* species distributed throughout the world.
  - Small outbreaks of TBRF are seen in the western US and spread by the saliva of a soft (argasid) tick vector (genus *Ornithodoros*) often carried into human dwellings (mostly rustic cabins, campsites, and caves) by rodents.
  - TBRF pathogens can last for years in tick salivary glands.
  - *Borrelia miyamotoi* is a recently described agent of HTRF. It is genetically similar to other relapsing fever pathogens but is transmitted by *Ixodes* ticks (as are Lyme disease, babesiosis, anaplasmosis, Powassan and likely several other infections) with a longer incubation period and a less well characterized clinical spectrum.
- The distribution of epidemic LBRF is determined by socioeconomic and ecologic factors.
- *Borrelia recurrentis* causes epidemics in crowded conditions, such as refugee camps, or during large-scale civil disruption and dislocation, such as war or famine.
  - Previously distributed worldwide, it is now most common in Africa.
  - Spread by the human body louse vector (*Pediculus humanus*)
  - Not considered a major health threat in the United States, although imported cases do occur in travelers.
  - Infection occurs by bites or when the vector is crushed by the host. *Borrelia* in louse feces or residing in the hemolymph of the vector enter the host via broken skin at the bite site.
- Tick-borne diseases are responsible for about 75% of vector-borne diseases in the United States and increasing

4.6 | Common human exposure routes

- Bite of tick or crushing the louse vector. Lice are infective for their lifetime (19–160 days)

4.7 | Likelihood of secondary transmission

- Secondary (as opposed to vectorial) transmission of relapsing fever from laboratory exposure, transplacentally and by transfusion is reported.

4.8 | At-risk populations

- Persons with exposure to the tick vector and people living in crowded conditions with degraded public health infrastructure

4.9 | Vector and reservoir involved

- Soft (argasid) ticks: TBRF; in the United States, TBRF is caused by *B. hermsii* (in western states) and *B. turicatae* (in south-central states).
- Human body louse: Louse-borne (epidemic) relapsing fever. No non-human reservoir.
- *Ixodes scapularis* and *pacificus* are vectors for HTRF in the United States and rodents are the reservoir (white-footed mouse, *Peromyscus leucopus*).

4.10 | Blood phase

- Bacteria are present in high numbers in the blood during febrile episodes and at lower levels between fevers.
- The duration of bacteremia of non-*burgdorferi* species is not well characterized, but recurrent fevers can persist for several weeks to months.

4.11 | Survival/persistence in blood products

- No information for *B. recurrentis*; however, laboratory studies indicate that *B. burgdorferi* and *B. miyamotoi* survive in contemporary blood components for the duration of their storage period, and this may be the case for other *Borrelia* species. In one study, human-spiked *B. miyamotoi* blood components were either injected into immunocompromised (SCID) or wild-type immunocompetent mice where all SCID mice challenged (prior to RBC storage or following 42-day storage) developed the infection. Wild-type mice also developed infection (all pre-storage) but at lower rates at 42 days. In vitro, spirochetes grew in samples from all components except frozen plasma.

4.12 | Transmission by blood transfusion

- LBRF and TBRF have been transmitted by laboratory exposure to clinical samples in over 40 cases.
- In the 1930s, 6 cases of relapsing fever borreliosis (unknown species) associated with transfusion were reported from China, with documentation of spirochetes in blood of donors and recipients.
- Surveillance from 2013 to 2019 in 9 US states where HTRF reporting occurred recorded 300 cases (166 confirmed and 134 possible infections); of those, 15/72 patients from whom data were available (9 confirmed and 6 possible infections) had received blood or organ transplants during the 30 days prior to diagnosis. All for whom the information was available reported recent tick bites. The observation may represent a higher likelihood of clinical illness and detailed evaluation in patients ill enough to require transfusion, but do raise the question of transmission by transfusion and transplantation.

