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Anaplasmosis and Ehrlichiosis

Surveillance and Investigation Protocol

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I. ABOUT THE DISEASE

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, 69 cases of ehrlichiosis were reported between 2011–2022. The first cases (2) of anaplasmosis were reported in West Virginia during 2011. Since then, there have been a total of 20 cases. Due to the relative difficulty of differentiating between these two diseases, there is also a category called "ehrlichiosis/anaplasmosis, undetermined". Since 2011 there have been 9 reported cases of undetermined ehrlichiosis/anaplasmosis in West Virginia.

A. Clinical Presentation

The 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[1,2]. The following table (Table 1) summarizes the most common clinical findings for ehrlichiosis and anaplasmosis in the United States. Severe complications of ehrlichiosis include fulminant multi-organ failure, central nervous system (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

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Leukopenia	62	49
Thrombocytopenia	71	71
Elevated liver function tests	83	71

*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 eauclairensis* 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 anaplasmosis[3].** 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.

B. 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 eauclairensis*) and one *Anaplasma* species *(Anaplasma phagocytophilum*) are currently known to infect humans.

C. 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 reservoir[4]. 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 reservoirs[5].

D. Incubation Period

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

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E. 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 (*Ixodes. pacificus*) are responsible for transmitting anaplasmosis.

Transmission can occur through blood transfusions for both anaplasmosis and ehrlichiosis. Perinatal transmission of anaplasmosis has also been documented.

F. Period of Communicability

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

II. DISEASE CONTROL AND PREVENTION

A. 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.

B. Disease Prevention Objectives

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

C. Disease Prevention and Control Intervention

There is no evidence that prophylactic antibiotic treatment following a tick bite is effective in preventing ehrlichiosis or anaplasmosis and may instead 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 people who 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-meta-0toluamide), 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 applied 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.
- Promptly removed 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 a year.

D. 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 Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases[6]. 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.

III. DISEASE INVESTIGATION

A. Criteria for Case Ascertainment

Report any infection to public health authorities that meets any of the following criteria:

Clinical Criteria for Reporting

N/A

Laboratory/Imaging Criteria for Reporting

Anaplasmosis:

- Detection of *A. phagocytophilum* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, nucleic acid amplification test (NAAT), or other molecular testing, **OR**
- Serological evidence of elevated IgG antibody reactive with *A. phagocytophilum* antigen by indirect immunofluorescence assay (IFA) at a tier ≥ 1:128, **OR**

- Microscopic identification of intracytoplasmic morulae in leukocytes, **OR**
- Demonstration of anaplasmal antigen in a biopsy or autopsy sample by immunohistochemical methods, **OR**
- Isolation of *A. phagocytophilum* from a clinical specimen in cell culture with molecular confirmation (e.g., PCR or sequencing)

Ehrlichiosis:

- Detection of *Ehrlichia* spp. deoxyribonucleic acid (DNA) in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, nucleic acid amplification test (NAAT), or other molecular testing, **OR**
- Serological evidence of elevated IgG antibody reactive with *Ehrlichia* spp. antigen by indirect immunofluorescence assay (IFA) at a tier ≥ 1:128, **OR**
- Microscopic identification of intracytoplasmic morulae in leukocytes, **OR**
- Demonstration of ehrlicial antigen in a biopsy or autopsy sample by immunohistochemical methods, **OR**
- Isolation of *Ehrlichia* spp. from a clinical specimen in cell culture with molecular confirmation (e.g., PCR or sequencing)

Epidemiologic Linkage Criteria for Reporting

N/A

Vital Records Criteria for Reporting

- A person whose death certificate lists anaplasmosis or ehrlichiosis as an underlying cause of death or a significant condition contributing to death.

Other Criteria for Reporting

- A person whose healthcare record contains a diagnosis of anaplasmosis or ehrlichiosis.

B. Case Definition and Case Classification

Ehrlichia spp. bacteria is closely related to *A. phagocytophilum*, and many patients are tested using panels that include targets for both species. As a result, it is not uncommon for jurisdictions to receive positive antibody results for both *Ehrlichia* spp. and *Anaplasma* with the same collection date for a single patient. Public health agencies should use a combination of titer levels, information about the location of possible exposures clinical manifestations, and the incidence of a particular disease in the geographic area of exposure to help determine the appropriate disease type

for individual patients. Patients should not be classified as cases for both anaplasmosis and ehrlichiosis based on serologic evidence alone.

Clinical Criteria

Anaplasmosis:

Objective clinical evidence: fever as reported by patient or healthcare provider, anemia, leukopenia, thrombocytopenia, any hepatic transaminase elevation, or elevated C-reactive protein.

