Ehrlichiosis/Anaplasmosis, Human

(*Ehrlichia chaffeensis, Ehrlichia ewingii, and Anaplasma phagocytophilum*)

PROTOCOL CHECKLIST

- ☐ Enter available information into Merlin upon receipt of initial report
- ☐ Review background information on the disease (see page 2), case definition (see page 3), and laboratory testing (see page 6)
- ☐ Visit Florida Department of Health Tick-Borne Disease in Florida for more information on tick-borne diseases: **http://www.doh.state.fl.us/Environment/medicine/arboviral/Tick_Borne_Diseases/Tick_Index.htm**
- ☐ Contact provider (see page 7)
- ☐ Interview case-patient
  - ☐ Review disease facts (see page 2)
    - ☐ Mode of transmission
    - ☐ Incubation period
    - ☐ Symptoms
  - ☐ Ask about exposure to relevant risk factors (see Section 5. Case Investigation)
    - ☐ History of tick bite or exposure to tick habitat (wooded, grassy, or bushy area including yard) 2 weeks prior to onset
    - ☐ Travel and activity history
    - ☐ Exposure to deer, rodents, or pets including dogs and cats
    - ☐ Recent transfusion or organ transplant
  - ☐ Provide education on transmission and prevention (see page 7)
    - ☐ Awareness of tick-borne diseases
    - ☐ Avoid tick-infested areas whenever possible
    - ☐ Wear light-colored clothing that covers arms and legs in tick-infested areas
    - ☐ Tuck pants into boots or socks and long-sleeved shirts button off at the cuff
    - ☐ Use insect repellent containing DEET on skin or clothing
    - ☐ Use permethrin according to manufacturer's directions on clothing and gear
    - ☐ Perform daily tick checks after entering tick-infested areas
    - ☐ Shower after entering tick-infested areas
    - ☐ Control tick populations in yard and on pets.
    - ☐ Protect pets from ticks by consulting with a veterinarian
- ☐ Enter additional data obtained from interview into Merlin (see page 7)

Ehrlichiosis/ Anaplasmosis, Human

1. DISEASE REPORTING

A. Purpose of reporting and surveillance

1. To identify the incidence of disease and risk factors associated with *Ehrlichia* and *Anaplasma* in terms of temporal, geographic, and demographic occurrences
2. To facilitate strategies designed to prevent and control disease transmission

B. Legal reporting requirements

Laboratories and physicians are required to report cases to the local county health department (CHD) within one working day of identification/diagnosis. Reports should not be delayed for convalescent samples as final laboratory confirmation.

C. County health department investigation responsibilities

1. Begin the investigation as soon as possible, but no longer than two business days, after receiving report from a provider or laboratory.
2. Report all confirmed, probable, and suspect cases in Merlin. **See Case Definitions** in **Section 3** for proper classification. The Tick-borne Rickettsial Disease Case Report form is available to assist in follow up and investigation: http://www.doh.state.fl.us/disease_ctrl/epi/topics/crforms.html
3. Note: *Anaplasma phagocytophilum* should be reported in Merlin as Ehrlichiosis/Anaplasmosis, HGE (code=08381), *Ehrlichia chaffeensis* should be reported in Merlin as Ehrlichiosis/Anaplasmosis, HME (code=08382), *Ehrlichia ewingii* should be reported in Merlin as Ehrlichiosis/Anaplasmosis (code=08383), and an undetermined species of Ehrlichiosis/Anaplasmosis should be reported in Merlin as Ehrlichiosis/Anaplasmosis (code=08384).

2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic agent

In the United States, human ehrlichiosis and anaplasmosis is the result of at least 3 different species of obligate intracellular gram-negative cocci ranging in size from 0.5 to 1.5 µm in diameter. All three species have a tropism for white blood cells. *E. chaffeensis* is found primarily in monocytes, while *A. phagocytophilum* and *E. ewingii* are found primarily in granulocytes. In addition, another *Ehrlichia* species has been provisionally call *Ehrlichia muris*-like (EML) has been identified in a small number of patients from the upper Midwest. In some instances, intracytoplasmic bacteria aggregates known as morulae may be visible in leukocytes.

