3 | *EHRLICHIA* SPECIES

3.1 | Disease agent

- *Ehrlichia chaffeensis, Ehrlichia ewingii, Ehrlichia muris eauclairensis, Ehrlichia muris* (Europe)

3.2 | Disease agent characteristics

- Order: Rickettsiales; Family: *Anaplasmataceae*; Genus: *Ehrlichia*.
- Pleomorphic, obligate intracellular Gram-negative bacterium of monocytes (*E. chaffeensis*) and granulocytes (*E. ewingii*).
- Size: 0.5–0.8 μm × 1.2–3 μm *Anaplasmataceae* have unusual cell wall compositions containing a rippled thin outer membrane that lacks thickening of the inner or outer leaflet and shows no sign of a peptidoglycan layer or lipopolysaccharide. Replication occurs in membrane-bound inclusions in the host cytoplasm secluded from host immune surveillance and destruction by lysosomes and reactive oxygen intermediates. The mechanism(s) by which these agents evade the microbicidal activity of the host are unknown.
- 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 min and dry heat (160°–170°C) for at least 1 h.
- *Anaplasmataceae* display several unique characteristics. They are extremely sensitive to mechanical stress such as sonication, freezing and thawing, and osmolarity changes likely related to their unique cell wall.

3.3 | Disease name

- Human ehrlichiosis, human monocytic ehrlichiosis (HME)

3.4 | Priority level

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

3.5 | 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. Two cases of transfusion-transmitted ehrlichiosis have been documented subsequently in 2011 and 2018.
- Between 1997 and 2020, 107 cases of ehrlichiosis were described among solid organ transplant recipients.
- *Ehrlichia ewingii* was first documented as a cause of human disease in 1999. Relatively few cases reported, but the agent is 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 has also been reported in a single transfusion transmission in 2011.
- Previously referred to as *E. muris*-like agent, *E. muris eauclairensis*, was first described in Wisconsin and Minnesota during 2009; represents the third *Ehrlichia* species described to cause disease in humans in the United States.

3.6 | Common human exposure route

- Bite of infected tick

3.7 | Likelihood of secondary transmission

- None documented

3.8 | 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 >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.

3.9 | Vector and reservoir involved

- Lone-star tick, *Amblyomma americanum*, distributed throughout southeastern and south-central US; transmits both *E. chaffeensis* and *E. ewingii*. Lone-star tick bites are also associated with Alpha-Gal syndrome causing an allergy to red meat. *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*.
- Dogs may serve as regional or local sentinels of potential risk for human infection with *Ehrlichia* species.
- Tick vector for *E. muris eauclairensis* found in Wisconsin and Minnesota is *I. scapularis*.
- White-tailed deer are thought to be the primary reservoir for *E. chaffeensis*. White-footed mice and other small mammals serve as reservoir hosts for *E. muris eauclariensis*.
- Dogs are the definitive host for *E. ewingii*, but white-tailed deer also serve as reservoirs.

3.10 | 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.

3.11 | Survival/persistence in blood products

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

3.12 | Transmission by blood transfusion

- Twelve *Erlichia* and *Anaplasma* infections in transfusion recipients and 120 in transplant recipients were investigated from 1997 to 2020. Twelve transfusion cases were judged to be donor-derived, of which 2 were ehrlichiosis and 10 were anaplasmosis. Most infections were mild.
- 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 were identified in granulocytes, infection was confirmed by PCR, patient was treated with doxycycline and recovered within 48 h. 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, Arkansas (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.
- Two cases of transfusion-transmitted *E. chaffeensis* have been subsequently documented in 2011 and 2018.

3.13 | Cases/frequency in population

- 3.6% seroprevalence for HME documented in selected areas.
- Among 413 patients from Missouri with possible ehrlichiosis, 60 (15%) tested PCR positive 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 0.6 cases/million population in 2001–2002 to 4.5/million 2012–2016.

- 261 cases of *E. ewingii* infection were reported to the CDC from 2008 to 2019; none was fatal.
- Majority of cases have an illness onset during the summer months, peaking in June/July.

3.14 | Incubation period

- 1–2 weeks (median: 9 days)

3.15 | 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.

3.16 | 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 *E. muris eauclairensis*.
- Leukopenia, thrombocytopenia, and elevated transaminases are common laboratory signs.

3.17 | 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 septic or toxic shock-like syndrome, acute respiratory failure, hepatic or renal failure, meningoencephalitis, coagulopathy, gastrointestinal bleeding or secondary hemophagocytic lymphohistiocytosis.
- Untreated disease may progress to death as early as the second week of illness.

3.18 | Mortality

- 1%–3% with *E. chaffeensis*. No reports of mortality with *E. ewingii* or *E. muris eauclairensis*.
- Since HME became a reportable disease in 1999, the annual case fatality rate has declined.