Subjective clinical evidence: chills/sweats, headache, myalgia, or fatigue/malaise.

Ehrlichiosis:

Objective clinical evidence: fever as reported by patient or healthcare provider, anemia, leukopenia, thrombocytopenia, or any hepatic transaminase elevation.

Subjective clinical evidence: chills/sweats, headache, myalgia, nausea/vomiting, or fatigue/malaise.

Laboratory/Imaging Criteria

Anaplasmosis:

Confirmatory laboratory evidence:

- Detection of A. phagocytophilum DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, nucleic acid amplification tests (NAAT), or other molecular testing, **OR**
- Serological evidence of a four-fold change in IgG specific antibody titer to A. phagocytophilum antigen by indirect immunofluorescence assay (IFA) in paired serum samples (one taken in the first two weeks after illness onset and a second taken two to ten weeks after acute specimen collection), **OR**
- Demonstration of anaplasmal antigen in a biopsy or autopsy sample by immunohistochemical methods, **OR**
- Isolation of A. phagocytophilum from a clinical specimen in cell culture with molecular confirmation (e.g., PCR or sequencing)

Presumptive laboratory evidence:

- Serological evidence of elevated IgG antibody reactive with A phagocytophilum antigen by IFA at a titer ≥1:128 in a sample taken within 60 days of illness onset, **OR**
- Microscopic identification of intracytoplasmic morulae in leukocytes in a sample taken within 60 days of illness onset.

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Ehrlichiosis:

Confirmatory Laboratory Evidence:

- Detection of *E. chaffeensis*, *E. ewingii*, *E. muris eauclairensis*, unspeciated *Ehrilchia* spp, or other *Ehrlichia* spp. DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, nucleic acid amplification tests (NAAT), or other molecular method, **OR**
- Serological evidence of a four-fold change in IgG specific antibody titer to *Ehrlichia* antigen by indirect immunofluorescence assay (IFA) in paired serum samples (one taken in first two weeks after illness onset and a second taken two to ten weeks after acute specimen collection), **OR**
- Demonstration of ehrlichial antigen in a biopsy or autopsy sample by immunohistochemical methods, **OR**
- Isolation of *E. chaffeensis*, *E. ewingii*, *E.muris eauclairensis*, unspeciated *Ehrlichia* spp., or other *Ehrlichia* spp. from a clinical specimen in cell culture with molecular confirmation (e.g., PCR or sequencing).

Presumptive Laboratory Evidence:

- Serological evidence of elevated IgG antibody reactive with *Ehrlichia* spp. antigen by IFA at a titer ≥1:128 in a sample taken within 60 days of illness onset, **OR**
- Microscopic identification of intracytoplasmic morulae in leukocytes in a sample taken within 60 days of illness onset.

Epidemiologic Linkage

N/A

Vital Records Criteria

N/A

Other Classification Criteria

N/A

Case Classifications

Confirmed:

Meets confirmatory laboratory evidence AND at least one of the objective or subjective clinical evidence criteria.

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Probable:

- Meets presumptive laboratory evidence with fever as reported by patient or healthcare provider AND at least one other objective or subjective clinical evidence criterion (excluding chills/sweats) **OR**
- Meets presumptive laboratory evidence without reported fever but with chills/sweats AND
    - At least one objective clinical evidence criterion, **OR**
    - Two other subjective clinical evidence criteria

Suspect:

- Meets confirmatory or presumptive laboratory evidence with no or insufficient clinical information to classify as a confirmed or probable case (e.g., a laboratory report only).

Criteria for a new case:

- A person previously reported as a probable or confirmed case patient may be counted as a new case when there is an episode of new clinically compatible illness with confirmatory laboratory evidence.

C. Reporting Timeframe to Public Health

All suspected cases of anaplasmosis/ehrlichiosis should be reported to the Local Health Department within one week.

D. 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 the Division of Infectious Disease Epidemiology (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 common[7].

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E. Healthcare 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 2-10 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

F. Laboratory Responsibilities

1. Report positive laboratory results for ehrlichiosis and anaplasmosis to the local health department within 1 week.

F. 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 West Virginia Electronic Disease Surveillance System (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).
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.

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G. 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.

H. Occupational Health

None.

IV. DISEASE SURVEILLANCE

A. 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 1337 cases in 2021[8]. The number of anaplasmosis cases also increased from 348 cases in 2000 to 6729 cases in 2021[9]. In addition, a new pathogenic species of *Ehrlichia* was identified in 2009 from 4 patients in Wisconsin and Minnesota. This new species is known as *Ehrlichia muris eauclairensis.*

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.

B. Disease Surveillance Objectives

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

C. 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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