B. Description of illness

All 3 species of human ehrlichiosis/anaplasmosis have similar disease manifestations. They are tick-borne illnesses with acute onset of fever and one or more of the following symptoms or signs: headache, myalgia, anemia, leucopenia, thrombocytopenia, elevated hepatic transaminases, nausea, vomiting, or rash. Rash is less common than other tick-borne diseases like Rocky Mountain spotted fever. Severe manifestations can occur including renal failure, disseminated intravascular coagulopathy, meningoencephalitis, severe abdominal pain, seizures, and coma. 2-3% of cases are fatal and severe symptoms occur in greater frequency for *E. chaffeensis* than for *A. phagocytophilum* infections. Symptoms typically last 1 to 2

weeks and recovery generally occurs without sequelae. People fifty years old and older or with underlying immunosuppression conditions are at increased risk for more severe disease.

C. Reservoirs

Human ehrlichiosis/anaplasmosis has many documented wildlife reservoirs outside of the ticks that transmit the disease. White-tailed deer, white-footed mice, *Neotoma* woodrats, dogs, cervids, ruminants and field rodents among others. Species of reptiles, birds, and small rodents may play an important role in the life cycle of the tick and can be responsible for changes in incidence of disease. The lone star tick (*Amyblyomma americanum)* is the primary tick vector for both *E. chaffeensis* and *E. ewingii.* Two closely related species of black-legged ticks (*Ixodes scapularis, the* deer tick and *Ixodes pacificus*, the western black-legged tick) are the primary tick vectors for *A. phagocytophilum*. A tick vector for EML has not yet been established.

D. Modes of transmission

Transmission is through the bite of a tick.

E. Incubation period

The typical incubation period for human ehrlichiosis and anaplasmosis ranges from 7 to 14 days with a median of 9 days following exposure to an infecting tick.

F. Period of communicability

There is no evidence of person to person transmission other than by blood transfusion.

G. Treatment

Doxycycline is the drug of choice for treatment of human ehrlichiosis/anaplasmosis. Treatment should continue for at least 3 days after defervescence for a minimum total course of 7 days. This disease can be severe or even fatal if a patient remains untreated. Failure for a patient to respond within 3 days to doxycycline should suggest an infection by an agent other than *Ehrlichia* or *Anaplasma*. Sulfa-based antimicrobials are contraindicated as they may lead to more severe disease complications.

H. Prophylaxis

None indicated.

I. Human ehrlichiosis/anaplasmosis in Florida

Since 2001, Florida has seen the number of cases of human ehrlichiosis/anaplasmosis range from 5 to 21 cases annually. Trends for Ehrlichia/Anaplasma infections have been increasing see the most recent MMWR ("Notifiable Diseases and Mortality Tables") for current numbers. *E. chaffeensis* has had consistently more cases identified in Florida than the other 2 species. Although disease transmission can occur year round in Florida, peak transmission typically occurs in the late spring and early summer months.

3. CASE DEFINITION

A. Clinical description

A tick-borne illness characterized by acute onset of fever and one or more of the following symptoms or signs: headache, myalgia, anemia, leukopenia, thrombocytopenia, elevated hepatic transaminases, nausea, vomiting, or rash. Intracytoplasmic bacterial aggregates (morulae) may be visible in the leukocytes of some patients.

B. Laboratory criteria for diagnosis

For the purposes of surveillance,

1. *Ehrlichia chaffeensis* infection (formerly included in the category Human Monocytic Ehrlichiosis [HME]):

Laboratory confirmed:

- Serological evidence of a fourfold change in immunoglobulin G (IgG)-specific antibody titer to *E. chaffeensis* antigen by indirect immunofluorescence assay (IFA) between paired serum samples (one taken in first week of illness and a second 2-4 weeks later)

OR

- Detection of *E. chaffeensis* specific DNA in a clinical specimen via polymerase chain reaction (PCR) assay

OR

- Demonstration of *E. chaffeensis* antigen in a biopsy or autopsy sample by immunohistochemical (IHC) methods

OR

- Isolation of *E. chaffeensis* from a clinical specimen in cell culture.

Laboratory supportive:

- Serological evidence of elevated IgG or IgM antibody reactive with *E. chaffeensis* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or assays in other formats (CDC uses an IFA IgG cutoff of >1:64 and does not use IgM test results independently as diagnostic support criteria.)

