

Ehrlichiosis & Anaplasmosis

Surveillance Protocol

Ehrlichiosis and anaplasmosis are tickborne diseases that are clinically similar but differ by their epidemiology and etiology. These diseases first became reportable in the United States in 1999. In West Virginia, nine cases of ehrlichiosis were reported between 2000–2011. The first cases (2) of anaplasmosis were reported in West Virginia during 2011.

Provider Responsibilities

1. Report suspect and confirmed cases of Ehrlichiosis and Anaplasmosis (including copies of lab results) to the local health department within one week of diagnosis. Supply requested clinical information to the local health department to assist with case ascertainment.
2. Follow recommended testing guidelines for Ehrlichiosis and Anaplasmosis. The gold standard serologic test is indirect immunofluorescence assay (IFA) using paired serum samples taken 2-4 weeks apart. Polymerase chain reaction (PCR) and microscopic examination of blood smears may also be performed.
3. Early treatment with doxycycline is associated with improved outcomes. See <http://www.cdc.gov/ehrlichiosis/symptoms/#treatment> for more information.
4. Providers are encouraged to complete a free webinar on recognizing and treating tick-borne diseases found at: <http://www.cdnetwork.org/NewCDN/LibraryView.aspx?ID=cdn552a>

Laboratory Responsibilities

1. Report positive laboratory results for Ehrlichiosis and Anaplasmosis to the local health department within 1 week.

Local Health Responsibilities

1. Conduct an appropriate case investigation.
 - a. Contact the healthcare provider that ordered the laboratory test to obtain the clinical information on the WVEDSS form.
 - b. If needed, contact the patient to obtain information regarding tick exposure and/or travel history.
 - c. Educate the patient and the patient's family on Ehrlichiosis and Anaplasmosis prevention.
 - d. Report all case data using WVEDSS.
2. Educate the public about Ehrlichiosis and Anaplasmosis, especially regarding the mode of tick transmission and use of personal protection. Prevention messages for these diseases are also effective for other tickborne diseases (e.g. Lyme disease).

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3. Educate providers and laboratories to report cases of Ehrlichiosis and Anaplasmosis to the local health department in the patient's county of residence within one week of diagnosis.

State Health Responsibilities

1. Review completed case reports from local health departments within one week.
2. Report all confirmed and probable cases to CDC upon confirmation of case status. Complete the supplemental case report form entitled, "Tick-Borne Rickettsial Disease Case Report" and submit to CDC upon confirmation of all confirmed and probable cases.
3. Provide training and consultation to local health departments regarding case ascertainment for Ehrlichiosis and Anaplasmosis.
4. Disseminate an annual Health Alert Network (HAN) message in early spring to increase awareness about Ehrlichiosis and Anaplasmosis (and other tickborne diseases) among healthcare providers and local health departments.

Disease Prevention Objectives

1. Reduce disease risk through public education regarding use of personal protective measures.

Disease Control Objectives

1. Reduce severe complications of disease by educating healthcare providers about the occurrence of Ehrlichiosis and Anaplasmosis and the importance of initiating early antibiotic treatment based on clinical symptoms and patient history.

Disease Surveillance Objectives

1. To identify and monitor the epidemiologic characteristics of Ehrlichiosis and Anaplasmosis in West Virginia, including the geographic distribution of cases.

Public Health Significance

Ehrlichiosis and anaplasmosis became nationally notifiable in 1999 and are considered to be emerging diseases. Passive surveillance data demonstrated an increase of *E. chaffeensis* cases from 200 in 2000 to 961 cases in 2008¹. However, active surveillance in HME endemic areas demonstrated an incidence that is 10-100 times higher than reported by passive surveillance². The number of anaplasmosis cases also increased from 348 cases in 2000 to 1,006 cases in 2008³. In addition, a new pathogenic species of

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Ehrlichia was identified in 2009 from 4 patients in Wisconsin and Minnesota. This new species is known as *Ehrlichia muris-like* (EML).

Surveillance for ehrlichiosis and anaplasmosis can help to inform healthcare providers of the seasonality, incidence, and geographic distribution of these diseases. This information can be useful in facilitating appropriate diagnoses and initiating early treatment to help avoid severe complications. Surveillance data can also help identify less common routes of transmission including blood transfusions and perinatal exposure.

