Anaplasmosis
(Human Granulocytic Anaplasmosis)

Manitoba
Public Health Branch

1. Case Definition

1.1 Confirmed Case
A clinically[I] compatible case that is laboratory confirmed[II] (1, 2, 3).

[I] Clinical evidence criteria include, fever plus one or more of the following: headache, myalgia, anemia, leukopenia, thrombocytopenia or any elevation of hepatic transaminase concentrations.

[II] Laboratory confirmation requires one of:

1) Serological evidence of a four-fold change in IgG specific antibody titre by indirect IFA assay between paired serum specimens (one taken during the first week of illness and a second 2 – 4 weeks later), OR by specific nucleic acid amplification test of blood specimen during acute phase of illness, **OR**
2) Detection of *Anaplasma phagocytophilum* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, **OR**
3) Demonstration of anaplasmal antigen in a biopsy/ autopsy sample by immunohistochemical methods, **OR**
4) Isolation of *A. phagocytophilum* from a clinical specimen in cell culture.

[III] Non-confirmatory laboratory results include:

1) Identification of morulae in the cytoplasm of neutrophils or eosinophils by microscopic examination, **OR**
2) Single *A. phagocytophilum* IgG antibody titre of 128 or greater plus *A. phagocytophilum* IgM antibody titre of 20 or greater.

1.2 Probable Case
A clinically compatible case with non-confirmatory laboratory results[III] (1)

2. Reporting and Other Requirements
In 2015 all cases became reportable to Manitoba Health, Healthy Living and Seniors

Laboratory:

- All positive laboratory tests for *Anaplasma phagocytophilum* (i.e. IFA serology, detection by specific nucleic acid amplification methods (NAAT), or identification of the characteristic morulae on a blood smear) are reportable by laboratory. Operators of Manitoba laboratories detecting evidence of Anaplasma in blood specimens must forward residual blood specimen to Cadham Provincial Laboratory within 7 days of report.

Health Professional:

- Clinical cases of Anaplasmosis are to be reported to Manitoba Health, Healthy Living and Seniors using the Tick-Borne Diseases Clinical Case Report form (www.gov.mb.ca/health/publichealth/cdc/protocol/tickborneform.pdf) and submitted by fax to the Communicable Disease Control Unit at (204) 948-2190 (secure fax line). It is important to supply a travel history or any exposure to ticks that is as complete and thorough as possible. Public Health practitioners may contact physicians/ clinicians for further information on reported cases as required.

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3. Clinical Presentation/ Natural History

Clinical evidence of Anaplasmosis is characterized by an acute onset of fever with one or more of the following non-specific symptoms or findings: chills, malaise, headache, myalgia, arthralgia, leukopenia, thrombocytopenia or elevated hepatic transaminases (1, 2, 4, 5). Less common non-specific symptoms may include: stiff neck, nausea, cough, anaemia and increased serum creatinine levels (4). It is important to obtain a thorough clinical history, including evidence of a tick bite, exposure to a Lyme disease risk area or travel to an area with suitable tick habitat within the previous 5 – 21 days prior to symptom onset (1, 6, 7). ***It should be cautioned that many patients have no recollection of a tick bite, which corresponds to the relatively painless bite and small size of nymphal ticks that play a key role in transmission*** (6, 8).

In most cases Anaplasmosis is a mild and self-limiting illness, and all clinical signs and symptoms resolve in most patients within 30 days, even in the absence of antibiotic treatment (5). However, more severe presentations are common in older patients (> 60 years of age), those with co-morbidities (i.e. immune-compromised) and in those where there has been a delay in diagnosis and treatment (9, 10). Significant complications resulting in hospitalization include: septic or toxic like shock syndrome, respiratory insufficiency, invasive opportunistic (viral & fungal) infections, rhabdomyolysis, pancarditis, acute renal failure, hemorrhage, and neurological conditions such as brachial plexopathy, demyelinating polyneuropathy and acute transient sensori-neural hearing loss (4, 9). The case fatality rate varies between 0.2 and 1.2% (2, 3, 6, 9).

Consideration of the possibility of co-infection with other tick-borne diseases such as Lyme disease and/ or babesiosis should always be considered when diagnosing and treating patients for Anaplasmosis (2, 9). Reported frequency of co-infection among Anaplasmsosis patients with *Borrelia burgdorferi* has been shown to range between 2.0 – 11.7% in endemic regions (4).