4.13 | Cases/frequency in population

- *Borrelia recurrentis* (LBRF) is rare (Western US).
- In the United States during 1990–2011, 504 cases of TBRF were reported from 12 western states where the disease is reportable; during 2012–2021, 251 cases were reported from 11 of the 12 states where reporting is required (a median of 20–24 cases reported annually since 1990). Most cases resulted in hospitalization with no fatalities. Cases are likely underreported complicated by no standard case definition.
- During 2013–2019 in 9 states in the Midwest and Northeastern US that reported HTRF due to *B. miyomotoi*, 300 clinical cases were identified via surveillance; cases peaked in August; detection increased from one state reporting cases in 2013 (Maine) to all 9 states by 2019; just over half of cases were males and the median age was 52 years; 28% reported recurrent fevers.
- A very low seroprevalence of *B. miyamotoi* has been found in California blood donors, but case reports predominate in Northeastern states with seroprevalence of 2.8% reported during 2018.
  - Seroprevalence studies are confounded by the non-specificity of the assays, with cross reactivity to other *Borrelia* species and to common bacteria (*E. coli* and *Hemophilus*)

4.14 | Incubation period

- LBRF: 8 days (range: 4–18 days)
- TBRF: 7 days (range: 4–18 days)

4.15 | Likelihood of clinical disease

- Appears to be significant

4.16 | Primary disease symptoms

- Characterized by relapsing fevers with rigors.
- Multiple non-specific symptoms are common (headache, fatigue, headache, chills, nausea, myalgias and arthralgias).

- Symptoms are absent between fevers that occur every 7–10 days.
- Central nervous system signs and symptoms may be more prominent with *B. miyamotoi* infections.

4.17 | Severity of clinical disease

- Can be severe, especially in debilitated persons.
- Rare complications from TBRF include neurologic and ocular diseases, myocarditis, and respiratory distress; can result in pregnancy loss.
- As expected for all, immunocompromised persons may have more severe symptoms including meningoencephalitis (as reported for HTRF).

4.18 | Mortality

- Case-fatality rates in untreated individuals is thought to be between 2% and 5% in TBRF disease and 4%–40% in LBRF disease.
- Fatalities may be much higher in famine victims and young children.

4.19 | Chronic carriage

- No information found but frequent relapses of TBRF suggest chronic infection. LBRF is generally associated with a single relapse.

4.20 | Treatment available/efficacious

- Antibiotics: tetracyclines; TBRF preferentially treated with doxycycline. Alternatives used include azithromycin, ceftriaxone, or penicillin.
- Jarisch–Herxheimer reactions may be as common as 50% with treatment.

4.21 | 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 very low.
- No sensitive or specific question is feasible. In endemic areas, questions on exposure to tick bites have been shown to be ineffective in distinguishing *Babesia*-infected from *Babesia*-uninfected donors. This question probably also lacks sensitivity and specificity for *Borrelia* species.

4.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Research NAT assays are used commercially to detect, but not speciate, *Borrelia* relapsing fever pathogens.
- Current diagnosis reliant on direct microscopic observation of relapsing fever spirochetes using stained peripheral blood smears (sensitivity during fever is ≈70%) and on culture and mouse inoculation; sensitivity is highest during periods of high fever (as correlated with the highest levels of spirochetemia)
- Serology is commonly used (IgM and IgG as well as the use of paired samples to detect a >4-fold increase in titer between paired acute and convalescent-phase serum samples). However, both serology and molecular methods may cross react with *B. burgorferi* and *B. miyomotoi*.
- Serologic reactivity to surface proteins is also used; glycerophosphodiester phosphodiesterase (GlpQ) is found in all relapsing fever group borreliae but not *B. burgdorferi* species that cause Lyme disease. Sensitivity for *B. miyomotoi* in PCR-confirmed patients was <55% at 20 days or less after illness onset but increased to 74%–86% when assayed at 21–150 days post illness onset.
- Tickborne panels in commercial laboratories are expanding and metagenomic approaches are also increasing in use for improved detected particularly of *B. miyomotoi* where spirochetes are present in sufficient quantities in blood for detection by molecular methods.

4.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- Prudent practice would be to defer donor until a course of treatment is completed and symptoms are gone.

4.24 | Impact on blood availability

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

4.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

4.26 | Leukoreduction efficacy

- Unlikely to be effective

4.27 | Pathogen reduction efficacy for plasma derivatives

- Specific data indicate that the multiple steps in the fractionation process are robust and capable of inactivating and/or removing bacteria at concentrations that may be present in plasma.

4.28 | Other prevention measures

- Standard tick avoidance measures.
- Institute de-lousing programs in refugee camps.
- In the developing world or refugee environments, blood collection should be avoided where louse-borne relapsing fever has been endemic.

SUGGESTED READING

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