Guidance for Primary Care and Emergency Medicine Providers

in the Management of Lyme Disease, Human Granulocytic Anaplasmosis, Babesiosis and Powassan virus infection

in Nova Scotia

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NOVA SCOTIA

Guidance for Primary Care and Emergency Medicine Providers in the Management of Lyme Disease, Human Granulocytic Anaplasmosis, Babesiosis and Powassan virus infection in Nova Scotia

Department of Health and Wellness

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Executive Summary

This document has been reviewed and updated to reflect recommendations in Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis, and Treatment of Lyme Disease (Lantos et al 2021).

Tick borne infections continue to evolve in Nova Scotia and the entire province is considered an at-risk area. Lyme disease is endemic, human granulocytic anaplasmosis (HGA) is emerging and there have been sporadic cases of babesiosis acquired within the province. On May 23, 2023, anaplasmosis (HGA), babesiosis and Powassan virus have been added to the Notifiable Diseases list in NS and are required to be reported to Public Health by law.

The Infectious Diseases Expert Group (IDEG) endorses the IDSA, AAN, and ACR guidelines (2020) for the prevention, diagnosis, and treatment of Lyme disease (Lantos et al., 2021). Two review articles (Hu 2016; Sanchez E et al., 2016) and the National Institute for Health and Care Excellence (NICE) guideline published in 2018 (***www.nice.org.uk/guidance/ng95***) are generally consistent with the IDSA, AAN, and ACR recommendations. IDEG continues to monitor developments in the management of Lyme disease and other tick borne infections and will update its guidance as new evidence becomes available. In Nova Scotia, pharmacists are authorized to assess and prescribe chemoprophylaxis for the prevention of Lyme disease. In addition, effective May 1st, 2024, that authority has expanded to authorize pharmacists to assess and prescribe for the treatment of early Lyme disease as outlined by the Infectious Disease Expert Group. This will increase accessibility for individuals who meet the criteria for prevention and treatment of Lyme disease. In addition, we have seen significant increases in cases of HGA predominantly in the Western zone of the province. As a result, the QEII laboratory now tests all Lyme specimens for *Anaplasma spp.* as an expanded tick borne infection (TBI) panel and those with positive results should receive treatment with doxycycline (see section on ***Anaplasmosis HGA***). This update expands guidance beyond Lyme disease to include these other newer emerging infections.

We highlight the following key points pertinent to the management of tick bites, Lyme disease, HGA and babesiosis in Nova Scotia:

Reducing Risk of Tick Bites

- Being at risk for tick borne infections including Lyme disease, HGA, babesiosis and Powassan virus requires outdoor activity in areas of long grass, brushes, and woods, including urban parks and gardens.
- The most reliable way to avoid getting a tick borne infection is to prevent deer/blacklegged tick bites (see prevention measures (***https://novascotia.ca/dhw/cdpc/lyme.asp***).

Reducing Risk AFTER Tick Bites

- Immediate and correct removal of an attached blacklegged tick is key to preventing the transmission of Lyme disease, HGA, babesiosis and Powassan virus infection.
- Examining the removed tick for species identification is important for anticipatory guidance and in determining if antibiotic prophylaxis to prevent Lyme disease is appropriate (see ***tick identification section*** for more information).
- ***eTick*** is a tick identification platform that is available for identification of tick species within 24 hours at no cost. Analysis of the blacklegged tick for the presence of infection with *Borrelia burgdorferi, Anaplasma phagocytophilum or Babesia spp.* does not reliably predict the risk of developing these tick borne infections after a bite and is not recommended for management decisions.
- The overall risk of Lyme disease after a bite from an infected tick is low and is dependent on how long the tick has been attached. Two of the most widely cited studies reported that the risk of Lyme disease in people who were found to have a blacklegged tick bite ranged from 1.2%-3.2% (Shapiro et al., 1992; Nadleman et al., 2001). However, the risk may exceed 20% when a tick has been attached ≥ 72 hours (Lantos et al., 2021). Most studies have found that the infected tick needs to be attached for at least 24 hours before it can transmit disease and the majority of transmission occurs after 36-48 hours of attachment (Eisen, 2018; Lantos et al., 2021).
- There are no data on duration of attachment and risk for human infection in HGA and *Babesia* infections. However, animal studies suggest that while transmission of *Anaplasma phagocytophilum* is possible with attachments of less than 24 hours, attachment times of > 36 - 48 hours are required for efficient transmission in the mouse model (Eisen, 2018; Levin et al., 2021). For *Babesia* this attachment period is likely > 48hrs (Eisen, 2018). Powassan can likely be transmitted after 15-30 minutes, based on animal studies.
- Use of antimicrobial prophylaxis for prevention of Lyme disease is recommended for adults when it can be administered within 72 hours of removal of an identified high-risk tick bite. For children, the option of antibiotic prophylaxis for an identified high-risk tick bite OR a wait-and-watch approach is recommended. (see ***Prophylaxis section*** for details).
- There is no prophylaxis for *Anaplasma* or *Babesia* infection.