Clinical Description

Initial symptoms of ehrlichiosis and anaplasmosis are non-specific and usually begin within 1-2 weeks of a bite from an infected tick. Both diseases are characterized by acute onset of fever, headache, myalgia, and malaise. Common laboratory findings include thrombocytopenia, leukopenia and evidence of hepatic injury^{4;5}. The following table (Table 1) summarizes the most common clinical findings for ehrlichiosis and anaplasmosis. Severe complications of ehrlichiosis include fulminant multi-organ failure, CNS involvement (meningitis or meningoencephalitis), and respiratory distress syndrome while anaplasmosis is more commonly associated with peripheral neuropathies.

Table 1. Summary of Clinical Findings Among Patients with Ehrlichiosis and Anaplasmosis

Symptom, Sign or Clinical Finding	Percent of Patients with Symptom	
	Ehrlichiosis	Anaplasmosis
Fever	97	93
Myalgia	57	77
Headache	80	76
Malaise	82	94
Nausea	64	38
Vomiting	33	26
Diarrhea	23	16
Cough	26	19
Arthralgias	41	46
Rash*	31	6
Stiff neck	3	21
Confusion	19	17
Leukopenia	62	49
Thrombocytopenia	71	71
Elevated liver function tests	83	71

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*Rash is most common with *E. chaffeensis* infections and is generally described as maculopapular to petechial in nature. Rash is not commonly reported with infections from *E. ewingii* or *E. muris*-like organism and is rarely reported in patients with anaplasmosis.

Diagnosis: The gold standard serologic test for diagnosing ehrlichiosis and anaplasmosis is the indirect immunofluorescence assay performed on paired serum samples taken 3-6 weeks apart. **Because of the similarities during presentation, acute and convalescent sera should be obtained and tested for both ehrlichiosis and anaplasmosis⁶.** A summary of options for diagnosis is found in Table 2. Additional testing for other tickborne diseases, such as Rocky Mountain spotted fever, may also be considered since there are similarities in clinical presentation.

Table 2. Summary of Diagnostic Options for Ehrlichiosis and Anaplasmosis

Test	Sensitivity	Specificity	Turn-around	Comments
Paired IgM and IgG using immunofluorescence assay (IFA) at a 3-6 week interval	'gold standard'	'gold standard'	weeks	<ul style="list-style-type: none"> Acute specimen is commonly negative High rates of cross-reactivity between Ehrlichia and Anaplasma – test acute and convalescent sera for both pathogens
Blood smear staining for morulae	3% (Ehrlichia) 25-75% (Anaplasma)		Same day	<ul style="list-style-type: none"> Blood smear with Wright or Giemsa stain Sensitivity is highest in the first week of infection Prior treatment reduces sensitivity
Polymerase chain reaction (PCR)	60-85% (Ehrlichia) 67-90% (Anaplasma)	60-85%	Same day	<ul style="list-style-type: none"> Collect blood samples in EDTA or sodium citrate anti-coagulant Prior treatment reduces sensitivity Sole diagnostic option for <i>Ehrlichia ewingii</i>
Isolation	Low (Ehrlichia) Similar to PCR (Anaplasma)	'gold standard'	weeks	<ul style="list-style-type: none"> Prior treatment reduces sensitivity
Immunohistochemistry				<ul style="list-style-type: none"> Tissue (biopsy) or bone marrow required Autopsy specimen for post-mortem diagnosis Prior treatment reduces sensitivity

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While serologic testing can help confirm ehrlichiosis and anaplasmosis infections, the decision to treat should be based on clinical signs (fever with or without systemic signs), laboratory findings (thrombocytopenia, leukopenia, and elevated serum transaminase levels), and the patient's history (travel to tick-infested area or history of tick bite). Doxycycline is the antibiotic of choice for treatment of ehrlichiosis and anaplasmosis in children and adults. Because doxycycline is most effective at preventing serious complication when initiated early in the course of disease, clinicians should not wait for laboratory test results to begin treatment.

