4 | *ORIENTIA TSUTSUGAMUSHI*

4.1 | Disease agent

- *Orientia tsutsugamushi* (formerly *Rickettsia tsutsugamushi*)

4.2 | Disease agent characteristics

- *Orientia* species, along with *Rickettsia* species, belong to the family *Rickettsiaceae*.
- *Orientia tsutsugamushi* is an obligate intracellular, Gram-negative bacterium that causes an arthropod-borne febrile illness, commonly called scrub typhus.
- 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, the *Orientia* genome is approximately 2000 kb. *O. tsutsugamushi* has diverse antigenic and genetic phenotypes.
- Physicochemical properties: Information specific to *Orientia* species is not available. The rickettsiae are 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).

4.3 | Disease name

- Scrub typhus (most common), tsutsugamushi fever, mite-borne typhus fever

4.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Very low
- Public perception and/or regulatory concern regarding blood safety: Low, but absent in the United States
- Public concern regarding disease agent: Absent

4.5 | Background

- Endemic across extensive parts of Asia, Australia, and the Pacific region, referred to as the "Tsutsugamushi Triangle." Recent reports of autochthonous infection in Africa, the Middle East, and South America suggest a wider global distribution.
- Scrub typhus has been clinically described in China as early as the 4th century. It is the leading cause of treatable non-malarial febrile illness in Southeast Asia.
- Over 1 billion people living in endemic areas are at risk.
- Localized, rural foci of risk are recognized where the vector (larval stages of trombiculid mites, referred to as chiggers), the *Leptotrombidium* mite, occurs and where natural environments are disturbed.
- US experience related to exposure of military personnel during wartime situations in areas of endemicity.
- Disease prevalence may be increasing in endemic areas, though this may include an increase in recognition of cases and access to diagnostic testing.

4.6 | Common human exposure routes

- Vector-borne: *Leptotrombidium* mites in the family *Trombiculidae*

4.7 | Likelihood of secondary transmission

- Vertical transmission during pregnancy is suspected based on clinical illness and serology in the mother and the presence of IgM antibodies in the infant.
- Infection is associated with an increase in spontaneous abortion.

4.8 | At-risk populations

- Residents of endemic areas, military personnel, and tourists

4.9 | Vector and reservoir involved

- *Leptotrombidium* mites are both the vector and reservoir for *O. tsutsugamushi*.
- *Leptotrombidium* larval mites are the transmitting stage. They mostly feed on small mammals. Mammals/humans are accidental hosts during feeding of the larvae.
- Transstadial (remaining in the vector from one life stage to the next) and transovarial transmission maintain *O. tsutsugamushi* in mites.

4.10 | Blood phase

- Bacteremia occurs during the symptomatic phase and for 1–3 days before symptom onset.

- Although chronic infection of lymph nodes can occur, there is no evidence of bacteremia during this phase.

4.11 | Survival/persistence in blood products

- Persistence and survival of *O. tsutsugamushi* in whole blood is well established.
- Survival in RBCs for 10, but not 30 days, and survival for at least 45 days in frozen and deglycerolized RBCs were demonstrated in spiking studies.

4.12 | Transmission by blood transfusion

- A single well-documented transmission from a peripheral blood stem cell donor to recipient confirmed by PCR and sequencing has been published (transmission of scrub typhus by needle-stick injury or transplacental transmission has previously been reported).

4.13 | Cases/frequency in population

- Estimated 1 million cases per year occur in endemic areas, but this is likely confounded by underreporting and under-recognition, and by changes in access to care and diagnosis.
- Seroprevalence studies suggest a prevalence of 9%–30%, but this may be an underestimate due to short-lived humoral immunity.
- Rare introduction into the US and other non-endemic areas.

4.14 | Incubation period

- Abrupt onset of illness usually occurs 7–10 days (range 6–21 days) after exposure.