Testing

Lyme Disease

- Serologic testing using the standard two-tiered (STTT) algorithm described by the Centers for Disease Control and Prevention (CDC) and the Canadian Public Health Laboratory Network (CPHLN) OR a validated modified two- tiered testing (MTTT) algorithm is currently the only recommended method for making a serological diagnosis of Lyme disease (Lantos et al., 2021). As of April 1, 2021, the Queen Elizabeth II Health Sciences Centre (QEII HSC) microbiology laboratory moved to using the MTTT algorithm (Khan et al., 2022).
- Laboratory testing is not necessary in patients presenting with the typical erythema migrans (EM) rash (> 5cm) who live in Nova Scotia or have travelled to an area where there is a risk for Lyme disease during Lyme season (anytime temperature reaches >4° C, with the greatest risk of transmission during summer months). In this situation, the diagnosis can be made based on the presence of EM alone and treatment started (Lantos et al., 2021).
- Patients with symptoms and signs suggestive of early disseminated and late Lyme disease should have serologic testing.
- In patients presenting with summertime influenza-like illness who lack the EM rash, confirmation of Lyme Borrelia infection can be difficult. In these patients it is reasonable to take a "watch and wait" approach when the patient can be monitored for ongoing or worsening symptoms or development of new symptoms. In these patients, it is reasonable to consider ordering serologic testing as the MTTT has increased sensitivity for early infection. If initial serology is negative, the patient can be retested 4 weeks later to look for evidence of seroconversion (Centre for Effective Practice, 2020).

Anaplasma and *Babesia*

- Co-infections with both Lyme (*B. burgdorferi*) and HGA (*Anaplasma*) have been documented in Nova Scotia. The laboratory at the QEII now tests for *Anaplasma* (PCR) on all serum specimens submitted for Lyme disease testing. Patients with positive results should be treated with doxycycline.
- Testing for *Babesia* is based on blood smear and should be considered in anyone being treated for Lyme or HGA who has persistent fever after 48 hours of doxycycline.
- Sending specimens to laboratories that 1) use interpretive criteria that are different from those of the CDC and Canadian Public Health laboratories, 2) bypass the ELISA and use immunoblots alone, or 3) perform IgM testing in the

setting of suspected chronic infection is NOT recommended as they produce false positive results in up to 50% of cases (Lantos et al., 2010; Lantos et al., 2021; Fallon et al., 2014).

Treatment

- Most cases of Lyme disease can be cured with a 2- to 4-week course of oral antibiotics. A minority of patients can have post treatment symptoms of pain, fatigue, or difficulty thinking that improves with time but can last for months in some.
- Studies have demonstrated that longer-term antibiotic treatment is not more effective than the standard recommended course of treatment and may be associated with complications. Longer-term antibiotics are not recommended (Lantos et al, 2021). (See ***Treatment and Chemoprophylaxis of Lyme disease*** for recommended treatment durations).
- Patients who have lingering symptoms after the standard recommended treatment for Lyme disease should be re-evaluated to determine if the diagnosis of Lyme disease was accurate and to assess for an alternative cause for their symptoms.
- See below for treatment guidance on other tick borne infections

The following are summary statements for tick borne infections which will divided into 4 sections:

1. Diagnosis and treatment of Lyme disease
2. Diagnosis and treatment of HGA
3. Diagnosis and treatment of Babesiosis
4. Powassan Virus

1.0 Lyme Disease (*Borrelia burgdorferi* infection)

INTRODUCTION

The case definition for Lyme disease is now aligned with the CDC case definition for high incidence jurisdictions, meaning that Nova Scotia has met the threshold described by the CDC of an average of ≥ 10 confirmed cases of Lyme disease/100,000 population for three consecutive years. Lyme disease is the most common tick borne infection transmitted in Nova Scotia. The clinical presentation of Lyme disease varies and is divided into early and late disease. Early disease usually presents with an acute illness characterized by the presence of localized erythema migrans (EM). Although described classically as a "bull's eye" rash, EM should be considered in any expanding oval erythematous rash, particularly if found on the body in regions that would be atypical for cellulitis (torso, behind the knee, back of neck, etc.). If untreated, this is sometimes followed by dissemination with multiple secondary annular lesions and systemic symptoms including fever, arthralgias, headache, and lymphadenopathy. Other manifestations of early disseminated infection can include Lyme carditis with conduction abnormalities and neuroborreliosis (neurologic Lyme), which may present as aseptic meningitis or with cranial nerve involvement (especially Bell's palsy). Late disease most commonly presents as a chronic arthritis and, more rarely, chronic neuroborreliosis (Hatchette et al., 2014; Lantos et al., 2021). Depending on the stage and extent of the illness, there are differences in the investigations, treatment, and follow-up required.

DIAGNOSIS OF LYME DISEASE

Laboratory testing for Lyme disease (Ld) in Nova Scotia is done by the Microbiology Laboratory at the QE II HSC. As of April 1, 2021, serological testing for Lyme disease transitioned to the MTTT algorithm, using 2 enzyme immunoassays (EIAs) (Khan et al., 2022). Prior to this date, serological testing for Lyme disease at the QEII HSC used the standard two-tier testing (STTT) algorithm, where specimens that are reactive or indeterminate on the first step EIA are forwarded to the National Microbiology Laboratory (NML) in Winnipeg for further testing using immunoblotting. With the MTTT algorithm, specimens are first tested using the Zeus C10/VlsE EIA (ZEUS ELISA *Borrelia* VlsE1/pepC10 IgG/IgM), with reactive specimens tested in our microbiology laboratory by a second EIA, the Zeus whole cell EIA (ZEUS ELISA *Borrelia burgdorferi* IgG/IgM), rather than an immunoblot. Specimens with positive results on both EIAs are considered to be positive. This approach has been approved by the United States Food and Drug Administration and endorsed by the CDC and the CPHLN (Mead et al., 2019; Hatchette et al., 2020).

