

07-ID-03

Committee: Infectious Diseases

Title: Revision of the National Surveillance Case Definition for Ehrlichiosis (Ehrlichiosis/Anaplasmosis)

Statement of the Problem:

The purpose of the recommended revisions to the case definitions of Ehrlichiosis, a tick-borne rickettsial disease under public health surveillance, is to update taxonomic changes in the pathogens, clarify misleading or poorly defined laboratory statements, and to improve case classification for reporting.

Statement of the desired action to be taken:

Revise the national surveillance case definition for Ehrlichiosis.

Goals of surveillance:

The improved case definition will provide the tools to help establish the burden of disease due to this pathogen. This will provide a greater understanding of this disease among physicians, nurses, and public health professionals and allow for appropriate prevention messages to the public.

Methods for surveillance:

Case finding is conducted through clinician and laboratory reporting. Core surveillance data will be reported to the National Notifiable Disease Surveillance System (NNDSS) through the National Electronic Telecommunications System for Surveillance (NETSS) or the National Electronic Disease Surveillance System (NEDSS), as per state protocol.

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. 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.

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**
- 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

Note: 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.

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 definition tables:

Suggested codes for case ascertainment

To be developed.

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).

Period of surveillance:

Ongoing. This revision of the surveillance case definition will be effective January 1, 2008.

Data sharing/release and print criteria:

States and territories will send CDC case data for all confirmed and probable cases. Final printed counts published in MMWR by CDC will distinguish between confirmed and probable cases. Provisional case report data will not be used until verification procedures are completed. Suspect cases will be excluded from final printed counts published by CDC.

Background and Justification:

The case definition for human ehrlichiosis was last updated in 2000. In that revision, cases could be subcategorized into three possible categories: 1) human ehrlichiosis due to *Ehrlichia chaffeensis*, 2) human ehrlichiosis due to *Ehrlichia phagocytophila*, or 3) human ehrlichiosis, undetermined (which was designed to include both cases without clear laboratory support for etiology at species-level and those cases due to the newly recognized *Ehrlichia ewingii*). However, in 1999, a major taxonomic revision of the genera comprising this group of pathogens was published. With gradual acceptance by the public health community, these changes in classification caused problems in nomenclature of the diseases and in loss of clarity in reporting. It became difficult to determine which category a particular case should be placed into due to these taxonomic changes. For example, the agent causing what was inappropriately named, *Ehrlichia phagocytophila*, was moved to the genus *Anaplasma*. The new name, *Anaplasma phagocytophilum*, thus was no longer an ehrlichiosis (infection by an *Ehrlichia* spp.) and had nomenclaturally become anaplasmosis (for which there was no category). *Ehrlichia ewingii* infections were originally expected to be categorized as Ehrlichiosis, undetermined or other, yet now could be correctly classified as another agent responsible for human granulocytic ehrlichiosis.

The current revision is designed to update the taxonomic changes and to clarify some of the wording used for the associated laboratory descriptions. It is proposed that the title of the category include Anaplasmosis to reflect the taxonomic issues with this disease grouping. However, this revision is not intended to create a separate new notifiable disease category as *Anaplasma phagocytophilum* already existed as a subcategory (as *Ehrlichia phagocytophila*), induces similar clinical manifestations, has similar epidemiologic features, and is often suspected and tested with at least one of the other species in this category. The traditional colloquial names would be avoided as they were never unique for that species (considering other infections by *Ehrlichia* globally) and caused confusion. The ehrlichiosis undetermined category would be utilized only to report those cases supported by laboratory tests that demonstrate elevated antibodies to more than one ehrlichial/anaplasma antigen.

References:

- [2000 Case Definition](#)

- [1998 Case Definition](#)
- [1996 Case Definition](#)
- 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.
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