



## Communicable Disease Case Reporting and Investigation Protocol **EHRlichiosis**

### I. IDENTIFICATION AND DEFINITION OF CASES

- A. **Clinical Description:** Human ehrlichiosis is a disease caused by at least three different ehrlichial species of rickettsial bacteria: *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, and *Ehrlichia muris eauclairensis* (formerly *E. muris*-like or EML). *E. chaffeensis*, which causes the disease previously referred to as human monocytic ehrlichiosis (HME), and *E. ewingii* are two separate species in the genus *Ehrlichia* that have been known to cause human ehrlichioses. In 2009, a third species of *Ehrlichia* was identified in Wisconsin and Minnesota, *E. muris* subsp. *eauclairensis* (EML), which genetically resembles the *E. muris* species that infects wild mice in Japan.

Initial signs and symptoms for ehrlichiosis generally include acute onset of fever, sweats, chills, headache, fatigue, and muscle aches. Other less common signs and symptoms may include nausea, vomiting, diarrhea, cough, joint pain, confusion, rigors, and rash. Some individuals may only experience very mild symptoms or remain asymptomatic and the combination of symptoms may vary significantly by individual. Clinical laboratory findings may include thrombocytopenia, leukopenia, anemia, and elevated liver enzymes. Intracytoplasmic bacterial aggregates (morulae) may be visible in the leukocytes of some patients. Ehrlichiosis may also progress to involve the central nervous system, resulting in life-threatening complications.

### B. Laboratory Criteria:

1. **Confirmatory laboratory evidence includes at least one of the following:**
  - a. Detection of DNA from an *Ehrlichia* species by polymerase chain reaction (PCR) assay performed in EDTA whole blood.
  - b. Fourfold change in IgG antibody titer to antigen from an *Ehrlichia* species by indirect immunofluorescence assay (IFA) between paired serum samples (with the first collected within one week of illness onset and the second collected two to four weeks later).
  - c. Immunohistochemical (IHC) detection of antigens from an *Ehrlichia* species in a skin biopsy or autopsy sample.
  - d. Isolation of an *Ehrlichia* species from a clinical specimen in cell culture.
2. **Supportive laboratory evidence includes at least one of the following:**
  - a. Serological evidence of elevated IgG (IgM antibody titer is not used independently) to an *Ehrlichia* species by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays in other format.
  - b. Identification of morulae in the cytoplasm of monocytes or macrophages by microscopic examination.

**NOTE:** Clinical signs of disease caused by *Ehrlichia* species are similar to those caused by *A. phagocytophilum*; therefore, it is important to perform testing for all ehrlichiosis- and anaplasmosis-causing agents.

Current commercially available ELISA tests cannot evaluate changes in antibody titers. IFA serology is the most common testing employed by commercial laboratories for the detection of *E. chaffeensis*. There is currently no commercial IFA test available for identification of *E. muris eauclairensis* (EML). The Centers for Disease Control and Prevention (CDC) has developed an in-house IFA serology test specific for detecting EML antibodies. PCR testing is the best method for determining a diagnosis between all the rickettsial agents because it is more specific, sensitive, and does not cross react. When performing PCR testing, an EDTA blood sample should be collected before the patient has been treated with antibiotics. Biopsy or autopsy specimens should be collected when performing IHC testing.

Serology testing (IFA) requires a fourfold titer change between two serum samples for confirmation of results. The first sample should be collected within one week of illness onset, and the second sample two to four weeks later. CDC uses an IFA IgG titer cutoff of  $\geq 1:64$  as positive but other laboratories may have their own positive cutoff. CDC does not use IgM test results independently because IgM tests may be unreliable as they lack specificity and can persist for a long time. When sera demonstrate elevated antibody responses to both *Ehrlichia* and *Anaplasma* species, the agent with the higher antibody response (at least fourfold) should be the disease agent.

reported. In cases where an elevated antibody response is demonstrated to both *Ehrlichia* and *Anaplasma* species, and a fourfold difference is *not* established, cases should be classified as Ehrlichiosis/Anaplasmosis, undetermined.

### C. Wisconsin Surveillance Case Definition:

Four categories of ehrlichiosis should be reported for the purpose of surveillance:

1. *Ehrlichia chaffeensis* infection: Formerly known as human monocytic ehrlichiosis (HME), OR
2. *Ehrlichia ewingii* infection: Formerly included in the human ehrlichiosis (HE) unspecified category, OR
3. *Ehrlichia muris* subsp. *eauclairensis* (EML) infection, OR
4. Ehrlichiosis/ anaplasmosis, undetermined includes:
  - a. Case-patients with test results demonstrating cross-reactivity or possible dual infection with more than one agent (cases with serology test results that have equivalent titers or less than a fourfold difference in titers between two different species, and that are unable to be resolved by further testing), and
  - b. Case-patients infected with novel species that have not been classified.