The MTTT approach offers advantages over the STTT approach:

- It is more sensitive for detecting early infection (formal evaluation showed MTTT detected 28% more cases of early infection).
- It has a similar specificity compared to the STTT (99.6% with our validation).
- Both EIAs can be performed at the QEII HSC, which will significantly improve turn-around-time for results.
- It simplifies the interpretation of Lyme disease serology results, which will now be reported as “positive” or “negative”.

The sensitivity of this testing approach depends on the stage of infection. In early, localized Lyme disease with EM, the sensitivity of the STTT is less than 50%, but increases with the duration of infection (Fallon et al., 2014; Moore et al., 2016; Molins et al., 2016; Waddell et al., 2016). The sensitivity of testing for patients with early neuroborreliosis or Lyme arthritis in one study was 87% and 96% respectively (Moore et al., 2016). While the MTTT approach has improved sensitivity for detecting early infection, it is important for clinicians to remember that patients presenting with early localized Lyme disease should be treated based on a clinical diagnosis, without relying on serology. The improved sensitivity and turn-around-time may be an advantage for investigating patients who lack EM but have other clinical symptoms suggesting early localized infection or where early disseminated Lyme disease is a consideration. History and clinical manifestations are important for estimating the likelihood of Lyme disease before the physician decides on proceeding with testing. If the pre-test probability for Lyme disease is low, there is a much higher likelihood that the positive result is a false positive test.

The use of immunoblots may still have value in patients with manifestations of late stage Lyme disease, such as Lyme arthritis, or in suspect false positive cases where serologic results do not fit with the clinical presentation. In these circumstances, it is reasonable to consider performing an IgG immunoblot as patients with late stage Lyme disease have high IgG antibody responses and the immunoblot may allow for the evaluation of the response to specific Borrelial proteins, which some clinicians may find helpful (Lantos et al., 2021). In these cases, the clinician can contact the microbiologist on call at the QEII to request the sample be sent to the NML for testing.

IDEG RECOMMENDS

1. Physicians need to be aware that the diagnosis of early Lyme disease with localized EM in season (anytime temperature reaches > 4° C, with the greatest risk of transmission during summer months) is a clinical one. Serological tests have poor sensitivity during the first four weeks of infection and are not recommended for management decisions.

2. Patients with 1) One or more skin lesions suggestive of, but atypical for, EM or 2) an EM-like rash out of season (regardless of exposure area) should undergo serological testing using the MTTT algorithm. If the test result is negative, serological testing should be repeated at least 2-3 weeks after collection of the first ("acute-phase") serum sample.
3. Patients presenting with a nonspecific febrile illness, but no EM-like rash, and have participated in activities that would potentially expose them to ticks while in Nova Scotia should be tested and monitored for other symptoms suggestive of Lyme disease. Repeat testing at least 2-3 weeks after collection of the first ("acute-phase") serum sample is suggested if there are still concerns that the patient has Lyme disease.
4. Patients who remain febrile after 48 hours of treatment with doxycycline should be assessed for other causes, including *Babesia* infection.
5. Patients with signs and symptoms suggestive of early disseminated and late Lyme disease should undergo serologic testing using the MTTT algorithm. These presentations take time to manifest and may present out of season.
6. Patients with signs and symptoms suggestive of Lyme carditis including dyspnea, edema, palpitations, lightheadedness, chest pain, and syncope should have an ECG. In the absence of symptoms suggesting Lyme carditis, ECG is not necessary as severe ECG abnormalities are uncommon (Lantos et al., 2021).
7. Patients in whom there is a concern for neuroborreliosis should undergo a lumbar puncture to look for cerebrospinal fluid abnormalities, in addition to serological testing at the same time. Consultation with an infectious diseases physician or neurologist would be appropriate.

IDEG RECOMMENDS AGAINST

1. Testing in the absence of symptoms or signs consistent with Lyme disease: the value of serologic testing is limited in the absence of symptoms or signs that support a reasonable likelihood of infection (Lantos et al., 2021).
2. Testing in asymptomatic persons who have had a blacklegged tick bite: antibodies to *B. burgdorferi* are not detected until a few weeks after infection. Thus, there is no point in testing at the time a tick is identified on the person and/or removed. Even if the person does develop Lyme disease from the tick bite, the serology will be negative at the time the tick is removed.
3. Testing in patients with the typical EM rash (> 5cm in size) in season (any time temperature reaches > 4°C, with greatest risk of transmission during summer months) and with appropriate outdoor exposure anywhere in Nova Scotia or an

area outside of Nova Scotia that is identified as at risk for Lyme disease. The diagnosis should be made based on the presence of the EM and treatment started.

4. Repeat testing after treatment: laboratory testing cannot be used to determine "cure." Like other infections, the antibodies remain positive even after effective treatment.
5. Sending specimens to laboratories that use interpretive criteria that are different from the CDC: the most common request that physicians get is to send the specimen to IGeneX, which has different interpretive criteria for their immunoblots, which may lead to false positive test results (Fallon et al., 2014; Molins et al., 2016).
6. Bypassing the ELISA and using immunoblots alone: Immunoblots done in the absence of preceding ELISA testing have been associated with a reduction in specificity and are NOT recommended. Immunoblots are semi- quantitative tests that can produce faint bands due to non-specific reactivity, which has been demonstrated in people with no history of exposure to ticks or Lyme disease or in illnesses other than Lyme disease (Molins et al., 2016).
7. The use of PCR on blood, serum, or plasma or the use of urinary antigen as a diagnostic test: these tests have not been validated.

