

Babesiosis

(Human Babesiosis)



Public Health Branch

There are a number of etiological agents responsible for Babesiosis worldwide (1, 2, 3). *Babesia microti* is the most common agent of Babesiosis in North America, while limited cases attributed to *B. microti*-like species have been reported from Asian and Oceanic countries. *B. duncani* and *B. duncani*-like species are the etiological agents of Babesiosis along the West Coast of North America. *B. divergens* and *B. venatorum* are the etiological agents of Babesiosis in Europe. *B. divergens* and *B. duncani* are the most pathogenic species, however in comparison to *B. microti*, few cases have been reported, and those that were, are often associated with conditions affecting host-immune function (1, 2). Consequently, given that the majority of Babesiosis cases are associated with *B. microti*, the protocol will largely address this specific etiological agent unless otherwise noted.

1. Case Definition

1.1 Confirmed Case

A confirmed case is one that has confirmatory laboratory results^I **AND** meets at least one of the objective^{II} or subjective^{III} clinical evidence criteria, regardless of the mode of transmission (4).

1.2 Probable Case

A probable case is one that has supportive laboratory results and meets at least one of the objective clinical evidence criteria (note subjective criteria are not sufficient) (4); **OR**

A case that is in a blood donor or recipient epidemiologically linked^{IV} to a confirmed or probable Babesiosis case (4), **AND**:

- Has confirmatory laboratory evidence but does not meet any objective or subjective clinical evidence criteria.

^I Clinical evidence criteria (4):

- Objective clinical evidence includes one or more of fever, anemia, or thrombocytopenia.
- Subjective clinical evidence includes one or more of chills, sweats, headache, myalgia or arthralgia.

^{II} Confirmatory laboratory evidence includes one of the following (4):

- Identification of intraerythrocytic *Babesia* organisms by light microscopy in a Giemsa, Wright or Wright-Giemsa stained blood smear; **OR**
- Detection of *Babesia species* DNA in a whole blood specimen by PCR; **OR**
- Isolation of *B. microti* organisms from a whole blood specimen by animal inoculation.

^{III} Supportive laboratory evidence includes one of the following (4):

- Demonstration of *Babesia species* by IFA with specific IgG antibody titre of greater than or equal to 1:256

^{IV} Epidemiological link, for the purposes of surveillance, between a transfusion recipient and a blood donor is demonstrated if all of the following criteria are met:

- In the transfusion recipient:
 - a) Received one of more red blood cell (RBC) or platelet transfusions within one year before the collection date of a specimen with laboratory evidence of Babesia infection, **AND**
 - b) At least one of these transfused components was donated by the donor described below, **AND**
 - c) Transfusion-associated infection is considered at least as plausible as tick-borne transmission, **AND**
- In the blood donor:
 - a) Donated at least one of the RBC or platelet components that was transfused into the above recipient, **AND**
 - b) The plausibility that this blood component was the source of infection in the recipient is considered equal to or greater than that of blood from other involved donors (more than one plausible donor may be linked to the same recipient).

2. Reporting and Other Requirements

In 2015 all confirmed cases became reportable to Manitoba Health, Healthy Living and Seniors.

Laboratory:

- All positive laboratory tests for all *Babesia species* (i.e. Giemsa-Wright blood smear, IFA serology, DNA detection by PCR assay, or positive IgG immunoblot) are reportable by laboratory.

Health Professional:

- Clinical cases of Babesiosis 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.

3. Clinical Presentation/ Natural History

Babesiosis infection can range from sub-clinical to life-threatening. The disease severity depends upon the underlying risk factors of the patient such as asplenia, advanced age (> 50 years of age) and impaired immune function (i.e. HIV, malignancy, corticosteroid therapy, cancer, hemoglobinopathy, chronic heart, lung or liver disease) (4, 5, 6, 7, 8). Approximately half of the children and a quarter of adults infected with Babesiosis who are immuno-competent develop no symptoms (1, 7). For suspected clinical babesiosis cases, it is important to consult with an Infectious Diseases specialist at an early stage.