4. Etiology

Anaplasmosis is a tick-borne infection caused by the obligate, intracellular gram-negative bacteria, *Anaplasma phagocytophilum* and transmitted in Manitoba by the blacklegged tick, *Ixodes scapularis* (3, 11). *Anaplasmsma* bacteria prefer to infect leukocytes, in particular granulocytes (9). There are biologically and ecologically distinct sub-populations of *A. phagocytophilum* adapted to specific reservoir hosts and tick species, which also exhibit varying pathogenicity. Human anaplasmosis is associated with the Ap-ha variant. The distribution of this variant corresponds closely with elevated incidence rates (7, 12).

5. Epidemiology

5.1 Vectors and Reservoir

In North America vectors of *Anaplasma phagocytophilum* include *Ixodes scapularis*, *Ix. pacificus* and *Ix. spinipalpis*, while in Europe and Asia the vectors are *Ix. ricinus* and *Ix. perulcatus* respectively (13, 14). It should be noted however, that none of these hard bodied ticks are capable of persistently supporting *A. phagocytophilum* infection and hence they are not reservoir hosts (14). The bacteria can be acquired while feeding on reservoir hosts by any of the three tick life stages (i.e. larvae, nymph or adult). However

once infected the pathogen can be transmitted to each stage – known as trans-stadial transmission (9). The bacteria is maintained in the epizootic cycle through a variety of reservoir hosts, which include white-footed and deer mice for juvenile ticks (larvae & nymphs) and white tailed deer and other large ruminants for adults (9). Studies have shown that the white-footed mouse is the principal reservoir for the pathogenic variant, Ap-ha (14).

5.2 Transmission

Anaplasmosis is transmitted primarily when an infected blacklegged tick takes a blood meal. Animal studies have shown the typical transmission window, the period between tick attachment and pathogen transmission, to be as little as 24– 48 hours (6, 15, 16, 17). Further, small numbers of infected nymphs were able to transmit the pathogen in less than 24 hours (15, 16). This narrow transmission window may reflect the shorter distance the bacteria have to travel, from the salivary glands, as opposed to the gut in the case of Lyme disease (15). This abbreviated transmission window is also thought to be true in humans.

Although the majority of transmission of *A. phagocytophilum* occurs via tick vectors, other transmission modes have been documented. These other modes include transplacental transmission, direct handling of infected reservoirs (i.e. white-tailed deer), and blood and marrow transfusion (4, 9, 10, 18, 19, 20).

5.3 Occurrence

General:
In North America the majority of Anaplasmosois cases are found in two endemic foci; the northeastern US and the upper Midwest (3). Six states (New York, Connecticut, New Jersey, Rhode Island, Minnesota and Wisconsin) account for 90% all reported cases (21). The distribution of Anaplasmosis cases in North America is similar to that observed for Lyme disease given the common vector, the blacklegged tick (8). In Europe, where the incidence is significantly lower (fewer than 100 confirmed cases reported continent-wide between 1997 and 2012) Anaplasmosis cases have been reported from a number of countries including: Belgium, Bulgaria, Croatia, France, Germany, Holland, Italy, Norway, Russia, Poland, Slovenia, Spain, Sweden, Switzerland and the U.K. (9, 13). The distribution of cases in Europe corresponds to the range of the principal vector, *Ix. ricinus* which stretches from Scandinavia to the Mediterranean and Russia to Portugal & Ireland (22). Elsewhere Anaplasmosis has been described, again at lower incidence rates compared to North America, in eastern Asian countries such as China, Japan, South Korea and Siberian Russia (4, 23).

Canada:
At present Anaplasmosis is reportable in Manitoba, but not in any other jurisdictions in Canada nor to the Public Health Agency of Canada. With the continued northward spread of *Ix. scapularis* populations, the risk of infection with tick-borne pathogens such as Anaplasmosis has increased. Recent studies have estimated the rate of expansion to be from 33 to 55 km per year (24).

Areas with evidence of established blacklegged tick populations and, hence, greater risk of tick-borne disease transmission, have been identified in Nova Scotia, New Brunswick, southern Quebec, eastern, southwestern & northwestern Ontario and southern Manitoba (24). Testing of ticks in these regions has shown evidence of *A.*

phagocytophilum circulation within the environment, with the highest prevalence rates seen in Manitoba, New Brunswick and Quebec (12). In addition, the rates of infection with the pathogenic Ap-ha strain were highest in the prairie (Manitoba) and Atlantic (Nova Scotia & New Brunswick) provinces.

Manitoba:
Since Anaplasmosis became provincially reportable on January 1, 2015, positive laboratory results have been reported in Manitoba. It should be cautioned that the calculation of incidence rates will require a minimum of 3 years of data.