IMPORTANT CAVEATS TO TESTING

1. Patients who are treated early for Lyme disease may have delayed seroconversion or never seroconvert (i.e., develop a positive MTTT).
2. Patients with Lyme disease who have had symptoms for greater than 4 weeks are very likely to have a positive MTTT. If the patient's symptoms have been present for greater than 4 weeks, a negative MTTT or Lyme IgG immunoblot (in cases where the symptoms do not fit the clinical picture and a Immunblot is sent to the NML for testing to rule out a false positive MTTT) suggests that the symptoms the patient is experiencing are not due to Lyme disease (AMMI 2019; Lantos et al., 2021).
3. Diagnosis of repeat infection is often difficult as EIAs and immunoblots can remain positive for years despite appropriate treatment (Lantos et al., 2021). Suspected repeat infections requiring serological testing should be discussed with a medical microbiologist.
4. The *Borrelia* species that cause Lyme disease in Europe can be different from those that cause disease in North America. Confirmation testing may require the use of an immunoblot for those species. If the history suggests exposure in Europe, this should be documented on the requisition so that the appropriate confirmatory testing can be done.

TREATMENT AND CHEMOPROPHYLAXIS OF LYME DISEASE

There have been several clinical trials that support treatment recommendations for Lyme disease. These form the basis for the IDSA/AAN/ACR treatment guidelines and recommendations found in clinical reviews (Lantos et al., 2021; Sanchez et al., 2016), the NICE Guideline, the Society of Obstetrics and Gynecologists of Canada Committee Opinion (Smith et al., 2020), and the American Academy of Pediatrics Red Book (American Academy of Pediatrics, 2018).

IDEG RECOMMENDS

Lyme disease should be treated in accordance with the IDSA/AAN/ACR (Lantos et al., 2021) and American Academy of Pediatrics guidelines (American Academy of Pediatrics, 2018).

Treatment of ADULT PATIENTS with Lyme disease

EM

- Doxycycline* 100 mg po bid X 10 days
- Amoxicillin 500 mg po tid X 14 days
- Cefuroxime 500 mg po bid X 14 days
- Azithromycin 500 mg po once daily X 7 days (second line agent reserved for patients in whom other antibiotic classes are contraindicated)

Cranial nerve palsy

- Doxycycline* 100 mg po bid X 14-21 days

Meningitis or radiculopathy

- Doxycycline* 100 mg po bid X 14-21 days
- Ceftriaxone 2 g IV once daily X 14-21 days

Lyme disease-related parenchymal involvement of the brain or spinal cord

- Consult Infectious Diseases

Carditis

- Doxycycline* 100 mg po bid X 14-21 days
- Amoxicillin 500 mg po tid X 14-21 days
- Cefuroxime 500 mg po bid X 14-21 days
- Ceftriaxone 2 g IV once daily X 14-21 days

Initial IV therapy is recommended for patients requiring hospital admission. Therapy can be completed orally for the same total duration.

Arthritis (initial)

- Doxycycline* 100 mg po bid X 28 days
- Amoxicillin 500 mg po tid X 28 days
- Cefuroxime 500 mg po bid X 28 days

Arthritis (recurrent or refractory)

- Doxycycline* 100 mg po bid X 28 days
- Amoxicillin 500 mg po tid X 28 days
- Cefuroxime 500 mg po bid X 28 days
- Ceftriaxone 2 g IV once daily X 14 days

(Repeat IV therapy can be extended to 28 days if inflammation is not resolving)

***** *A recent systematic review of doxycycline use in pregnant individuals found no increased risk of teratogenicity, permanent teeth staining, hepatotoxicity or permanent inhibitory effects on bone growth in the developing fetus (Cross et al., 2016). The decision to use it in these patients should be individualized to the likely risks and benefits of alternative antibiotics.*

Treatment of PEDIATRIC PATIENTS with Lyme disease

The American Academy of Pediatrics Committee on Infectious Diseases endorses the use of doxycycline in children younger than 8 years of age for the management of Lyme disease based on the low risk of dental staining in reports of treatment of young children with Rocky Mountain Spotted Fever. Use of doxycycline is therefore preferred for isolated facial palsy or central nervous system (CNS) disease due to Lyme disease for children of any age.

EM (single or multiple) only (no neurological/cardiac signs or symptoms)

- **For patients ≥ 8 years of age:**
  Doxycycline 4.4 mg/kg/24h PO divided q12h for 10 days
  Maximum: 200mg/24h
  [Round dose to nearest 25 mg (1/4 tablet)]
- **For patients < 8 years of age:**
  Amoxicillin 50 mg/kg/24h PO divided q8h for 14 days Maximum: 1.5 gram /24h
- **If penicillin allergy:**
  Cefuroxime 30 mg/kg/24h PO divided q12h for 14 days Maximum: 1 gram /24

Isolated Facial Palsy

- Consult Infectious Diseases
- If other neurological symptoms present, consider lumbar puncture
- Corticosteroids are not recommended
- Doxycycline 4.4 mg/kg/24h PO divided q12h for 14 days for all ages
- Maximum: 200mg /24h
  [Round dose to nearest 25 mg (1/4 tablet)]

  Amoxicillin for treatment of facial palsy due to Lyme disease has not been studied.