4.15 | Likelihood of clinical disease

- Assumed to be very high

4.16 | Primary disease symptoms

- Abrupt onset of febrile illness that can range from mild/self-limiting to severe/fatal
- Typical signs and symptoms: fever/chills, headache, myalgia, eschar (scabs), altered mental status, lymphadenopathy, rash
  - Eschar may develop around the bite before systemic symptoms begin.
  - The rash occurs in 20%–25% of those infected. It is usually macular or maculopapular and begins on the trunk and spreads to the extremities.
- Laboratory findings: thrombocytopenia, elevated liver enzymes, bilirubinemia, elevated creatinine.
- Eschar develops at the site of mite bite, and lymphadenopathy in nodes draining area may be prominent.
- Severe disease may occur within the first week and can include multiple organ dysfunction, acute respiratory distress syndrome, encephalitis, pneumonia, kidney or liver failure, and death.
- Relapse is uncommon with adequate treatment.

4.17 | Severity of clinical disease

- The severity is very dependent on the particular strain of *O. tsutsugamushi*, area of acquisition, previous exposure, and host characteristics. Delayed treatment is associated with severe complications.

4.18 | Mortality

- Case-fatality rates vary from <1% with appropriate treatment to 30%–50% without treatment.

4.19 | Chronic carriage

- Viable organisms can be isolated from lymph nodes for up to 1–2 years after untreated infection.
- There is no evidence of long-term persistence after adequate therapy.

4.20 | Treatment available/efficacious

- Doxycycline is the treatment of choice. Individuals are treated for at least 3 days after becoming afebrile and showing clinical improvement. Azithromycin, chloramphenicol, or rifampin are alternatives when tetracyclines are contraindicated.
- Due to the extensive antigenic diversity, immunity is short-lived and not cross-reactive among other strains

4.21 | Agent-specific screening question(s)

- No specific question is in use.
- Not indicated because transfusion transmission has not been definitively demonstrated.
- No sensitive or specific question is feasible.

4.22 | Laboratory tests available

- No FDA-licensed blood donor screening test exists.
- Serologic tests are the mainstay of laboratory diagnosis, but IgM appears 5–6 days after symptom onset and is thus not useful for donor screening.
  - Specific IgM identified by immunofluorescence assay (IFA) is the test of choice.
  - An immunoperoxidase test is available as a less costly alternative.
  - Enzyme immunoassay tests have been developed, and these have been found to be closely equivalent to IFA for early detection of antibody.
  - The complement fixation test for *O. tsutsugamushi* antibodies is strain specific, so all suspect strains must be included in the reagent.
  - Dot blot assays for antibody are available but are also strain specific.
- Direct detection:
  - Isolation in cell culture, animals, and embryonated chicken eggs.
  - Immunofluorescence and immunoperoxidase staining can demonstrate organisms in tissue.
  - Monoclonal antibodies are now available for strain identification.
  - PCR has been used to detect *O. tsutsugamushi* in skin biopsies, peripheral mononuclear cells, whole blood, blood clots, and serum.
    - Nested PCR with specific primers allows determination of particular strains.
    - PCR is the only potentially rapid and specific practical approach to early diagnosis.

4.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists, but malaria deferral will exclude many at-risk donors.
- Prudent practice would be to defer donor until signs and symptoms are gone and a course of treatment is completed.

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

- A mouse model suggests current filters can remove as many as 10^5 *O. tsutsugamushi* organisms from packed red blood cells spiked with infected mononuclear cells.

4.27 | Pathogen reduction efficacy for plasma derivatives

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

4.28 | Other prevention measures

- Tick avoidance measures (e.g., long pants, long sleeves, insect repellant).
- Riboflavin and Ultraviolet (UV) light (available outside of the US) have been demonstrated to reduce infectivity by a factor of 10^5 in RBCs, platelets, and plasma in a mouse model.
- *Orientia tsutsugamushi* was inactivated to below the limit of detection of >5.5 logs in plasma and >5.0 logs in platelets (suspended in 65% additive solution or 100% plasma), by treatment with amotosalen HCl and UVA illumination using a mouse infectivity assay with in vitro testing by PCR, IFA and Giemsa staining.

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