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Considerations for Cellular Therapy Products

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ORIGINAL RESEARCH

TRANSFUSION

Other bacterial agents (4th section)

1 | *ANAPLASMA PHAGOCYTOPHILUM*

1.1 | Disease agent

- *Anaplasma phagocytophilum* (formerly referred to as *A. phagocytophila, Ehrlichia phagocytophila* and *Ehrlichia spp*)

1.2 | Disease agent characteristics

- Obligate, intracellular, Gram-negative bacterium with tropism for neutrophils.
- Order: Rickettsiales; Family: *Anaplasmataceae*.
- Size: 0.5–0.8 μm × 1.2–3 μm.
- Nucleic acid: A circular DNA of about 1500 kb.
- Physicochemical properties: The rickettsiae are susceptible to 1% sodium hypochlorite, 70% ethanol, glutaraldehyde, formaldehyde, and quaternary ammonium disinfectants, and are sensitive to moist heat (121°C for at least 15 min) and dry heat (160°–170°C) for at least 1 h.

1.3 | Disease name

- Human granulocytic anaplasmosis (HGA); previously known as human granulocytic ehrlichiosis (HGE)

1.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Moderate
- Public perception and/or regulatory concern regarding blood safety: Low
- Public concern regarding disease agent: Low/moderate in focal endemic areas

1.5 | Background

- Emergent; first described in 1994 as the causative agent of HGE. HGA became a reportable disease in 1999. Most cases (90%) reported to CDC come from New York, Connecticut, New Jersey, Rhode Island, Minnesota and Wisconsin. Incidence of reported cases has increased from 348 in 2000 to a peak of 5762 in 2017 probably due to both increased awareness resulting in better diagnosis and surveillance, and/or spread of infected ticks resulting in a true increased incidence.

1.6 | Common human exposure routes

- Tick-borne zoonosis; humans are accidental/incidental hosts.
- Transmitted by the same tick vectors as those that transmit Lyme disease and babesiosis, and others: *Ixodes scapularis* ticks in the Northeast and upper Midwest (also known as the deer tick or the black-legged tick); incidence peaks synchronized to tick seasons in affected areas. The majority of cases occur during the summer months with a peak observed during June/July. A second but smaller peak can occur in October and November.
- *I. pacificus* (western black-legged tick) transmits the infection in the western US, while *I. ricinus* and *I. persulcatus* are the principal vectors in Europe and Asia, respectively.
- *Ixodes* spp were reported in 1531 counties in 43 states in 2016, representing a 44.7% increase since 1998.
- Reports of transfusion transmission increasing.

1.7 | Likelihood of secondary transmission

- None documented

1.8 | At-risk populations

- Individuals at enhanced risk for exposure to infected ticks through outdoor activity, including those involved in hiking, gardening, clearing brush, and so forth.
- The frequency of reported cases is higher among males and anyone over 40 years of age.

- A compromised immune system due to cancer treatments, advanced HIV infection, prior organ transplants, or immune suppression may increase the risk of severe outcome.

1.9 | Vector and reservoir involved

- Ticks of genus *Ixodes* (*I. scapularis, I. pacificus, I. ricinus, I. persulcatus*).
- The tick nymph is primarily responsible for transmission of Lyme disease, babesiosis, and HGA, although adult stages also can transmit infection. Because of its small size, the bite may not be noticed and consequently the tick may not be removed before disease transmission occurs.
- While white-footed mice (*Peromyscus leucopus*) are the primary reservoir, raccoons (*Procyon lotor*), gray squirrels (*Sciurus carolinensis*), Northern short-tailed shrews (*Blarina brevicauda*), Eastern chipmunks (*Tamias striatus*), and several other small mammals have demonstrated competency as reservoir hosts in the United States.
- White-tailed deer (*Odocoileus virginianus*) harbor a strain of *A. phagocytophilum* not associated with human infections; therefore, they are not the principal reservoir for strains that cause HGA.

1.10 | Blood phase

- The bacteremia lasts for days to a few weeks after the occurrence of symptoms.
- The duration and frequency of asymptomatic bacteremia have not been documented.

1.11 | Survival/persistence in blood products

- Viable organisms have been recovered from anticoagulated, refrigerated whole blood from infected patients for 2 weeks and transmitted by transfusion in animal models (sheep) after 13 days. In a single case, RBCs stored for 30 days from a seropositive/PCR-negative donor transmitted the organism to a recipient who at diagnosis was seroconverting, PCR positive, and febrile. Among other cases, *A. phagocytophilum* survived 8–30 days in packed RBCs.