Lyme Arthritis

- Consult Infectious Diseases or Rheumatology
- **For patients ≥ 8 years of age:**
  Doxycycline 4.4 mg/kg/24h PO divided q12h for 28 days
  Maximum: 200mg/24h
  [Round dose to nearest 25 mg (1/4 tablet)]
- **For patients < 8 years of age:**
  There are limited safety data on the use of doxycycline for
  > 21 days in children < 8 years of age
  Amoxicillin 50 mg/kg/24h PO divided q8h for 28 days
  Maximum: 1.5 gram/24h
- **If penicillin allergy:**
  Cefuroxime 30 mg/kg/24h PO divided q12h for 28 days
  Maximum: 1 gram /24h

Persistent Lyme Arthritis

- Consult Infectious Diseases and Rheumatology

For persistent arthritis after first course of therapy for patients who have responded incompletely or who respond and then relapse soon after stopping therapy:

- **For patients ≥ 8 years of age:**
  Doxycycline 4.4 mg/kg/24h PO divided q12h for 28 days
  Maximum: 200mg/24h
  [Round dose to nearest 25 mg (1/4 tablet)]
- **For patients <8 years of age:**
  There are limited safety data on the use of doxycycline for > 21 days in children < 8 years of age
  Amoxicillin 50 mg/kg/24h PO divided q8h for 28 days
  Maximum: 1.5 gram/24h
- **If penicillin allergy:**
  Cefuroxime 30 mg/kg/24h PO divided q12h for 28 days
  Maximum: 1 gram /24h
- **For patients who experience worsening of their arthritis:**
  Ceftriaxone 50-75 mg/kg/day IV once daily for 14-28 days
  Maximum: 2 gram /24h

Atrioventricular heart block or carditis

- Consult Infectious Diseases
- **For patients ≥ 8 years of age:**
  Doxycycline 4.4 mg/kg/24h PO divided q12h for 14-21 days
  Maximum: 200mg/24h
  [Round dose to nearest 25 mg (1/4 tablet)]
- **For patients < 8 years of age:**
  Amoxicillin 50 mg/kg/24h PO divided q8h for 14-21 days
  Maximum: 1.5 gram/24h
- OR if IV therapy required
  Ceftriaxone 50-75 mg/kg/day IV once daily for 14-21 days
  Maximum: 2 gram /24h
  Once patient is stabilized without ongoing symptoms or signs, can be switched to oral therapy as above to finish 14-21 days
- **If penicillin allergy:**
  Cefuroxime 30 mg/kg/24h PO divided q12h for 14-21 days
  Maximum: 1 gram /24h

OR

Ceftriaxone 50-75 mg/kg/day IV once daily for 14-21days
Maximum: 2 gram /24h
Once patient is stabilized without ongoing symptoms or signs,
can be switched to oral therapy as above to finish 14-21 days

Meningitis

- Consult Infectious Diseases
- Ceftriaxone 50-75 mg/kg/day IV once daily for 14days
  Maximum: 2g /24h

OR

- Doxycycline 4.4 mg/kg/24h PO divided q12h for 14days
  Maximum: 200mg /24h
  [Round dose to nearest 25 mg (1/4 tablet)]

PROPHYLAXIS OF LYME DISEASE IN ADULTS AND CHILDREN

Nova Scotia has expanded accessibility for prophylaxis by authorizing pharmacists to prescribe doxycycline for the purposes of preventing Lyme disease in individuals who satisfy the criteria for prophylaxis and cannot access their primary care clinician. The SOGC has recommended that a single dose of doxycycline is acceptable for use in pregnant individuals who satisfy criteria to warrant prophylaxis (Smith et al., 2020).

Prophylaxis is recommended in adults only when it can be given within 72 hours of removal of an identified high-risk tick bite, which is defined by meeting all three criteria (Lantos et al., 2021):

- The attached tick was an identified adult or nymphal blacklegged (Ixodes spp.) tick.
- The tick was attached for ≥36 hours, generally based on the degree of engorgement or by certainty about the time of tick acquisition.
- It occurred in an endemic area, which includes the province of Nova Scotia. If a tick bite cannot be classified with a high level of certainty as a high-risk bite, a wait-and-watch approach is recommended.
- For children, the option of antibiotic prophylaxis for a high-risk tick bite as identified above OR a wait-and-watch approach is recommended.

The wait-and-watch approach includes daily monitoring for the development of an expanding erythematous lesion at the site of the tick bite or other skin sites, fever, or any other unexplained illnesses for 3-30 days after the tick bite and seeking medical attention should one of these symptoms occur.

Recommended prophylaxis if above criteria are met and there are no contraindications to doxycycline:

- Adults: single dose of doxycycline 200 mg PO.
- Children of any age: single dose doxycycline 4 mg/kg to a maximum of 200 mg PO [Round dose to nearest 25 mg (1/4 tablet)].

Amoxicillin is not recommended for prophylaxis due to its short half-life.