OR

- Identification of morulae in the cytoplasm of monocytes or macrophages by microscopic examination

2. *Ehrlichia ewingii* infection (formerly included in the category Ehrlichiosis [unspecified, or other agent]):

Laboratory confirmed:

- Because the organism has never been cultured, antigens are not available. Thus, *Ehrlichia ewingii* infections may only be diagnosed by molecular detection methods: *E. ewingii* DNA detected in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay

3. *Anaplasma phagocytophilum* infection (formerly included in the category Human Granulocytic Ehrlichiosis [HGE]):

Laboratory confirmed:

- Serological evidence of a fourfold change in IgG-specific antibody titer to *A. phagocytophilum* antigen by indirect immunofluorescence assay (IFA) in paired serum samples (one taken in first week of illness and a second 2-4 weeks later)

OR

- Detection of *A. phagocytophilum* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay

OR

- Demonstration of anaplasmal antigen in a biopsy/autopsy sample by immunohistochemical methods

OR

- Isolation of *A. phagocytophilum* from a clinical specimen in cell culture

Laboratory supportive:

- Serological evidence of elevated IgG or IgM antibody reactive with *A. phagocytophilum* antigen by IFA, enzyme-linked immunosorbent Assay (ELISA), dot-ELISA, or assays in other formats (CDC uses an IFA IgG cutoff of ≥1:64 and does not use IgM test results independently as diagnostic support criteria.)

OR

- Identification of morulae in the cytoplasm of neutrophils or eosinophils by microscopic examination

4. Human ehrlichiosis/anaplasmosis – undetermined:

- See case classification

Exposure

Exposure is defined as having been in potential tick habitats within the past 14 days before onset of symptoms. A history of a tick bite is not required.

Case classification

Confirmed: A clinically compatible case (meets clinical evidence criteria) that is laboratory confirmed.

Probable: A clinically compatible case (meets clinical evidence criteria) that has supportive laboratory results. For ehrlichiosis/anaplasmosis – an undetermined case can only be classified as probable. This occurs when a case has compatible clinical criteria with laboratory evidence to support ehrlichia/anaplasma infection, but not with sufficient clarity to definitively place it in one of the categories previously described. This may include the identification of morulae in white cells by microscopic examination in the absence of other supportive laboratory results.

Suspect: A case with laboratory evidence of past or present infection but no clinical information available (e.g., a laboratory report).

Comment

There are at least three species of bacteria, all intracellular, responsible for ehrlichiosis/ anaplasmosis in the U.S.: *Ehrlichia chaffeensis*, found primarily in monocytes, *and Anaplasma phagocytophilum* and *Ehrlichia ewingii,* found primarily in granulocytes. The clinical signs of disease that result from infection with these agents are similar, and the range distributions of the agents overlap, so testing for one or more species may be indicated. Serologic cross-reactions may occur among tests for these etiologic agents.

Four sub-categories of confirmed or probable ehrlichiosis/anaplasmosis should be reported: 1) human ehrlichiosis caused by *Ehrlichia chaffeensis*, 2) human ehrlichiosis caused by *E. ewingii*, 3) humananaplasmosis caused by *Anaplasma phagocytophilum*, or 4) human ehrlichiosis/anaplasmosis-undetermined. Cases reported in the fourth sub-category can only be reported as “probable” because the cases are only weakly supported by ambiguous laboratory test results. Problem cases for which sera demonstrate elevated antibody IFA responses to more than a single infectious agent are usually resolvable by comparing the levels of the antibody responses, the greater antibody response generally being that directed at the actual agent involved. Tests of additional sera and further evaluation via the use of PCR, IHC, and isolation via cell culture may be needed for further clarification. Cases involving persons infected with

more than a single etiologic agent, while possible, are extremely rare and every effort should be undertaken to resolve cases that appear as such (equivalent IFA antibody titers) via other explanations. Current commercially available ELISA tests are not quantitative, cannot be used to evaluate changes in antibody titer, and hence are not useful for serological confirmation. Furthermore, IgM tests are not always specific and the IgM response may be persistent. Therefore, IgM tests are not strongly supported for use in serodiagnosis of acute disease.

Acute and convalescent sera from reported and suspect cases should be acquired on all cases and sent to the Bureau of Laboratories.

Reporting: Next business day; triggers for reporting include: any cases with compatible clinical and laboratory evidence or ehrlichiosis or anaplasmosis, healthcare records that contain a diagnosis of ehrlichiosis or anaplasmosis, or a death certificate that lists ehrlichiosis or anaplasmosis as cause of death or a significant condition

Acute and convalescent sera from reported and suspect cases should be acquired on all cases and sent to the Bureau of Laboratories.