Mild to moderate symptoms which are common in immuno-competent individuals typically include the gradual onset of malaise and fatigue accompanied by intermittent fever (peak can be as high as 40.9°C) and one or more of the following: chills, drenching sweats, anorexia, headache, myalgia, nausea, non-productive cough, arthralgia and generalized weakness (1, 2, 3, 4, 5, 7, 8, 9). Less common symptoms which may be associated with higher levels of parasitemia, may include: neck stiffness, vomiting, diarrhea, sore throat, weight loss, shortness of breath, and hematuria (3, 6, 7). Emotional lability, mild depression, transient hyperesthesia, photophobia, conjunctival injection, abdominal pain, petechia and ecchymoses have also been described (3).

On physical examination fever is the predominant feature and may be accompanied by: splenomegaly. Less common findings include hepatomegaly, mild pharyngeal erythema, jaundice, and retinopathy with splinter hemorrhages and retinal infarcts (7, 9). Laboratory abnormalities may include: hemolytic anemia, thrombocytopenia, proteinuria, hemoglobinuria, and elevated levels of liver enzymes, blood urea nitrogen and creatinine (4, 5, 7, 8, 9).

Severe disease often requires hospitalization and typically occurs in individuals with underlying risk factors. Complications associated with severe presentation include: acute respiratory distress syndrome, disseminated intravascular coagulation, hemodynamic instability, congestive heart failure, renal failure, hepatic compromise, myocardial infarction, severe hemolysis, splenic rupture and death (4, 7, 9). Mortality rates for those with clinically apparent *B. microti* infections are around 5% (6, 8), but can be as high as 6 - 21% among hospitalized immuno-compromised patients (1, 7). Mortality rates for those infected with *B. divergens* in Europe are around 42% (6).

The possibility of co-infection with other tick-borne diseases such as Lyme disease and/ or

Anaplasmosis should always be considered when Babesiosis is diagnosed (10). Co-infection with *B. burgdorferi* often results in a presentation with more severe clinical manifestations (6).

4. Etiology

Babesiosis is a parasitic disease caused by intraerythrocytic protozoa of the genus *Babesia* (4, 9). While there are more than 100 *Babesia* species worldwide that can cause disease in both domestic and wild mammals, only a handful have been recorded to cause disease in humans (11). There are four distinct *Babesia* species capable of causing disease in humans; *B. microti*, *B. divergens*, *B. duncani* and *B. venatorum* (2). The majority of Babesiosis cases reported in North America are caused by *B. microti* (10).

5. Epidemiology

5.1 Vectors and Reservoir

Only *Ixodes*, or hard bodied ticks have been identified as vectors of *Babesia* species worldwide (6). In North America the principal vector of *Babesia microti* is *Ixodes scapularis* (5, 9). *Ixodes pacificus* has been hypothesized as the vector of *B. duncani* along the West coast (5, 9, 11), while *Ix. ricinus* is the principal vector of *B. divergens* and *B. venatorum* in Europe (6, 7).

None of the *Ixodes* species are capable of persistently supporting *Babesia* infection, and consequently they must feed on an infected reservoir host. The principal reservoir for *Babesia* parasites is the white-footed mouse (*Peromyscus leucopus*), upon which both larvae and nymphs feed maintaining the epizootic cycle (9). Within some endemic regions between 40 – 60% of the white-footed mice are infected with *B. microti* (2, 6).

5.2 Transmission

Babesiosis is transmitted primarily when an infected blacklegged tick takes a blood meal, with

most cases occurring in the summer months, typically between May and July, when nymphs are most active (6, 9). Transmission of *B. microti* requires between 36 – 72 hours of an infected tick feeding on a host, as infectious sporozoites located within the tick salivary glands are only activated upon exposure to warm blooded hosts (9).

While tick transmission is limited seasonally, transmission associated with blood transfusion can occur year round. Babesiosis is the most common transfusion-transmitted pathogen in the U. S. likely because prolonged asymptomatic parasitemias are possible (12, 13). Under normal blood bank conditions *B. microti* parasites were able to survive for 35 days (7, 8, 9). More than 170 transfusion-transmitted cases have been documented in the U. S. since 1980, with more than three-quarters of these reported since 2000 (8, 14).

Transplacental transmission, although rare, has been documented a handful of times in the U. S. (15). All cases were characterized by asymptomatic maternal infection and development of fever, hemolytic anemia and thrombocytopenia within the infant's first seven weeks of life.