IDEG RECOMMENDS AGAINST

Prolonged courses of antimicrobials for the treatment of Lyme disease that are not in keeping with courses recommended by the IDSA/AAN/ACR treatment guidelines (Lantos et al., 2021) as detailed above.

2.0 Human Granulocytic Anaplasmosis (HGA)

INTRODUCTION

HGA is a vector borne disease caused by the bacterium *Anaplasma phagocytophilum*, which is transmitted by the same tick that transmits *B. burgdorferi*, the cause of Lyme disease, and *Babesia spp*., the cause of babesiosis. Historically Nova Scotia has had a very small number of known cases of HGA in humans, with the first human case confirmed in 2017. With the increased number of sporadic cases in 2021, the QEII microbiologists undertook a quality project in partnership with NML to determine if there were coinfections with Lyme disease that were being missed. Of 500 sera from individuals with positive Lyme serology, 11 (2.2%) were identified as having *Anaplasma* by PCR testing (unpublished currently). This finding, as well as clinical reports of an increase in clinical cases of HGA, prompted the QEII laboratory to add *Anaplasma* PCR to all Lyme disease samples beginning in late July 2022.

The incubation period following a tick bite ranges from 5-21 days, but most patients will present within 7-14 days. The most common symptoms are acute onset of fever, with one or more of malaise, arthralgias, myalgias, and headache, and occasionally GI complaints. Patients often have mildly elevated transaminases and can have an abnormal CBC with thrombocytopenia, leukopenia, neutropenia, or anemia (Sanchez et al., 2016; Madison-Antenucci et al., 2020). Although the clinical syndrome can be non-specific, these laboratory abnormalities would be uncommon with Lyme disease and their presence suggests anaplasmosis, with or without Lyme disease. On May 23, 2023, HGA was added to Nova Scotia's list of Notifiable Diseases.

DIAGNOSIS OF HGA

Although microscopy can be used to diagnose acute infections, it lacks sensitivity as it relies on the recognition of intragranulocytic clusters or morulae in peripheral blood (figure 1) which may only be present in 25%–75% of cases. Serology has been traditionally the most common method of diagnosis, however, like Lyme disease, serology is often negative in acute infection, so confirmation requires both acute and convalescent serology. Identification of the bacteria using PCR is the most sensitive method to diagnose HGA within the first two weeks of infection. While whole blood has traditionally been the specimen of choice, we recently showed that testing serum was an acceptable alternative which has allowed the QEII laboratory to add it to all Lyme disease requests as part of a TBI panel. Serology may be useful to document prior infection but has little relevance for acute infection when all samples are being tested by PCR. Serology is performed at the NML and will only be forwarded after discussion with a medical microbiologist.

