



Infectious Disease Epidemiology Section
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EHRlichiosis / ANAPLASMOSIS

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In the United States, human monocytic ehrlichiosis (HME), and human granulocytic ehrlichiosis (HGE) represent two clinically indistinguishable yet epidemiologically and etiologically distinct diseases caused by *Ehrlichia chaffeensis* and a bacterium similar or identical to *E. equi*, respectively.

- HME *E.chaffeensis*
- HGE *E.equi* and *E. phagocytophila*

Human anaplasmosis (HA), formerly known human granulocytic ehrlichiosis (HGE), is a bacterial disease transmitted to humans by *Ixodes scapularis* (deer tick or blacklegged tick), the same tick that transmits Lyme disease. The HA agent was recently named *Anaplasma phagocytophilum* and was believed to be similar or identical to two veterinary pathogens: *Ehrlichia equi* and *Ehrlichia phagocytophila*.

A third human ehrlichial pathogen, *Ehrlichia sennetsu*, causes Sennetsu Fever, a self-limited mononucleosis-like illness that occurs in Japan and Malaysia. *Ehrlichia ewingii*, an agent reported as a cause of granulocytic ehrlichiosis in dogs, reportedly causes disease in humans.

Infection with these emerging tickborne pathogens results in acute, influenza-like illnesses with fever, headache, malaise and frequently, leukopenia and thrombocytopenia.

Epidemiology

E. chaffeensis infections occur most frequently in southeastern and midwestern states with abundant lone star ticks (*Amblyomma americanum*). The black-legged tick (*Ixodes scapularis*) is the principal vector of the HGE agent in the northeast and upper midwestern United States. This tick also transmits *Borrelia burgdorferi*, which causes Lyme disease. Most recognized HGE cases have originated from states with high rates of Lyme disease, particularly Connecticut, Minnesota, New York and Wisconsin.

Since 1985, approximately 500 ehrlichiosis cases have been confirmed by the Centers for Disease Control and Prevention (CDC). The occurrence of these cases reflects the seasonal activities and geographic distributions of the tick vectors. The average annual reporting rate for the years 1995-1997 was 1.8 cases per 100,000 population (range: 1.1 in 1995 to 2.9 in 1997).

The incubation period is seven to fourteen days after a tick bite or exposure (median, 10 days).

Clinical Description

The frequencies of specific signs and symptoms were:

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| ▪ Fever (defined as greater than or equal to 38.0 °C | 85% |
| ▪ Leukopenia (WBC < 5,000/mm ³) | 61% |
| ▪ Thrombocytopenia (platelet count <150,000) | 68% |

Less than 30% of persons with ehrlichiosis required hospitalization.

Due to its nonspecific signs and symptoms, ehrlichiosis can be difficult to be diagnose based on clinical findings alone. Cases have been initially diagnosed as a viral syndrome, RMSF, septic shock, upper respiratory tract infection, thrombocytopenic purpura, viral hepatitis and cholangitis. Ehrlichiosis should be considered for any patient presenting with fever, headache, chills and myalgia who has a history of a tick bite or has been in wooded areas in a region endemic for *I. Scapularis* (same arthropod responsible for *Borrelia burgdorferi*) or *A. americanum* (also known as the Lone Star tick) within 21 days prior to onset.

HME can cause aseptic meningitis, Acute Respiratory Distress Syndrome, multisystem disease resembling Rocky Mountain Spotted Fever, toxic shock syndrome or overwhelming fatal infection in immunocompromised patients.

HE/Anaplasmosis

Unexplained fever, myalgias, headache, rigors, chills, sweating
Nausea, vomiting, abdominal pain, diarrhea
Rash or cough

Improvement within 24 to 48 hours of doxycycline treatment is a diagnostic clue. If no improvement occurs in 48 hours, Ehrlichiosis can be ruled out.

Laboratory Tests

The presence of morulae in peripheral blood leukocytes is diagnostic when present but may often be missed. A false positive may be due to toxic granulations, Dohle bodies or superimposed platelets.

Indirect fluorescent antibody (IFA) assays to detect antibodies against *E. chaffeensis* and *E. equi* in serum or EDTA anticoagulated whole blood. IFA detects both IgM and IgG antibodies. *E. chaffeensis* antigens should be used for HME and *E. equi* or *phagocytophila* for HGE.

