

***Ehrlichia* Species**

Disease Agent:

- *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, *Ehrlichia muris*-like (EML)

Disease Agent Characteristics:

- Obligate intracellular Gram-negative bacterium of monocytes (*E. chaffeensis*) and granulocytes (*E. ewingii*)
- Order: Rickettsiales; Family: Anaplasmataceae
- Size: 0.5-0.8 µm x 1.2-3 µm
- Nucleic acid: Rickettsial genomes are among the smallest of bacteria. *Ehrlichia* are approximately 1200-1600 kb.
- Physicochemical properties: 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 minutes and dry heat (160-170°C) for at least 1 hour

Disease Name:

- Human ehrlichiosis, human monocytic ehrlichiosis (HME)

Priority Level:

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

Background:

- Human ehrlichiosis is an emerging tick-borne zoonosis with exposure occurring in rural and suburban tick habitats during recreational and peridomestic activities. First became a reportable disease (i.e., HME) in 1999. Infections caused by *E. ewingii* became a separate reportable disease in 2008.
- Documented HME has been reported from 47 states, especially in the south central and southeast US. This corresponds to the distribution of the major vector tick, *Amblyomma americanum*, and the white-tailed deer (*Odocoileus virginianus*) that serves as the reservoir host.
- Concern over potential transfusion transmission first arose in 1997 during an outbreak of febrile disease at Fort Chaffee, where a large blood drive was conducted just after military donors had extensive exposure to infected ticks. No transfusion transmission was documented in the subsequent investigations.
- *E. ewingii* was first documented as a cause of human disease in 1999. Relatively few cases reported, but agent likely widely distributed throughout the central and southeastern US. In some cases, infections with *E. ewingii* may be misdiagnosed and attributed to infection with *E. chaffeensis*. This species also reported in a single transfusion transmission.

- The *E. muris*-like or EML agent was first described in Wisconsin and Minnesota during 2009; represents the third *Ehrlichia* sp. described to cause disease in humans in the United States.

Common Human Exposure Route:

- Bite of infected tick

Likelihood of Secondary Transmission:

- None documented

At-Risk Populations:

- Individuals at enhanced risk for exposure to infected ticks through outdoor activity, including those involved in hiking, gardening, clearing brush, etc.
- The frequency of reported cases is higher among males and anyone > 50 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.

Vector and Reservoir Involved:

- Lone star tick, *Amblyomma americanum*, distributed throughout southeastern and south central US; transmits both *E. chaffeensis* and *E. ewingii*. *Dermacentor variabilis* (American dog tick) and *Rhipicephalus sanguineus* (brown dog tick) have been identified as secondary vectors of *E. chaffeensis* and/or *E. ewingii*.
- Cases in the western US suggest additional tick vectors that are thought to be *D. variabilis* and *Ixodes pacificus*.
- Tick vector for EML found in Wisconsin and Minnesota has not been identified, but may be *I. scapularis*.
- White-tailed deer are thought to be the primary reservoir for *E. chaffeensis*. *E. ewingii* has been demonstrated to infect white-tailed deer, but the current status of deer as a reservoir host has not been established.
- Dogs are the definitive host for *E. ewingii*.

Blood Phase:

- Although data are scant, the recently reported transfusion transmission of *E. ewingii* demonstrates asymptomatic bacteremia for this species.
- Experimental infection in dogs suggests that the agent may circulate in blood for over 3 weeks.
- Asymptomatic human infection is suspected. An *Ehrlichia* species related to *E. canis* was isolated from the blood of an asymptomatic persistently infected patient in South America.

Survival/Persistence in Blood Products:

- *E. chaffeensis* remains viable when infected monocytes are inoculated into RBCs stored at 4-6°C for at least 11 days, with

supernatant organisms found, suggesting the potential for transfusion transmission.

- *E. ewingii* transmitted by platelets at day 5 of storage.

Transmission by Blood Transfusion:

- One case involving *E. ewingii* occurred in 2011. Recipient was a 9-year old boy with a history of acute lymphoblastic leukemia and anemia secondary to chemotherapy. Morulae (microcolonies of *Ehrlichia*) were identified in granulocytes, infection was confirmed by PCR, patient was treated with doxycycline and recovered within 48 hours. Patient denied any risk factors for exposure other than transfusion. Implicated donor (IgG titer 1:512) reported frequent tick attachment at home in Florida and wooded property in South Carolina in the month prior to donation. Transfused product was a day 5 leukoreduced and irradiated apheresis platelet unit.
- In 1997, following deployment to Fort Chaffee, AR, a number of National Guard personnel developed febrile illnesses. Investigation of both symptomatic and asymptomatic individuals demonstrated serological evidence for infection with both *Rickettsia rickettsii*, the agent of Rocky Mountain spotted fever, and *E. chaffeensis*. Blood drives had been conducted during the deployment. Evaluation of 10 recipients of components from 377 personnel with confirmed or probable infections did not demonstrate transmission of either organism.