In Manitoba, blacklegged ticks are active from snow melt until the first permanent snow fall, or when air temperatures are consistently below 4°C (typically April – November), and they are typically found:

- Within and along the edges of wooded or forest habitat; and
- In areas with thick, woody shrubs and other vegetation that provide sufficient cover and typically high humidity.

Areas with established blacklegged tick populations, referred to as Lyme disease risk areas, carry the highest Anaplasmosis risk. However, because these ticks can attach to migrating birds and large ruminants (i.e. white-tailed deer), it is possible to find blacklegged ticks in other areas of the province. The risk of Anaplasmosis transmission outside of the endemic areas is relatively low.

Regular surveillance activities have identified Lyme disease risk areas throughout much of southern Manitoba stretching from the Ontario border as far west as Brandon and from the US border as far north as Norris Lake Provincial Park (in the Interlake). For updated information regarding the distribution of Lyme disease risk areas in Manitoba see http://www.gov.mb.ca/health/publichealth/cdc/tickborne/index.html

5.4 Incubation Period

The incubation period for Anaplasmosis ranges between 5 to 21 days following the bite of an infected tick (2, 5). Most symptomatic patients who recall a tick bite report exposure between 7 – 14 days prior to symptom onset (4).

5.5 Susceptibility and Resistance

It is reasonable to assume that individuals who reside, work and/or engage in recreational activities within Lyme disease risk areas remain at risk for Anaplasmosis transmission. However, the frequency of re-infection has yet to be clarified. (4). It is also possible that patients who develop elevated anti-body titres in response to *A. phagocytophilum* infection may be protected against re-infection. Studies have shown persistent elevated anti-body titres for 12 – 36 months post-infection (9).

6. Laboratory Investigation

A fundamental understanding of the signs, symptoms and epidemiology of Anplasmosis is necessary to guide requests for tests and subsequent interpretation. Testing should be limited to patients with clinical presentations consistent with the illness.

Laboratory confirmation requires one of:
Serological evidence of a four-fold change in IgG antibody titre to *A. phagocytophilum* antigen by indirect IFA in paired serum samples (one taken

during the first week of illness and a second 2 – 4 weeks later). The titre in the convalescent sample should be 1:128 or higher (1, 6, 9, 13);

    - IFA tests have been shown to have poor sensitivity during the acute phase of illness (< 1 week following symptom onset) (25). However, the sensitivity increases significantly as the illness progresses and if samples are paired (6).
- Detection of *A. phagocytophilum* DNA in a clinical specimen via amplification of a specific target by PCR assay (1);
    - PCR tests are typically positive when the patient is tested during the acute phase of illness, usually within the first week (25).
- Demonstration of anaplasmal antigen in a biopsy/ autopsy sample by immunehisto-chemical methods;
- Isolation of *A. phagocytophilum* from a clinical specimen in cell culture.

Bacteremia may persist for 28 days; there are no reports of active clinical (i.e. chronic) illness persisting beyond two month (9)

7. Key Investigations

Positive laboratory and non-confirmatory serology results are referred to the health region of residence for public health investigation. Results of the investigation are to be reported to Manitoba Health, Healthy Living & Seniors using the Tick-Borne Diseases Clinical Case Report Form (www.gov.mb.ca/health/publichealth/cdc/protocol/tickborneform.pdf) and submitted by fax to the Communicable Disease Control Unit at (204) 948-2190 (secure fax line). It is important to complete the form as fully as possible, with emphasis on:

- detailed clinical history, including history of transfusion, transplantation, or pregnancy;
- actual and/ or potential tick exposure activity within 21 days prior to symptom onset;
- travel history (including local excursions) within 21 days prior to symptom onset.

Central Public health will consider travel history, exposure to potential tick habitat(s) and patient residence to determine potential exposure location.

It is also essential that residual blood specimens be submitted to Cadham Provincial Laboratory within 7 days of reporting, to allow for confirmation.

8. Control & Prevention

8.1 Management of Cases

Appropriate antibiotic treatment should be initiated immediately when a clinician suspects Anaplasmosis, based on clinical, laboratory or epidemiological findings, given the potential for serious and even fatal outcomes (2, 6, 9, 11, 13, 23). As it is not possible to predict which patients may have a self-limiting illness, all symptomatic

patients should receive appropriate antibiotic treatment.