It is important to note that anaplasmosis has also been transmitted through blood transfusion and perinatal exposure. Therefore, patients with clinically compatible symptoms and laboratory findings but without a possible history of tick exposure should also be considered for ehrlichiosis and anaplasmosis testing.

Etiologic Agent

The etiologic agents of ehrlichiosis and anaplasmosis are gram-negative obligate intracellular bacteria. Three *Ehrlichia* species (*E. chaffeensis*, *E. ewingii*, and *E. muris*-like organism) and one *Anaplasma* species (*Anaplasma phagocytophilum*) are currently known to infect humans.

Reservoir

The bacteria that cause ehrlichiosis and anaplasmosis are thought to be maintained in nature by mammalian reservoirs. For *E. chaffeensis*, white-tailed deer are an important reservoir⁷. Goats, dogs, and coyotes have also been found to be naturally infected with this bacterium. For *E. ewingii* less is known about its ecological features, however dogs and deer have been found to be naturally infected with this bacterium. Small mammals, such as the white-footed mouse, have shown reservoir competence for *A. phagocytophilum*; however other wild mammals may also be important reservoirs⁸.

Mode of Transmission

Ehrlichiosis and anaplasmosis are tickborne diseases primarily transmitted to humans through the bite of an infected tick. Ticks in the nymphal and adult life stages are most frequently associated with transmitting these diseases. The lone star tick (*Amblyomma americanum*) is responsible for transmitting Ehrlichiosis; the black-legged tick (*Ixodes scapularis*) and the western black-legged tick (*I. pacificus*) are responsible for transmitting Anaplasmosis.

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Transmission has also occurred through blood transfusions for anaplasmosis and is thought to be possible for ehrlichiosis. Perinatal transmission of anaplasmosis has also been documented.

Incubation Period

The incubation period is generally 1 to 2 weeks following a bite from an infected tick.

Period of Communicability

Person-to-person transmission does not ordinarily occur and humans are considered to be incidental hosts.

Outbreak Recognition

There is a low likelihood of outbreaks occurring due to ehrlichiosis and anaplasmosis. However, because *Ehrlichia* species and *A. phagocytophilum* infect white blood cells and circulate in the blood stream, outbreaks of ehrlichiosis and anaplasmosis could potentially occur by transfusion or transplantation of contaminated blood products. Patients who develop ehrlichiosis or anaplasmosis within one month of a blood transfusion or solid organ transplant should be reported to DIDE. Additionally, community outbreaks may occur if people are exposed to infected ticks in a localized geographic area. For example, in 1989, an outbreak of Ehrlichiosis was reported among members of an army reserve unit who trained together in a distinct geographic area where ticks were common⁹.

Case Definition (CSTE-CDC 2012)

The 2008 case definition is the most current version (CSTE Position Statement Number: 09-ID-15).

Subtypes

Ehrlichia chaffeensis infection (formerly Human Monocytic Ehrlichiosis [HME])

Ehrlichia ewingii infection (formerly Ehrlichiosis [unspecified or other agent])

Anaplasma phagocytophilum infection (formerly Human Granulocytic Ehrlichiosis [HGE])

Ehrlichiosis/Anaplasmosis, human, undetermined

Clinical Description

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,

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thrombocytopenia, or elevated hepatic transaminases. Nausea, vomiting, or rash may be present in some cases.

Clinical evidence

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

Ehrlichia Chaffeensis: (formerly Human Monocytic Ehrlichiosis [HME])

Laboratory criteria for diagnosis

Supportive:

1. 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
2. Identification of morulae in the cytoplasm of monocytes or macrophages by microscopic examination

Confirmed:

1. 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
2. Detection of *E. chaffeensis* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, OR
3. Demonstration of ehrlichial antigen in a biopsy or autopsy sample by immunohistochemical methods, OR
4. Isolation of *E. chaffeensis* from a clinical specimen in cell culture

Ehrlichia Ewingii: (formerly Ehrlichiosis [unspecified or other agent])

Laboratory criteria for diagnosis

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.

Anaplasma Phagocytophilum: (formerly Human Granulocytic Ehrlichiosis [HGE])

Laboratory criteria for diagnosis

Supportive:

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1. 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
2. Identification of morulae in the cytoplasm of neutrophils or eosinophils by microscopic examination.