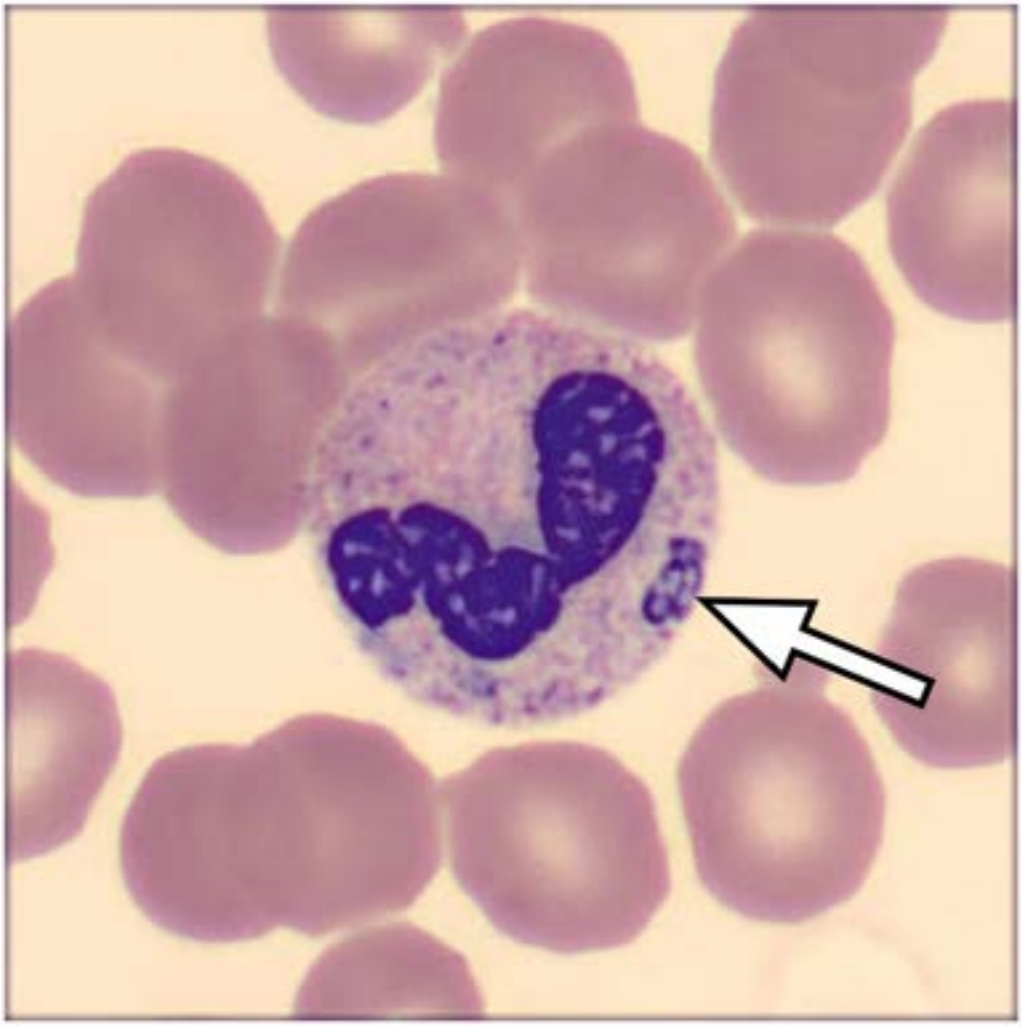

Figure 1: Intracellular inclusions of *Anaplasma* bacteria in granulocytes

Source: *NS Hematopathology Laboratory*

IDEG RECOMMENDS

The initial presentation is non-specific and requires a high degree of suspicion. Patients presenting with compatible symptoms should have a CBC with differential, blood smears for granulocyte inclusion bodies, transaminases and PCR for *Anaplasma* (which will be automatically tested on any Lyme disease samples).

TREATMENT OF HGA

While the case fatality rate is low (estimated at 0.3%) (Madison-Antenucci et al, 2020), it is not possible to predict who will have self-limiting illness. Anyone who has symptoms and is suspected/confirmed to have HGA should be treated.

- Primary regime: doxycycline (100 mg bid) for 10 days (Wormser et al., 2006; Sanchez et al., 2016).
- In those with a severe doxycycline allergy, rifampin can be used.
- If Rifampin or doxycycline cannot be given, Infectious Diseases should be consulted. There is increasing data to suggest doxycycline is safe to use in pregnancy. A systematic review in 2016 found that there was no increased risk of teratogenicity, permanent teeth staining, hepatotoxicity or permanent inhibitory effects on bone growth when doxycycline was used in pregnant individuals (Cross et al., 2016). Doxycycline can be considered in pregnancy after an informed discussion of risks with the patient. Response to treatment is usually rapid, generally within 24 hours. Fever persisting after 48 hours suggests an infection not susceptible to doxycycline, including another tick borne infection such as babesiosis (Wormser, et al., 2006; Sanchez et a. 2016).

3.0 Babesiosis

INTRODUCTION

Babesiosis is a parasitic infection transmitted by *Ixodes scapularis*, the same vector that transmits *B. burgdorferi*, the cause of Lyme disease, and *Anaplasma phagocytophilum*, the cause of HGA. Although there are a number of *Babesia* species, the most common cause of human infection in North America is *Babesia microti* (Madison-Antenucci et al, 2020). This is a rare but emerging infection. Although the last tick survey done in Nova Scotia in 2016 did not identify any ticks infected with *Babesia microti*, the total number of ticks surveyed was small. There have been sporadic cases of *Babesia* in Nova Scotia, suggesting that the pathogen may be emerging in Nova Scotia (Allehebi et al., 2022). This is similar to Ontario and Manitoba where sporadic cases have been identified (Yang et al., 2021).

The incubation period for babesiosis, after being bitten by an infected tick is 1-4 weeks. Most people do not recall a tick bite and 25% of adults and 50% of children are asymptomatic or present with a mild "flu-like" illness characterized by fevers, chills, and myalgias. Less commonly, severe disease can present as acute respiratory distress, which is associated with high levels of parasitemia that can result in severe anemia with multiorgan dysfunction (respiratory, heart, and renal failure). Individuals who are immunocompromised, have had a splenectomy or have a non-functioning spleen, who have COPD, CHF or liver disease, as well as neonates and the elderly are at higher risk for severe infection. It is estimated that 2-9% of *Babesia* infections that require hospitalization are fatal. (Madison-Antenucci et al, 2020).

On May 23, 2023, babesiosis was added to Nova Scotia's list of Notifiable Diseases.

DIAGNOSIS OF BABESIOSIS

The diagnosis of *Babesia* infection should be considered in an individual who presents with a summertime febrile illness with anemia, thrombocytopenia, evidence of hemolysis (elevated lactate dehydrogenase, hyperbilirubinemia), and/or increased transaminases, for which no other etiology is apparent and who could have exposure to ticks (Sanchez et al., 2016; Lantos et al., 2021). Recollection of a specific tick bite is not necessary to consider or make this diagnosis.

Babesia parasites infect red blood cells and so babesiosis is diagnosed in the same way as malaria, with blood smears. Ring forms may be seen in red blood cells and the appearance can mimic Plasmodium falciparum malaria. However, *Babesia spp.* can be distinguished from malaria by a negative rapid antigen test for malaria and by a number of unique features on the blood smear such as "Maltese cross" ring forms. (figure 2)

Clinicians suspecting babesiosis should order a blood smear and malaria testing on these patients. The requisition should document travel history and whether the patient has had a splenectomy.

Low grade parasitemia (<0.1%) can be missed on a blood smear (Madison-Antenucci et al, 2020). If the test is negative for *Babesia* but clinical suspicion remains, consult with Medical Microbiology on the role for PCR testing. *Babesia* specific serology should not be used for the routine diagnosis of acute infection. Its usefulness is limited to epidemiologic studies (Krause et al., 2021). Given that co-infections can happen from the bite of infected *Ixodes* ticks, when babesiosis is being considered, testing for Lyme disease and HGA should also be requested.