4. LABORATORY TESTING

A. Criteria for diagnosis

The diagnosis of human ehrlichiosis/anaplasmosis can be made using a variety of testing methods Note: To have a laboratory confirmed case of human ehrlichiosis/anaplasmosis IFA a four-fold change in IgG titer is required using paired serum samples (one taken in the first week of illness and a second 2-4 weeks later)

B. Services available at the Bureau of Public Health Laboratories (BPHL)

BPHL can test clinical specimens for either *Ehrlichia* or *Anaplasma.*

C. Testing requests

1. Submitting specimens/isolates to BPHL
   a. All submissions should be accompanied by Clinical Lab Submission Form 1847 (http://www.doh.state.fl.us/lab/addpages/BOL_Forms.html).
   b. In the Clinical Lab Submission Form 1847, select option 1710 (Rickettsia/Ehrlichia) under the Virology section on the form, and fill out additional mandatory information in the box below
   c. Including clinical history is important for laboratory testing

3. Packaging and shipping
   a. All specimens and isolates for *Ehrlichia* and *Anaplasma* testing should be sent to the Jacksonville BPHL laboratory.
   b. Place labeled vial in the proper inner/outer container (aluminum screw-cap inner container with spill absorber holds the primary vial and that is then placed in an outer cardboard screw-cap container). Please place the Clinical Lab Submission Form 1847 in a plastic Ziploc bag between the inner and outer container. Package according to International Air Transport Association (IATA) regulations, labeling the outer shipping container: *UN3373, Biological Substance Category B.*
   c. Specimens and isolates should be sent at ambient temperature or cooler, but cool packs should not be in direct contact with vials.

   d. http://www.doh.state.fl.us/lab/PDF_Files/Packaging_Flowchart_0422051.pdf
   e. http://www.doh.state.fl.us/lab/PDF_Files/Packaging_Flowchart_notes_0422051.pdf
4. Contact the Jacksonville BPHL with questions: http://www.doh.state.fl.us/lab/addpages/BOL_Contacts.html.

D. Interpretation of results

For any questions about lab results from BPHL or other labs, consult the Bureau of Environmental Public Health Medicine or the Jacksonville BPHL.

5. CASE INVESTIGATION

A. Contact the physician or hospital

1. **Tick-borne Rickettsial Disease Case Report form (required):** http://www.doh.state.fl.us/disease_ctrl/epi/topics/crforms.html. This form can be used to guide the interview and can be completed during the interview.
2. Confirm that an Ehrlichiosis/Anaplasmosis infection has been diagnosed in the reported case.
3. Obtain the following:
   a. Date of onset
   b. Signs and symptoms
   c. Potential exposure to tick habitats
   d. Predisposing conditions (e.g., immunosuppression)
   e. Tests performed (including IFA, ELISA, EIA, PCR, IHC, culture, microscopic examination or any other tests performed)
   f. Treatment (especially antibiotics).
4. Ask what information has been given to the patient, including whether the patient knows about the diagnosis.
5. Obtain as much demographic information as possible, including contact information (home, cellular, pager and/or work numbers). Ask how and where the patient can be contacted (i.e., at hospital or home).
6. Notify the physician that you will be contacting the case as DOH follows up on all cases of human ehrlichiosis and anaplasmosis to assess risks factors, to better characterize the occurrence of these infections in Florida, and to identify potential means for preventing further illness. It may also be appropriate at this point to determine if the physician has any concerns about the health department contacting the case.

B. Interview the case

1. Contact the case to complete an interview as soon as possible after being reported to optimize recall.
   a. Make at least 3 phone call attempts to reach the case.
   b. Calls should be made at different times of the day, with at least one attempt in the evening.
2. **Tick-borne Rickettsial Disease Case Report form (required):** http://www.doh.state.fl.us/disease_ctrl/epi/topics/crforms.html. This form can be used to guide the interview and can be completed during the interview.
   Warning: Merlin requires additional info not found on CRF
3. Items to cover during interview include:
   a. Provide brief background on disease, including mode of transmission, potential exposure sites, incubation period, symptoms, etc.

