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## Ehrlichiosis/Anaplasmosis

### Overview <sup>(1, 2, 3)</sup>

Ehrlichiosis and anaplasmosis are tick-borne illnesses that begin with a sudden onset of fever, chills, and headache. Patients often report malaise and muscle aches, as well as other flu-like symptoms. Without prompt treatment, these diseases can be fatal. Doxycycline is the accepted treatment of presumptive ehrlichiosis or anaplasmosis in adults and children.

Ehrlichiosis and anaplasmosis are caused by three related bacterial zoonotic pathogens that infect animal reservoir hosts and require a tick to be transmitted to humans. Ehrlichiosis resulting *Ehrlichia chaffeensis* infection occurs primarily in the southeastern and south-central regions of the U.S., while *E. ewingii* infections have been reported mainly in immunocompromised patients from Missouri, Oklahoma, and Tennessee. The lone star tick transmits both pathogens. *Anaplasma phagocytophilum* (formerly *E. phagocytophila*), the agent that cause human anaplasmosis, occurs primarily in the northeastern and upper mid-western U.S. and is transmitted by the deer tick.

Early in the course of infection, ehrlichiosis and anaplasmosis can resemble other infectious and non-infectious diseases, making diagnosis difficult. Traditional diagnostic tests that detect rising antibodies cannot provide diagnosis confirmation early in the course of disease, which is when the patient typically first visits a physician. Newer molecular-level assays are able to identify the infecting bacteria DNA, but direct detection assays may not provide timely results that help guide treatment decisions of acutely ill patients. Treatment decisions must be based on epidemiologic and clinical clues and should never be delayed while waiting for laboratory confirmation of a diagnosis.

### Prevention

- Avoid tick habitats during the peak time of year (generally April through September).
- Tick repellents with 20 to 50% DEET offer the best protection. The American Academy of Pediatrics has recommended that repellents containing up to 30% DEET can be used on children over 2 months of age.
- Wear clothes that will help shield you from ticks.
- Check frequently for ticks and remove them promptly.

For a more complete description of ehrlichiosis and anaplasmosis, refer to:

- *Control of Communicable Diseases Manual* (CCDM), American Public Health Association, 2004
- American Academy of Pediatrics. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. 2006.
- U.S. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report, Recommendations and Reports #4. Diagnosis and Management of Tick-borne Rickettsial Diseases*, 2006.

### Case Definition <sup>(4)</sup>

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***Clinical presentation:***

A tick-borne illness characterized by acute onset of fever and one or more of the following symptoms or signs: headache, myalgia, malaise, anemia, leukopenia, thrombocytopenia, or elevated hepatic transaminases. Nausea, vomiting, or rash may be present in some cases. Intracytoplasmic bacterial aggregates (morulae) may be visible in the leukocytes of some patients. There are at least three species of bacteria, all intracellular, responsible for ehrlichiosis/anaplasmosis in the United States: *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) Human anaplasmosis 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.)

***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.**

***Clinical evidence:***

Any reported fever and one or more of the following: headache, myalgia, anemia, leucopenia, thrombocytopenia, or any hepatic transaminase elevation.

***Laboratory evidence:***

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**



Laboratory confirmed, continued:

- Detection of *E. chaffeensis* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, **or**
- Demonstration of ehrlichial antigen in a biopsy/autopsy sample by immunohistochemical 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  $\geq 1:64$  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 anaplasma 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  $\geq 1:64$  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 section below

**Comment:** 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. Further, 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.

***Detailed definitions for 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).

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## **Information Needed for Investigation**

### **Verify the diagnosis.**

- Determine what laboratory tests were conducted and the results.
  - Patients might lack diagnostic IgG and IgM antibody titers in the first 7 days of illness. A positive IgG titer or index value can indicate a past infection or early response to current infection. IgM tests are not always specific and the IgM response may be persistent. For these reasons, IgM titers or index values without IgG response should be interpreted with caution.
  - Determine whether complete blood cell count and comprehensive metabolic panel laboratory findings exist, indicating anemia, thrombocytopenia, leucopenia, or any hepatic transaminase elevation.
- Verify with the care provider the presence of a clinically compatible illness, i.e., acute onset of fever, which may be accompanied by headache, malaise, myalgia, nausea and vomiting, or neurologic signs. In addition, rash is observed in approximately one third of all patients with HME and described in up to 66% of children.<sup>(3)</sup>
- Lack of a confirmed recent tick bite does not exclude the diagnosis.

**Establish the extent of illness.** Investigation should consider family members, coworkers, pets, and other contacts that have or have recently had a febrile illness and shared environmental exposures with the patient.<sup>(3,5)</sup>

## **Notification And Control Measures**


Ehrlichiosis and anaplasmosis are not transmitted from person-to-person.