**Clinically compatible illness:** Any reported fever and one or more of the following: headache, myalgia, anemia, leucopenia, thrombocytopenia, or any hepatic transaminase elevation. All positive (IgG titer  $\geq 1:64$ ) laboratory results need to be accompanied with the patient's clinical information to determine case status as listed below:

- **Confirmed:** A clinically compatible illness that is laboratory confirmed for one of the four disease categories above.
- **Probable:** A clinically compatible illness that has supportive laboratory results for one of the four disease categories above.
- **Suspect:** A positive laboratory result without any clinical information (no follow-up information).

**Note:** If equivalent titers are present for both *Anaplasma* and *Ehrlichia* and patient meets compatible clinical symptoms, it can be classified as probable Ehrlichiosis/Anaplasmosis, undetermined. Since ehrlichiosis is less common in Wisconsin, it is important to ask about travel history outside of the county of residence and out of state within 30 days of symptom onset for all *Ehrlichia* species detected.

## II. REPORTING

- A. **Wisconsin Disease Surveillance Category II—Methods for Reporting:** This disease shall be reported to the patient's local health officer or to the local health officer's designee within 72 hours of recognition of a case or suspected case, per Wis. Admin. Code § [DHS 145.04\(3\)\(b\)](#). Report electronically through the Wisconsin Electronic Disease Surveillance System (WEDSS), or mail or fax a completed [Acute and Communicable Disease Case Report](#) (form [F-44151](#)) to the address on the form.
- B. **Responsibility for Reporting:** According to Wis. Admin. Code § [DHS 145.04\(1\)](#), persons licensed under Wis. Stat. ch. [441](#) or [448](#), laboratories, health care facilities, teachers, principals, or nurses serving a school or day care center, and any person who knows or suspects that a person has a communicable disease identified in [Appendix A](#).
- C. **Clinical Criteria for Reporting:** Any reported fever and one or more of the following: headache, myalgia, anemia, leucopenia, thrombocytopenia, or any hepatic transaminase elevation. All positive (IgG titer  $\geq 1:64$ ) laboratory results need to be accompanied with the patient's clinical information to determine case status as described in the surveillance case definitions above.
- D. **Laboratory Criteria for Reporting:** Confirmatory or supportive laboratory findings.

## III. CASE INVESTIGATION

- A. **Responsibility for case investigation:** It is the responsibility of the local health department (LHD) to investigate or arrange for investigation of suspected or confirmed cases as soon as is reasonably possible. A case investigation may include information collected by phone, in person, in writing, or through review of medical records or communicable disease report forms, as necessary and appropriate.

- B. **Required Documentation:** Complete the WEDSS disease incident investigation report, including appropriate, disease-specific tabs. This may be facilitated by completing the [Wisconsin Tickborne Rickettsial Disease Case Report Worksheet](#) (form [F-00336](#)) available at the DHS website. Upon completion of investigation, set WEDSS disease incident process status to “Sent to State.”

#### IV. PUBLIC HEALTH INTERVENTIONS AND PREVENTION MEASURES

- A. In accordance with Wis. Admin. Code § [DHS 145.05](#), local public health agencies should follow the methods of control recommended in the current editions of *Control of Communicable Diseases Manual*, edited by David L. Heymann, published by the American Public Health Association, and the American Academy of Pediatrics’ *Red Book: Report of the Committee on Infectious Diseases*, unless otherwise specified by the state epidemiologist.
- B. Contact providers for clinical signs and symptoms using the [Wisconsin Tickborne Rickettsial Disease Case Report Worksheet](#) for all positive laboratory results.
- C. Once a report is determined as a confirmed or probable case, interview patients for travel history (out of county and out of state) within 30 days from onset of symptoms for exposure risk assessment.
- D. Educate patients as needed to reduce the risk of exposure to infected ticks, methods to prevent future infection, and how to create tick-safe zones around patient’s home. Offer [Ehrlichiosis fact sheet](#).

#### V. CONTACTS FOR CONSULTATION

- A. Local health departments and tribal health agencies: <https://www.dhs.wisconsin.gov/lh-depts/index.htm>
- B. Bureau of Communicable Diseases, Communicable Diseases Epidemiology Section, vectorborne epidemiologists: 608-267-9003
- C. Wisconsin State Laboratory of Hygiene: 1-800-862-1013

#### VI. RELATED REFERENCES

- A. Heymann DL, ed. Ehrlichiosis. In: *Control of Communicable Diseases Manual*. 20th ed. Washington, DC: American Public Health Association, 2015: 183-186.
- B. Kimberlin DW, ed. *Ehrlichia, Anaplasma, and Related Infections*. In: *Red Book: 2018-2021 Report of the Committee on Infectious Diseases*. 31<sup>st</sup> ed. Itasca, IL: American Academy of Pediatrics, 2018: 323-328.
- C. Centers for Disease Control and Prevention Ehrlichiosis website: <http://www.cdc.gov/ehrlichiosis/index.html>
- D. 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. *MMWR*. 2016;65:1-44.
- E. Wisconsin Tickborne Rickettsial Disease Case Report Worksheet: <https://www.dhs.wisconsin.gov/forms/f0/f00336.pdf>
- F. Wisconsin Anaplasmosis and Ehrlichiosis Fact Sheet: <https://www.dhs.wisconsin.gov/publications/p4/p42045.pdf>