Confirmed:

1. 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
2. Detection of *A. phagocytophilum* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, OR
3. Demonstration of anaplasma antigen in a biopsy/autopsy sample by immunohistochemical methods, OR
4. Isolation of *A. phagocytophilum* from a clinical specimen in cell culture

Ehrlichiosis/Anaplasmosis, human, undetermined:

See case classification below.

Case classification:

Suspected

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

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.

Confirmed

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

Preventive Interventions

There is no evidence that prophylactic antibiotic treatment following a tick bite is effective in preventing ehrlichiosis or anaplasmosis, and may actually delay the onset of disease. Instead, a person bitten by a tick should be alert for symptoms suggestive of tickborne illness and consult a physician if fever, rash, or other symptoms of concern develop. Also, there is no human vaccine for ehrlichiosis or anaplasmosis.

Avoiding tick bites is the main stay of ehrlichiosis and anaplasmosis prevention. The following are important personal protective measures that should be followed, especially for persons that live, work, or spend leisure time in an area likely to have ticks:

- Stick to main pathways and the centers of trails when hiking.
- Wear long-sleeved, light-colored shirts, and long pants tucked into socks when weather permits.
- Talk to a veterinarian about the best ways to protect pets and livestock from ticks.
- Use repellents containing DEET (N, N-diethyl-m-toluamide), and choose a product that will provide sufficient protection for the amount of time spent outdoors. DEET products should not be used on children <2 months of age. The following precautions should be observed when using DEET products:
 - Avoid using DEET products that combine the repellent with a sunscreen. Sunscreens may need to be reapplied too often, resulting in an over application of DEET.
 - Apply DEET on exposed skin, using only as much as needed.
 - Do not use DEET on the hands of young children, and avoid applying repellent to areas around the eyes and mouth.
 - Do not use DEET over cuts, wounds, or irritated skin.
 - Wash treated skin with soap and water after returning indoors, and wash treated clothing.
 - Avoid spraying DEET products in enclosed areas.
- Permethrin-containing products will kill mosquitoes and ticks on contact. Permethrin products are not designed to be applied to the skin. Clothing should be treated and allowed to dry in a well-ventilated area prior to wearing.
- Check yourself, children, and pets for ticks upon returning from outdoors. Make sure to check the following areas: between the toes, back of the knees, groin, armpits, neck, along the hairline, and behind the ears.

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- Promptly remove attached ticks using fine-point tweezers. Grasp the tick close to the skin and pull straight up using steady pressure; do not squeeze or twist the tick.

Environmental Measures:

Prevention of ehrlichiosis and anaplasmosis can also involve actions to keep ticks out of yards.

- Keep grass cut short.
- Remove leaf litter and brush from around the yard.
- Prune low lying bushes to let in more sunlight.
- Keep woodpiles and bird feeders off the ground and away from the home.
- Keep the plants around stone walls cut short.
- Use a three-foot wide woodchip, mulch, or gravel barrier where the lawn meets the woods, and remind children not to cross that barrier.
- Ask a landscaper or local nursery about plants to use in the yard that do not attract deer.
- Use deer fencing (for yards 15 acres or more).

If applying a pesticide outdoors, a licensed applicator experienced with tick control should be hired. In general, good tick control can be achieved with no more than two pesticide applications in any year.

Treatment

Doxycycline is the drug of choice for treating both ehrlichiosis and anaplasmosis infections in adults and children. Doxycycline is most effective at preventing severe complications if started early in the course of illness.

The use of doxycycline to treat suspected ehrlichiosis in children is standard practice recommended by both CDC and the AAP Committee on Infectious Diseases¹⁰. Unlike older generations of tetracyclines, the recommended dose and duration of medication needed to treat ehrlichiosis has not been shown to cause staining of permanent teeth, even when five courses are given before the age of eight.

Surveillance Indicators

1. Proportion of cases with complete demographic information.
2. Proportion of cases with complete clinical information (i.e. presence of fever and other clinical signs meeting clinical criteria of case definition).
3. Proportion of cases with risk factor information (i.e. history of potential tick exposure through recreational or occupational activities).

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Reference List

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