5.3 Occurrence

General:

In North America the majority of Babesiosis cases, associated with *B. microti*, occur in the northeast U. S. (i.e. Massachusetts, Connecticut, New Jersey, New York and Rhode Island) and the upper Midwest (i.e. Minnesota and Wisconsin) (5, 9). The distribution of cases coincides with the distribution of the principal reservoir – the white footed mouse (2). Additional *B. microti* cases have been identified in Germany, Poland and Australia (2); infections with *B. microti*-like organisms have been observed in Taiwan, Japan and South Korea.

Babesiosis cases associated with *B. duncani* are limited to the U. S. Pacific coast (11), and cases associated with *B. divergens* are limited to the UK, Western and Eastern Europe, Ireland, Sweden and Russia and commonly found in cattle rearing regions (1, 11). *B. venatorum* is distributed in Europe. Sporadic cases of Babesiosis have been reported from Africa, Asia and South America.

Canada:

At present Babesiosis is reportable in Manitoba. It is not reportable in any other jurisdiction in Canada, or to the Public Health Agency of Canada. However with the continued northward expansion of *Ix. scapularis* populations the risk of infection with tick-borne pathogens such as Babesiosis should be expected to increase. Recent studies have estimated the rate of said expansion to vary between 33 and 55 km per year (16). Although Babesiosis and Lyme disease have a common vector, the geographical expansion of Babesiosis has been unfolding at a substantially slower rate (9).

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 (16). *B. microti* parasites were detected at low rates in ticks collected from Manitoba, Ontario, Quebec and New Brunswick (17). The highest infection rates were observed in Manitoba (17).

Manitoba:

Since Babesiosis became provincially reportable in 2015 there have been no cases reported in Manitoba. However, in 2013 the first locally acquired Babesiosis case in Canada was reported for a Manitoba resident with no history of travel outside of the province (18). Several years of surveillance data will be needed to establish baseline rates in Manitoba.

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 Babesiosis 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 Babesiosis transmission outside of these 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 Babesiosis typically ranges between 1 to 6 weeks following the bite of an infected tick, and 1 to 9 weeks (and up to 6 months) following transfusion with infected blood products (3, 7, 9).

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 are at risk of potential Babesiosis transmission. Any subsequent resistance to *B. microti* conferred by the adaptive immune system in response to prior

infection, is not life-long, but rather decreases with age (7, 9). For instance, a mouse model demonstrated that the ability to clear parasites from the body declined with age, resulting in an increase in periodic parasitemia (6).

5.6 Period of Communicability

Person to person transmission of Babesiosis, while rare, has been demonstrated via blood transfusion (6, 7, 8, 9, 10, 14) and transplacentally (14).

6. Laboratory Investigation

Diagnosis should be considered when a patient has a history of travel or residence in an endemic area, or who has received a blood transfusion in the previous 6 months and presents with symptoms consistent with Babesiosis.

Laboratory evidence includes:

- Confirmatory laboratory evidence includes one of the following (4):
 - Identification of intraerythrocytic *Babesia* organisms by light microscopy in a Giemsa, Wright or Wright-Giemsa stained blood smear; **OR**
 - Detection of *Babesia species* DNA in a whole blood specimen by PCR; **OR**
 - Isolation of *Babesia species* organisms from a whole blood specimen by animal inoculation.
- Supportive laboratory evidence includes one of the following (4):
 - Demonstration of *Babesia species* by IFA with specific IgG antibody titre of greater than or equal to 1:256

Serum titres of 1:1024 or greater are indicative of recent or active infections, while those equal to or less than 1:64 or indicative of previous infection (3). A four-fold rise in IgG *Babesia* antibody titre between acute and convalescent sera is required to confirm recent infection. *Babesia species*

antibodies can persist for months or years following resolution of infection (2, 3).

Parasitemia will remain detectable in peripheral blood for 3 – 12 weeks however levels are often < 1% early in infection, when most individuals seek medical attention (5, 6, 7). Multiple peripheral blood smears repeated over several days should be examined, with an experienced microscopist viewing a minimum of 300 microscopic fields (3, 5, 7). In cases where parasites are not identified on blood smears, but symptoms are suggestive of Babesiosis, PCR should be considered (3). The detection of *Babesia* by PCR is a highly sensitive diagnostic option (3, 5).

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/tickbo/reform.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,
- 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.

8. Control & Prevention

8.1 Management of Cases

Babesiosis should be considered in any patient presenting with an unexplained febrile illness who has resided in or traveled to an area where the infection is endemic within the previous two months, **OR** who has received a blood transfusion within the previous 6 months (7).