b. Activities during exposure period (30 days before onset):
   i. History of tick bite or exposure to tick habitat (wooded, grassy, or brushy area including yard) in 2 weeks prior to onset of symptoms
   ii. Travel and activity history: occupation, hobbies (e.g., camping, hunting, other outdoor activities, especially in wooded areas), travel outside of Florida.
   iii. Animal investigation: residence surrounded by woods or forest with deer or rodents on property. Any animals that could have ticks on them that come into the home.
   iv. Recent blood transfusions or organ transplant
c. Provide basic education to cases about precautions to limit exposures to ticks including:
   i. Avoiding tick habitats if possible
   ii. Covering up by wearing shoes, socks, long pants, and long-sleeved shirts (light colored clothing preferred for spotting ticks)
   iii. Use insect repellent containing DEET on skin or clothing
   iv. Use permethrin according to manufacturer's directions on clothing or gear
   v. Perform daily tick checks: check your body and your clothes, check your children for ticks,
   vi. Showering soon after being outdoors reduces your risk of being bitten by ticks and tick-borne diseases transmission
   vii. Control tick populations in yards and on pets
   viii. Protect pets from ticks by consulting with your veterinarian
   ix. Reduce ticks in your yard
      i. Modify your landscape to create tick-safe zones
      ii. Provide a vegetation-free play area
      iii. Use a chemical control agent
      iv. Discourage deer from entering your yard

C. Merlin data entry

1. Create a case in Merlin under the appropriate disease code.
   a. *A. phagocytophilum* should be reported in Merlin as **Ehrlichiosis/Anaplasmosis, HGE (code=08381)**
   b. *E. chaffeensis* should be reported in Merlin as **Ehrlichiosis/Anaplasmosis, HME (code=08382)**
   c. *E. ewingii* should be reported in Merlin as **Ehrlichiosis/Anaplasmosis (code=08383)**
   d. An undetermined species of Ehrlichiosis/Anaplasmosis should be reported in Merlin as **Ehrlichiosis/Anaplasmosis (code=08384)**.
2. Enter the data collected into Merlin, being sure to include all required fields on the Basic Data screen, complete the Case Symptoms screen, and attach all relevant labs. Please attach **ALL** labs received via electronic laboratory reporting (ELR) to the case. For questions regarding lab results, please contact the Bureau of Environmental Public Health Medicine.

6. CONTROLLING FURTHER SPREAD

A. Patient/household education on prevention recommendations

1. Avoiding tick habitats if possible.

2. If exposure to tick habitats cannot be avoided, cover up by wearing shoes, socks, long pants, and long-sleeved shirts (light colored clothing preferred for spotting ticks)
3. Use insect repellent containing DEET on skin or clothing
4. Use permethrin according to manufacturer's directions on clothing or gear
5. Perform daily tick checks: check your body and your clothes, check your children for ticks.
6. Showering soon after being outdoors reduces your risk of being bitten by ticks
7. Control tick populations in yards and on pets
8. Protect pets from ticks by consulting with your veterinarian
9. Reduce ticks in your yard
    a. Modify your landscape to create tick-safe zones
    b. Provide a vegetation-free play area
    c. Use a chemical control agent
    d. Discourage deer from entering your yard

7. IMPORTANT LINKS

A. Ehrlichiosis/Anaplasmosis, Human Case Report Form:
http://www.doh.state.fl.us/disease_ctrl/epi/topics/crforms.html

B. Florida Department of Health Tick-Borne Disease in Florida:
http://www.doh.state.fl.us/Environment/medicine/arboviral/Tick_Borne_Diseases/Tick_Index.htm

C. Surveillance and Control of Selected Tick-borne Diseases in Florida, 2009 Guidebook - DRAFT
http://www.doh.state.fl.us/Environment/medicine/arboviral/Tick_Borne_Diseases/PDFs/2009TickGuide.pdf

D. Tick-borne Disease Surveillance Reports
http://www.doh.state.fl.us/Environment/medicine/arboviral/Tick_Borne_Diseases/Tick_surveillance_reports.html

E. CDC Features: Stop Ticks
http://www.cdc.gov/Features/StopTicks/

F. MMWR on Rickettsial Diseases Diagnosis and Management
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm

8. REFERENCES

A. Heymann, D.L. (Ed.). (2008). Control *of communicable diseases manual* (19th ed.). Washington: American Public Health Association.

B. American Academy of Pediatrics. (2012). *Red Book: 2012 Report of the Committee on Infectious Diseases* (29th ed.). Grove Village, IL: American Academy of Pediatrics.

C. Division of Environmental Health. (2009). *Surveillance and Control of Selected Tick-borne Diseases in Florida 2009 Guidebook DRAFT*. Tallahassee, FL: Florida Department of Health.