3.19 | Chronic carriage

- Not documented

3.20 | 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.

3.21 | 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.

3.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Available diagnostic tests include immunofluorescence assay (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% to 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.

- *Ehrlichia chaffeensis* and *E. ewingii* not distinguishable by clinical signs or serologic assays; only by molecular-based tests.

3.23 | 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.

3.24 | Impact on blood availability

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

3.25 | Impact on blood safety

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

3.26 | 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.

3.27 | 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.

3.28 | Other prevention measures

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

SUGGESTED READING

1. Arguin PM, Singleton J, Rotz LD, Marston E, Treadwell TA, Slater K, et al. Transfusion-associated tick-borne illness task force. An investigation into the possibility of transmission of tick-borne pathogens via blood transfusion. Transfusion. 1999; 39:828–33.
2. Buller RS, Arens M, Hmiel SP, Paddock CD, Sumner JW, Rikhisa Y, et al. *Ehrlichia ewingii*, a newly recognized agent of human ehrlichiosis. N Engl J Med. 1999;341:148–55.
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. Morb Mortal Wkly Rep MMWR. 2016;65:1–44.
4. Demma LJ, Holman RC, McQuiston JH, Krebs JW, Swerdlow DL. Epidemiology of human ehrlichiosis and anaplasmosis in the United States, 2001-2002. Am J Trop Med Hyg. 2005;73: 400–9.
5. Dumler JS, Madigan JE, Pusterla N, Bakken JS. Ehrlichioses in humans: epidemiology, clinical presentation, diagnosis, and treatment. Clin Inf Dis. 2007;45(Suppl 1):S45–51.
6. Heitman KN, Dahlgren FS, Drexler NA, Massung RF, Behravesh CB. Increasing Incidence of Ehrlichiosis in the United States: a summary of national surveillance of *Ehrlichia chaffeensis* and *Ehrlichia ewingii* Infections in the United States, 2008–2012. Am J Trop Med Hyg. 2016;94:52–60.
7. Ismail N, McBride JW. Tick-borne emerging infections: ehrlichiosis and anaplasmosis. Clin Lab Med. 2017;37:317–40.
8. Mah A, Viola GM, Ariza Heredia E, Rezvani K, Kebriaei P, Bhatti MM, Han X, et al. Graft loss attributed to possible transfusion-transmitted ehrlichiosis following cord blood stem cell transplant. Transpl Infect Dis. 2018;20:e12899. https://doi.org/10.1111/tid.12899
9. McKechnie DB, Slater KS, Childs JE, Massung RF, Paddock CD. Survival of *Ehrlichia chaffeensis* in refrigerated ADSOL-treated RBCs. Transfusion. 2000;40:1041–7.
10. Mogg M, Wang HH, Baker A, Derouen Z, Borski J, Grant WE. Increased incidence of *Ehrlichia chaffeensis* infections in the United States, 2012 through 2016. Vector Borne Zoonotic Dis. 2020;20:547–50.
11. Mowla SJ, Drexler NA, Cherry CC, Annambholta PD, Kracalik IT, Basavaraju SV. Ehrlichiosis and Anaplasmosis among transfusion and transplant recipients in the United States. Emerg Infect Dis. 2021 Nov;27(11):2768–75. https://doi.org/10.3201/eid2711.211127
12. Otrock ZK, Eby CS, Burnham CD. Human ehrlichiosis at a tertiary-care academic medical center: clinical associations and outcomes of transplant patients and patients with hemophagocytic lymphohistiocytosis. Blood Cells Mol Dis. 2019;77: 17–22.

13. Paddock CD, Folk SM, Shore GM, Machado LJ, Huycke MM, Slater LN, et al. Infections with *Ehrlichia chaffeensis* and *Ehrlichia ewingii* in persons coinfected with human immunodeficiency virus. Clin Infect Dis. 2001;33:1586–94.
14. Perez M, Rikihisa Y, Wen B. Ehrlichia canis–like agent isolated from a man in Venezuela: antigenic and genetic characterization. J Clin Microbiol. 1996;34:2133–9.
15. Pritt BS, Sloan LM, Johnson DK, Munderloh UG, Paskewitz SM, McElroy KM, et al. Emergence of a new pathogenic *Ehrlichia* species, Wisconsin and Minnesota, 2009. N Engl J Med. 2011;365:422–9.
16. Regan J, Matthias J, Green-Murphy A, Stanek D, Bertholf M, Pritt BS, et al. A confirmed *Ehrlichia ewingii* infection likely acquired through platelet transfusion. Clin Infect Dis. 2013;56:e105–7.
17. Yabsley MJ, Varela AS, Tate CM, Dugan VG, Stallknecht DE, Little SE, et al. *Ehrlichia ewingii* infection in white-tailed deer (Odocoileus virginianus). Emerg Inf Dis. 2002;8:668–71.