All patients with diagnosed Babesiosis (i.e. those with viral-like infection symptoms and positive laboratory diagnosis) should be treated with the recommended anti-parasitic drugs due to the risk of complications. Early diagnosis and prompt treatment is essential for patients who are asplenic, immunocompromised, or elderly, given their greater risk of severe complications and mortality (5, 10). Consultation with an Infectious Disease specialist is recommended.

Treatment of those presenting with mild Babesiosis is also recommended to shorten the duration of symptoms and prevent chronic infection which may be a risk for transmission with blood transfusion, or recrudescence infection should the individual become immune-compromised (7).

Recommended treatment for Babesiosis includes: Combination of **atovaquone** and **azithromycin** for 7 – 10 days (3, 5, 9) –

- Adults:
 - Atovaquone, 750mg orally every 12h, and azithromycin, 500 – 1000 mg on day 1 and 250 – 500 mg orally once per day thereafter (3, 5, 9, 19).
- Children:
 - Atovaquone 20mg/kg every 12h (to a maximum of 750mg/ dose), and azithromycin 10mg/kg on day 1 (to a maximum of 500mg/ dose) and 5mg/kg once per day (up to a maximum of 250mg/ dose) orally thereafter (3, 5, 9).

Combination of **clindamycin** and **quinine** for 7 – 10 days (3, 5) –

This is recommended for severe disease

presentations. Therapy should be continued for more than 6 weeks (including 2 weeks during which parasites are not seen on the blood smear) in patients who have asplenia or are immune-compromised (1, 2, 9).

- Adults:
 - Clindamycin 300 – 600 mg every 6h intravenously, or 600 mg orally every 8h and quinine, 650 mg every 6 – 8 h orally (3, 5, 9).
- Children:
 - Clindamycin 7 – 10 mg/kg given intravenously or orally every 6 – 8 h (up to a maximum of 600 mg per dose), and quinine 8 mg/kg orally every 8 h (up to a maximum of 650 mg per dose) (3, 5, 9).

The combination of clindamycin and quinine may be associated with severe side effects including: hearing loss, tinnitus, syncope, hypotension and gastrointestinal distress (6). Despite these adverse effects, the benefit outweighs these risks for high-risk patients (i.e. immune-compromised) (3, 5). Partial or complete RBC exchange transfusion should be considered for patients presenting with severe Babesiosis as indicated by high grade parasitemia (greater than or equal to 10%), severe anemia (hemoglobin < 10 g/ dL), significant hemolysis, or renal, hepatic or pulmonary compromise (3, 5, 9). In cases where an exchange transfusion is being considered consultation with both Infectious Diseases and Hematologist specialists is essential.

In patients with mild to moderate presentations clinical improvement should be observed within 48 hours following the start of therapy (3, 5). Most symptoms typically resolve within 1 – 2 weeks, but others such as fatigue, myalgia and anemia may persist for up to three months (3, 7, 9).

Co-infection with other tick borne pathogens, such as *Borrelia burgdorferi* and/or *Anaplasma phagocytophilum*, should be considered if there is

a more severe clinical presentation, if symptoms persist or there is a poor response to the recommended therapy (5, 7). Patients with a co-infection with *B. burgdorferi* should be treated concurrently with doxycycline and anti-Babesial agents (11).

Parasitemia may occasionally persist in both treated and untreated patients leading to subsequent recrudescence weeks or months later (5). This is more common in immunocompromised patients.

8.2 Management of Contacts

In the U.S. prospective blood donors are screened via survey for a history of Babesiosis, and those with a history are deferred indefinitely from donating (8, 9, 14). The efficiency of survey screening, however, is questionable as the majority of donors implicated in transfusion transmission are asymptomatic and don't recall tick exposure (8). While there are currently no approved blood screening tests, states within highly endemic areas have instituted protocols that use both serology and PCR (9).

Although screening for Babesiosis is not conducted at this time and the risk to the blood supply remains very low, Canadian Blood Services (CBS) continues to maintain ongoing vigilance. In 2013 a pilot survey screened more than 10,000 donors from areas of potential risk and no positives were detected (17, 20).

8.3 Preventative Measures

Given their greater risk of developing severe and potentially fatal disease, immune-compromised individuals should consistently adopt preventive measures and take precautions to avoid suitable tick habitat (1).

Educate the public about Babesiosis transmission and personal protection measures that should be adopted to minimize the risk or 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 (21). 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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