The whole blood or serum using polymerase chain reaction (PCR) assays to detect Ehrlichia spp. DNA.

Serologic cross-reactivity between *E. chaffeensis* and *E. equi* is well recognized and can hinder epidemiologic distinction between HME and HGE. There are ten recognized species of Ehrlichia and substantial serologic cross-reactivity exists among individual species within subgroups of this genus. Some "serologically confirmed" cases of HME and HGE may represent infections with the alternate agent or infections with other, antigenically-related ehrlichial species. Although IFA is the principal diagnostic tool for detecting ehrlichial infection, neither this assay nor PCR-based diagnostics are standardized.

New techniques, including enzyme immunoassays using recombinant ehrlichial antigens and multiplex fluorescence-detection PCR, are under investigation.

Single or paired sera are sent to the CDC for serological testing. Please consult the laboratory in advance as to the timing of specimen collection and transport to the lab so that special reagents will be on-hand to begin analysis without unnecessary delay. Direct questions to the State Laboratory's Bacteriology Section at (504) 568-7683 or the Infectious Disease Epidemiology Section.

Surveillance

Ehrlichiosis is a condition with reporting required within five business days.

Case Definition

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.

Clinical evidence

Any reported fever and one or more of the following: headache, myalgia, anemia, leukopenia, 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**
- 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 or 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 >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

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 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, 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.

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.

References

Dumler JS, Barbet AF, Bekker CP, Dasch GA, Palmer GH, Ray SC, Rikihisa Y, Rurangirwa FR. 2001. Reorganization of genera in the families Rickettsiaceae and Anaplasmataceae in the order Rickettsiales: unification of some species of Ehrlichia with Anaplasma, Cowdria with Ehrlichia and Ehrlichia with Neorickettsia, descriptions of six new species combinations and designation of *Ehrlichia equi* and 'HGE agent' as subjective synonyms of *Ehrlichia phagocytophila*. International Journal of Systematic & Evolutionary Microbiology. 51(Pt 6):2145-2165. Medline UI: 11760958

Investigation

The purpose of investigation is to identify cases, to confirm the diagnosis, to identify high-risk areas within the state and to provide information to the communities involved.

Upon receipt of a report of a case, contact the physician and/or hospital to confirm the diagnosis and obtain laboratory confirmation.

If the diagnosis is based on symptoms with laboratory findings such as thrombocytopenia, leukopenia, elevated liver enzymes and anemia, obtain paired sera to be tested for serologic tests that yield more accurate diagnostic information (immunofluorescent assays, PCR).

Check the patient's history for exposure to ticks (i.e., personal pets, travel history, camping or other outdoor exposures).

Case Management - Treatment

Careful removal of all ticks from patients. (Be sure the head of the tick is not left beneath the skin.)

Coinfection with pathogens of the prioplasm family (*Babesia microti*) or *Borrelia burgdorferi* (Lyme) should be considered in patients with tick exposure history since all three zoonoses are transmitted by the same *Ixodes* ticks and may perhaps be transmitted through the same tick bite.

Doxycycline is the drug of choice for persons infected with ehrlichiosis. The optimal duration of therapy has not been established, but current regimens recommend continuation of treatment for at least three

days following defervescence, for a minimum total course of five to seven days. Severe or complicated disease can require longer treatment courses. Because tetracyclines are contraindicated in pregnancy, rifampin has been used successfully in a limited number of pregnant women with documented HGE.

Prevent exposure to ticks

Limiting exposure to ticks reduces the likelihood of ehrlichial infection. In persons exposed to tick-infested habitats, prompt careful inspection for and removal of crawling or attached ticks remains an important method of preventing disease because Ehrlichia-infected ticks appear to require 24 to 48 hours of attachment to the host before the agent can be transmitted. As with Lyme disease, peridomestic activities account for many of the tick exposures responsible for HGE in the northeastern United States and strategies to reduce vector tick densities through area-wide application of acaricides and control of tick habitats (e.g., leaf litter and brush) have been effective in small-scale trials. New methods being developed include applying acaricides to rodents and deer and using baited tubes, boxes and deer feeding stations in areas where these pathogens are endemic.

Community-based integrated tick management strategies may be an effective public health response to reduce the incidence of tickborne infections.

Hospital precaution and isolation: Standard precautions