1.12 | Transmission by blood transfusion

- 12 Erlichia and Anaplasma infections in transfusion recipients and 120 in transplant recipients were investigated from 1997 to 2020. Of the twelve transfusion cases judged to be donor-derived, 2 were ehrlichiosis and 10 were anaplasmosis. Most infections were mild. Patients ranged in age from 34 to 85 years, but the majority ($n = 8$) were over 50 years of age. Gender distribution: 6 female and 5 male.
  - HGA generally suspected by identifying morulae (microcolonies of Anaplasma) on blood smear; confirmation by PCR and/or seroconversion.
  - Implicated donors ranged in age from 42 to 81 years and most reported risk factors for exposure to *A. phagocytophilum* including tick bites, time spent in an endemic area or febrile illness prior to donation. For most cases, index donation was PCR positive.
- Leukoreduced, as well as non-leukoreduced products have been implicated in transmission including two leukoreduced apheresis platelet products. A cluster of cases of apparent human-to-human transmission of *A. phagocytophilum* infection (and the first report of HGA in China) associated with blood contact was reported in 2008. The infection was not confirmed by blood smear or culture in the index patient, but *A. phagocytophilum* DNA was amplified and sequenced from the patient who had been bitten by a tick, and nine family members or healthcare workers who reported contact with the patient's blood; seven had contact with respiratory secretions. The index patient died before seroconversion, but all nine contacts seroconverted.

1.13 | Cases/frequency in population

- Seroprevalence:
  - Blood donors: 11.3% of Westchester County, New York donors, 0.5% of Wisconsin donors, and 3.5% of Connecticut donors had antibodies to *A. phagocytophilum*.
  - Residents: 0.4% in northern California, 3.4% in New York, 14.9% in northwestern Wisconsin had antibodies to *A. phagocytophilum*.
- Incidence: During 2008–2012, the average annual US incidence was 6.3 cases per million persons. The annual incidence rate increased from 4.1 to 8.7. In 2018, 4008 cases were reported to the CDC. The number of infected individuals and clinical cases are likely much higher due to underreporting and lack of recognition of this often-nonspecific infection.

1.14 | Incubation period

- 5–14 days from tick bite to bacteremia and acute symptoms; may take as long as 3 weeks.

1.15 | Likelihood of clinical disease

- Low to moderate.
- Males outnumbered females by a 1.5:1 ratio in 2018.
- Immunocompromised and elderly patients are at greater risk to develop more severe manifestations of disease.

1.16 | Primary disease symptoms

- Nonspecific febrile illness characterized by high-grade fever (>39°C), rigors, generalized myalgias, severe headache, and malaise often accompanied by thrombocytopenia, leukopenia, and elevated liver transaminases that occurs approximately 5–21 days after a bite from an infected tick.
- Anorexia, arthralgias, nausea, nonproductive cough, and rash are sometimes present.
- Median duration of illness is 9 days (1–60 days).

1.17 | Severity of clinical disease

- Generally, not severe.
- Severe cases are characterized by prolonged fever, acute renal failure, gastrointestinal bleeding, septic shock-like illness, rhabdomyolysis, respiratory insufficiency, and secondary opportunistic infections.

1.18 | Mortality

- <1% mortality

1.19 | Chronic carriage

- Not documented in humans. A chronic, subclinical infection of almost one year was reported in dogs inoculated with a human isolate from New York.

1.20 | Treatment available/efficacious

- Patients treated with doxycycline or rifampin demonstrated rapid improvement and resolution of infection, except for the last case reported.
- Tetracyclines (e.g., doxycycline) are therapeutically effective.
  - Rifampin may be effective based on limited data in those who cannot take tetracyclines (e.g., pregnant women or those with allergy).

1.21 | Agent-specific screening question(s)

- No specific question is in use.
- Not indicated at this time because relatively few cases of transfusion transmission have been reported.
- 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 *A. phagocytophilum*.

1.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Options for laboratory testing include blood smear microscopy, cell culture, immunofluorescence (IFA), enzyme immunoassay, and nucleic acid test.
  - During the first week of infection, examination of peripheral blood smears may reveal morulae in the cytoplasm of white blood cells in 25%–75% of patients. Morulae are most frequently observed in granulocytes.
  - Specialized cell culture techniques can be used to amplify the infection and observe infected cells. Sensitivity is >55% in the first week, falling to 33% during week two.
  - IFA and enzyme-linked immunosorbent assay are the current serologic tests. A four-fold rise in IgG antibody levels to *A. phagocytophilum* antigen is considered diagnostic for a recent infection. Sensitivity ranges from 22% to 4% in the first week after onset to >95% at 3 weeks and beyond. Antibody sensitivity is highest about 2 weeks after initial infection.
  - PCR detection primarily during first week of infection (67%–90%); thereafter, sensitivity rapidly declines, particularly after administration of appropriate antibiotics.

1.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- In an individual who receives treatment, prudent practice would be to defer donor until signs and symptoms are gone and treatment is complete.

- Based on the natural history of infection, it may be prudent to defer an untreated individual for a minimum of 90 days (30 days beyond the longest duration of illness).

1.24 | Impact on blood availability

- Agent-specific screening question(s): Not applicable.
- Laboratory test(s) available: Not applicable; serologic testing, if implemented in the future, could result in a deferral rate of 3%–5% in selected collection areas.

1.25 | Impact on blood safety

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

1.26 | Leukoreduction efficacy

- Preliminary studies indicate that leukoreduction reduces but does not eliminate transmission risk associated with *A. phagocytophilum*. Recent transfusion cases implicating leukoreduced products support this observation. Efficacy of leukoreduction has been hypothesized to be related to the bacterial load of the product and breakthrough from those with the highest bacterial burdens.

1.27 | Pathogen reduction efficacy for plasma derivatives

- Not expected to be transmitted by plasma derivatives

1.28 | Other prevention measures

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

SUGGESTED READING

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