Recommended treatment for Anaplasmosis includes:

Doxycycline –

- For patients over 8 years of age the recommended dose is 100mg twice daily either intravenously or orally for 10 to 14 days. If co-incubating infection with *Borrelia burgdorferi* is suspected, a 14 day treatment is recommended (4, 5, 9).
- For patients less than 8 years of age the recommended dose is 2.2mg/kg (maximum of 100mg/dose) twice daily either intravenously or orally for 4 – 5 days (2, 4). This normally corresponds to 3 days after resolution of fever.
    - Where potential coinfection with *Borrelia burgdorferi* is suspected, the remainder of the 14 day therapy should be completed with an alternative agent (i.e. amoxicillin or cefuroxime axetil) (5, 23).

Tetracycline –

- For patients over 8 years of age the recommended dose is 500mg orally four times daily for 10 – 14 days (4).

Rifampin –

- Pediatric (< 18 years of age) 20mg/kg/day (maximum 600 mg) in two divided doses orally for 5 – 7 days (4)
- Adult (18 years or older) 300mg orally twice daily for 5 – 7 days (4).
    - Rifampin is recommended for pregnant patients and those with drug allergies unable to take either doxycyline or tetracycline (6, 9).
    - As rifampin is not an effective therapy for Lyme disease, patients with a co-infection with *Borrelia burgdorferi* should also be treated with amoxicilllin or cefuroxime (5)

Fever typically subsides within 24 – 48 hours after treatment. Adult patients have symptoms resolve following doxycycline or rifampin therapy with no subsequent relapse or chronic infection (5). The majority of symptoms typically resolve within 30 days of onset, even in the absence of antibiotic therapy (13). Severely ill patients may have a longer duration of symptoms before clinical improvement is noted (6).Failure to respond to antibiotic therapy after 48 – 72 hours may indicate infection with another tick-borne pathogen or a secondary opportunistic infection not susceptible to tetracyclines (13). Patients with co-infections (i.e. *Borrelia burgdorferi* and/ or *Babesia microti*) present with more severe illness and effective treatment may require multiple different therapies (7).

Consultation with an infectious disease specialist is recommended for management of complex cases.

8.2 Management of Contacts

Screening of blood donors for a history of tick bite or exposure to a tick habitat is unlikely to be sensitive or specific, given that in endemic regions, such exposures are common and bites are often not recalled (19). Physicians are encouraged to consider Anaplasmosis in their differential diagnosis in patients who develop post-transfusion acute thrombocytopenia or leukopenia, especially when accompanied by fever (20).

Where Anaplasmosis is diagnosed during pregnancy the newborn should be evaluated for

presence of the bacteria, and treated with appropriate antibiotics if infection is identified (18).

8.3 Preventative Measures

Educate the public about Anaplasmosis transmission and personal protection measures that should be adopted to minimize the risk of exposure to potentially infected ticks, including the following:

- After spending time outdoors, inspect yourself and your children for ticks and remove any ticks found as soon as possible. Bathing or showering within 2 hours of coming indoors is a good way to find ticks.
- Apply an appropriate repellent (it should state 'for use against ticks' on the product label), as per instructions, on clothing and exposed skin.
- Use trails, wherever possible, and stay to the center of hiking trails or paths
- Wear light-colored clothing to make it easier to see ticks crawling on your clothing.
- Wear long pants and long sleeved shirt so that most exposed skin is covered.
- Tuck your shirt into your pants and your pants into your socks; this will make it more difficult for the ticks to attach to your skin.
- Regularly inspect pets for ticks, as they can bring ticks into the home.
- If a tick is attached to the skin, remove it with tweezers:
    - Grasp the tick close to the skin with tweezers and pull slowly upward with steady pressure; avoid twisting or crushing the tick (a video demonstration is available at http://www.gov.mb.ca/health/publichealth/cdc/tickborne/index.html).
    - Other methods such as using a match, petroleum jelly, soap, etc. are not recommended.
    - Cleanse the skin around the tick bite with soap and water or disinfectant.
    - Mark the date and location of the tick bite on a calendar for future reference.
    - If symptoms develop, see your doctor.

In Lyme disease risk areas, a large number of landscape management practices can be employed to help reduce the abundance of ticks, and thereby minimize the risk of exposure to Anaplasmosis and other tick-borne diseases (26). In general, tick numbers can be lowered through activities such as keeping grass mowed short, removing leaf litter and trimming other vegetation (shrubs and trees) to minimize shade cover in commonly used areas. Further, tick 'unfriendly' habitats can be created by using drier, less water demanding materials such as mulch, gravel, decks or cement in commonly used areas. More landscape management details can be found in the Connecticut Agricultural Experimental Station's 'Tick Management Handbook' at http://www.ct.gov/caes/lib/caes/documents/publications/bulletins/b1010.pdf.

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