Cases/Frequency in Population:

- 3.6% seroprevalence for HME has been documented in selected areas.
- Among 413 patients from Missouri with possible ehrlichiosis, 60 (15%) tested positive by PCR from EDTA whole blood for *Ehrlichia* spp: 56 (14%) for *E. chaffeensis* and 4 (1%) for *E. ewingii*.
- The number of ehrlichiosis cases due to *E. chaffeensis* has increased steadily, from 200 cases in 2000 (< 1 case/million population), to 961 cases in 2008 (3.4/million). A decrease in the number of *E. chaffeensis* cases was noted in 2010 (2.5/million).
- 28 cases of *E. ewingii* infection reported to the CDC from 2008-2010.
- Majority of cases have an illness onset during the summer months, peaking in June/July.

Incubation Period:

- 1-2 weeks (median: 9 days)

Likelihood of Clinical Disease:

- Low/Moderate, based on serosurveys
- Symptoms are often subclinical or are usually mild and flu-like.
- Immunocompromised individuals who are infected may develop more severe manifestations of disease.

Primary Disease Symptoms:

- Fever with headache, myalgia, and malaise
- Gastrointestinal, respiratory, or central nervous system involvement also may occur.
- Rash appears in up to 60% of children and less than 30% of adults with HME. Not common in patients infected with *E. ewingii* or EML.
- Leukopenia, thrombocytopenia and elevated transaminases are common laboratory signs.

Severity of Clinical Disease:

- Currently most infections are not diagnosed, but HME can be a life-threatening disease, with hospitalization in 41-63% of recognized cases.
- Severely affected patients can develop acute respiratory failure, renal failure, meningoencephalitis, coagulopathy, and GI bleeding.
- Untreated disease may progress to death as early as the second week of illness.

Mortality:

- 1-2%
- Since HME became a reportable disease in 1999, the annual case fatality rate has declined.

Chronic Carriage:

- Not documented

Treatment Available/Efficacious:

- Tetracyclines (e.g., doxycycline) are effective.
- Rifampin may be an alternative when tetracyclines cannot be used (pregnancy and tetracycline allergy), but data are limited.

Agent-Specific Screening Question(s):

- No specific question is in use.
- Not indicated because to date transfusion transmission has been rare.
- No sensitive or specific question is likely to be 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, and probably also lacks sensitivity and specificity for *Ehrlichia* spp.

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening test exists.
- Available diagnostic tests include IFA (some cross reactivity with other *Ehrlichia* species) and western blot, PCR, visualization of morulae in blood smear, immunohistochemical staining, and culture isolation.
 - During the first week of infection, examination of peripheral blood smears may reveal morulae in the cytoplasm of white blood cells (2-38% for HME).

- Specialized cell culture techniques can be used to amplify the infection and observe infected cells (highly variable sensitivity and may be delayed for weeks for HME).
- IFA is considered the gold standard serologic test. A four-fold rise in IgG antibody level is considered diagnostic for a recent infection (for HME sensitivity ranges from 22-55% in the first week after onset, to > 90% after 3 weeks).
- PCR detection primarily during first week of infection (HME, 60-85%); thereafter, sensitivity rapidly declines, particularly after administration of appropriate antibiotics.
- Up to 12% of currently healthy people in some areas may have elevated antibody titers due to past exposure to *Ehrlichia* species or similar organisms.
- *E. chaffeensis* and *E. ewingii* not distinguishable by clinical signs or serologic assays; only by molecular-based tests.

Currently Recommended Donor Deferral Period:

- No FDA Guidance or AABB Standard exists.
- Prudent practice would be to defer 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
- Laboratory test(s) available: Not applicable

Impact on Blood Safety:

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

Leukoreduction Efficacy:

- Recent transfusion case implicating a leukoreduced apheresis platelet product suggests leukoreduction does not eliminate transmission risk. Likely that leukoreduction reduces risk, but does not eliminate all infected cells or extracellular organisms.
- A related rickettsia, *Orientia tsutsugamushi*, has been shown to be removed (>4 log) by leukoreduction.

Pathogen Reduction Efficacy for Plasma Derivatives:

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

Other Prevention Measures:

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

Other Comments:

- Dogs may serve as regional or local sentinels of potential risk for human infection with ehrlichial agents.

Suggested Reading:

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