### **Prevention and Control Measures** (*For detailed information see*)

- American Academy of Pediatrics. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. 2006, “Prevention of Tick-borne Infections”
- U.S. Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report, Recommendations and Reports #4, Diagnosis and Management of Tick-borne Rickettsial Diseases, 2006, “Prevention.”  
<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm> (January 2008)

## **Laboratory Procedures For Tick-Borne Rickettsial Diseases**

Laboratory confirmation of infection is vital to understanding the epidemiology and public health impact of tick-borne rickettsial diseases (e.g., Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis). The Missouri State Public Health Laboratory (SPHL) cannot overemphasize the importance of obtaining paired, appropriately timed specimens for serological analysis. Traditional diagnosis and confirmation of rickettsial diseases is fundamentally retrospective in nature, and based upon serology. A single serologic test does not provide the diagnostic strength of the standard testing strategy (paired acute and convalescent specimens).

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**At no time should the empiric treatment of the patient with doxycycline be delayed for laboratory testing results.**

#### RECOMMENDATIONS

- The SPHL will submit whole blood in EDTA and biopsies for PCR testing and paired serum specimens for serological analysis to the U.S. Centers for Disease Control and Prevention (CDC) for testing. The SPHL does not test for rickettsial diseases. A negative result on any of the tests does not rule out rickettsial diseases.
- No fees are assessed for specimens referred to CDC through the SPHL.
- The most efficient diagnostic testing strategy for acutely ill patients is to obtain:
  - An EDTA whole blood specimen
  - A skin punch biopsy (for rash-associated illnesses)
  - Paired acute and convalescent serum specimens
- Many commercial reference laboratories offer several diagnostic methods, including PCR and serology.
  - 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.
  - 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.


#### CONFIRMATORY DIAGNOSTIC TESTS

##### FOR MOLECULAR (PCR) TESTING

- Whole blood in EDTA is very useful for ehrlichiosis and anaplasmosis diagnosis, **and is the only acceptable specimen for *e. ewingii* testing.**
- Whole blood is not the best possible specimen for RMSF. This is due to the low numbers of organisms circulating in the blood during acute illness.
- Skin punch biopsies, taken at the site of the rash and before antibiotic therapy, are extremely valuable. These biopsies contain larger numbers of organisms due to their localization within the endothelial cells of blood vessels and capillaries.
- **PCR may not be useful if the patient has been on antibiotics for > 24hrs.**

##### FOR SEROLOGIC TESTING

- The first sample in a red top tube should be taken within the first week after onset of illness. The second sample should be taken 2-3 weeks later. Beyond this interval, diagnostic success cannot be assured. Testing a second sample, several months later will not provide helpful information.
- The acute-phase serum should be retained and submitted at the same time with a follow-up convalescent serum specimen obtained 2-3 weeks later. In some

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- cases, a third late convalescent serum specimen, taken 2 weeks later, may be necessary to show rising levels.
- Acute blood can be collected, centrifuged, and the serum removed and frozen until the convalescent blood is collected. Alternatively, the SPHL will hold the blood and send a reminder letter for the convalescent specimen. Single acute-phase specimens will not be submitted to CDC for analysis.
  - **CSF is NOT the optimal specimen for serology testing.**

#### IMMUNOHISTOCHEMICAL STAINING

- Skin punch biopsies, taken at the site of the rash and before antibiotic therapy, are extremely valuable. These biopsies contain larger numbers of organisms due to their localization within the endothelial cells of blood vessels and capillaries.
- IHC may be performed on autopsy specimens.

#### CELL CULTURE

- Culture is not readily available due to the biosafety risks, the Select Agent issues, and technical difficulty. As a result, culture is rarely used for diagnosis, and other methods (e.g., serology, PCR, or immunostaining) are used to confirm infection.

#### **CDC SPECIMEN SUBMISSION FORM**

To submit laboratory specimens, complete a CDC specimen submission form (CDC 50.34), which can be downloaded from: [http://www.cdc.gov/ncidod/dvbid/misc/CDC50\\_34.pdf](http://www.cdc.gov/ncidod/dvbid/misc/CDC50_34.pdf) (84 KB), or call the Missouri State Public Health Laboratory at (573) 751-0633.

#### **NOTE: Testing will not be initiated without the inclusion of:**


- a. Type of specimen (e.g. serum, csf, skin punch biopsy)
- b. Suspected etiology
- c. Date of onset of symptoms
- d. Brief clinical description
- e. Date of specimen collection
- f. Pertinent travel history
- g. Antibiotic treatment received and date

For information on shipping, specimen types and amount, or for further assistance Additional information on rickettsial detection can be obtained from the Virology Unit at the SPHL (573) 751-0633.

#### **Reporting Requirements**

Ehrlichiosis is a Category II disease and shall be reported to the local health authority or to the Missouri Department of Health and Senior Services (DHSS) within three days of first knowledge or suspicion by telephone, facsimile or other rapid communication.



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1. For all cases, complete a “Disease Case Report” (CD-1).
2. For all cases complete a “Tick-Borne Rickettsial Disease Case Report” (MO 580-2602, 3-10).
  - Obtain the pertinent symptoms, treatment, and health history from the patient’s health care provider or other affiliated health care professional.
  - Exposure and travel history can be obtained from the patient or the patient’s health care provider family, social worker, or family.
3. Entry of the completed CD-1 into MOHSIS negates the need for the paper CD-1 to be forwarded to the District Health Office.
4. Send the completed secondary investigation form to the District Health Office.
5. All outbreaks or “suspected” outbreaks must be reported as soon as possible (by phone, fax, or e-mail) to the Regional Communicable Disease Coordinator. This can be accomplished by completing the Missouri Outbreak Surveillance Report (CD-51)
6. Within 90 days of the conclusion of an outbreak, submit the final outbreak report to the Regional Communicable Disease Coordinator.

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1. Control of Communicable Diseases Manual. “Ehrlichiosis (Sennetsu fever, Human ehrlichiosis found in the USA).” Heymann, David L., ed. 18<sup>th</sup> ed. Washington, DC: American Public Health Association, 2004: 187-190.
2. American Academy of Pediatrics. “*Ehrlichia* Infections (Human Ehrlichiosis).” In: Pickering, LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26<sup>th</sup> ed. Elk Grove Village, IL. 2003: 266-269.
3. Centers for Disease Control and Prevention. *Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis – United States*. MMWR 2006; 55 (Recommendation and Report 4): 1-27. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm> (4/08)
4. Centers for Disease Control and Prevention. *Nationally Notifiable Infectious Diseases United States*, Epidemiology Program Office, Division of Public Health Surveillance and Informatics, <http://www.cdc.gov/epo/dphsi/phs/infdis.htm> (4/08)
5. New England Journal of Medicine. Ehrlichiosis in a golf-oriented retirement community. Standaert SM, Dawson JE, Schaffner W, et al. 1995 Aug 17;333(7):420-5.

## **Other Sources of Information**

1. Mandell, Douglas, and Bennett’s *Principles and Practice of Infectious Diseases*. “*Ehrlichia chaffeensis* (Human Monocytotropic Ehrlichiosis), *Ehrlichia phagocytophila* (Human Granulocytotropic Ehrlichiosis), and Other Ehrlichiae.” G. Mandell, J. Bennett, R. Dolin, eds. 6<sup>th</sup> ed. Vol. 2, 2005: 2311-2315.
2. Clinical Pediatrics. Absence of Tooth Staining With Doxycycline Treatment in Young Children. Volovitz B., et al. 2007, Vol. 46, No. 2, 121-126.
3. New England Journal of Medicine. “*Ehrlichia Ewingii*, A Newly Recognized Agent of Human Ehrlichiosis.” Buller, RS, Arens, M, Hmiel, SP, Paddock, CD, et al. 1999: 341(3), 148-155.

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4. Journal of Clinical Microbiology. Outcome of diagnostic tests using samples from patients with culture-proven human monocytic ehrlichiosis: implications for surveillance. Childs, J.E., Sumner, J.W., Massung, R.F., Standaert, S.M., & Paddock, C.D. 1999, 37(9), 2997-3000. <http://jcm.asm.org/cgi/reprint/37/9/2997> (4/08)
5. The Merck Veterinary Manual. 8<sup>th</sup> Ed. Ed. Susan E. Aiello. Whitehouse Station, NJ: Merck & Co., Inc., 1998. <http://www.merckvetmanual.com/mvm/index.jsp> (search “ehrlichiosis”). (4/08)

### **Web Resources and Information**

1. Free tick-borne disease prevention posters and bookmarks from the Missouri Department of Health and Senior Services (DHSS website) <http://www.dhss.mo.gov/TicksCarryDisease/Publications.html> (4/08)
2. Downloadable tick-check promotion radio public service announcements (DHSS website—spots require .mp3 player such as Windows Media Player or Real Player) <http://www.dhss.mo.gov/TicksCarryDisease/Prevention.html> (4/08)
3. University of Missouri Outreach and Extension Home and Garden Guide “Ticks,” (University of Missouri Extension website) <http://muextension.missouri.edu/explore/agguides/pests/g07382.htm> (4/08)
4. David H. Walker and J. S. Dumler. “Emergence of the Ehrlichiosis as Human Health Problems.” Emerging Infectious Diseases. 1996 January-March; 2(1): 18-29 <http://www.cdc.gov/ncidod/EID/vol2no1/walker1.htm> (4/08)
5. Cunha, B.A., eMedicine Journal, August 25 2006, Volume 7, Number 8, Ehrlichiosis, <http://author.emedicine.com/med/topic3391.htm> (4/08)
6. MedlinePlus Medical Encyclopedia for Ehrlichiosis (MedlinePlus website – National Library of Medicine) <http://www.nlm.nih.gov/medlineplus/ency/article/001381.htm> (4/08)

### **Ehrlichiosis/Anaplasmosis Physician Education Materials**

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