TREATMENT OF BABESIOSIS

Guidelines on the diagnosis and management of babesiosis have recently been published by the IDSA (Krause et al., 2021). Mild to moderate infection with parasitemia levels < 4% is treated with a combination of atovaquone and azithromycin for 7-10 days. Longer courses of treatment may be required for those with severe infection, immunocompromised patients, particularly those receiving Rituximab who are at risk for relapse. Note that atovaquone is not recommended in pregnancy. For pregnant patients or those that cannot tolerate the first line therapy, clindamycin and quinine sulfate can be used. For patients with high grade parasitemia (>10%) or evidence of severe end organ damage, exchange transfusions maybe considered. Infectious disease physicians should be consulted to help with treatment decisions.

There is no prophylaxis for preventing *Babesia* infection after a tick bite. Minimizing the risk of exposure to ticks and prompt tick removal reduces your risk. If the tick was infected, the longer the tick stays attached, the higher your risk of becoming infected. If the tick has been removed within 48 hours, the chances of getting the infection are very low. (Eisen, 2018) For more information on tick prevention visit the Nova Scotia DHW website (https://novascotia.ca/dhw/cdpc/lyme.asp).

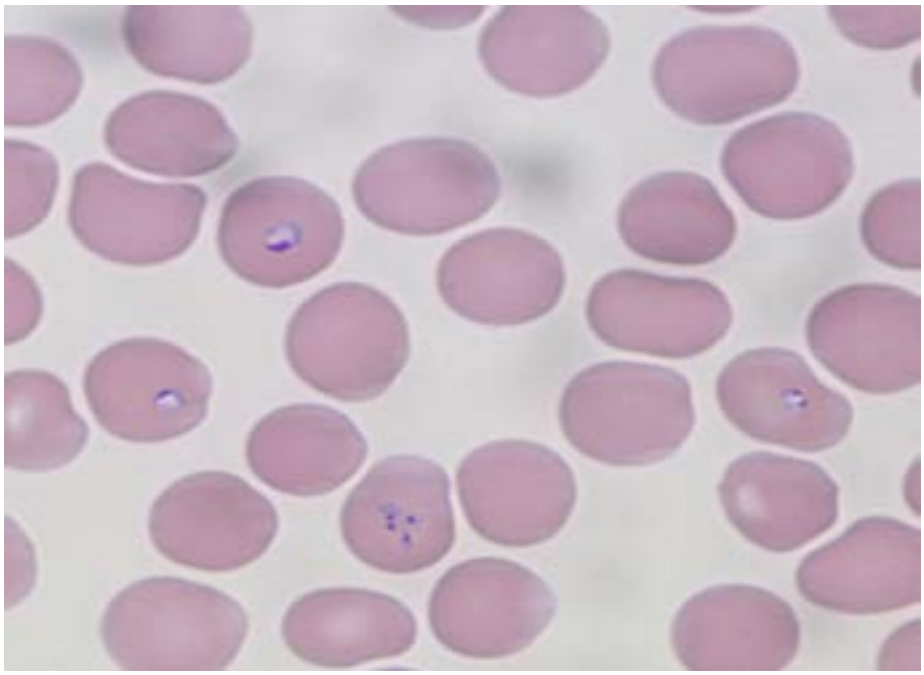

Figure 2: Blood smear showing intraerythrocytic ring forms of *Babesia*

Source: *NS Hematopathology Laboratory*

4.0 Powassan Virus

INTRODUCTION

Powassan virus (POWV) is a flavivirus that can be transmitted by deer ticks (*Ixodes scapularis*) and other ticks such as the squirrel tick (*Ixodes marxi*) or groundhog tick (*Ixodes cookie*) which do not frequently bite humans. There are two distinct genetic lineages of POWV and Deer tick virus (DTV) that are indistinguishable by serologic testing. Although the ecology of the two lineages can overlap, it appears the DTV circulates in the same *Ixodes*/white footed mouse cycle as *B. burgdorferi,* the bacteria that causes Lyme disease (Kemenesi and Banyai, 2018). POWV/DTV is an uncommon pathogen. Since its identification in 1958 there have been sporadic cases identified each year in the US (rage 2 -22 cases) (CDC 2023). There have also been sporadic cases in Canada (27 cases since 2017) (NCCID, 2023) but its true prevalence is not clear as the infection is not currently nationally reportable. In NS there have been no cases of POWV/DTV infection, but the virus was identified in a single tick in 2016.

Animal studies suggest that the time required for tick attachment to transmit the virus is much more rapid than Lyme disease, HGA or babesiosis, requiring only 15-30 minutes for effective transmission (Kemenesi and Banyai, 2018; Eisen 2018). As with other tick borne infections most people do not recall a specific tick bite and it is the recognition of activities that put them at risk for tick bites that is the most important consideration. The incubation period for POWV infection ranges from 7 -34 days and most people infected with POWV/DTV are asymptomatic or develop mild self-limiting influenza-like symptoms with headache and fever being common. However, some can present with a viral meningitis or encephalitis with altered sensorium (reviewed in Kemenesi and Banyai, 2018; PHAC). In those that develop neuroinvasive disease the case fatality rate is estimated to be 10% and 50% and those that survive have long term health consequences and neurologic deficits. (Reviewed in Kemenesi and Banyai, 2018; CDC).

DIAGNOSIS

Clinicians should consider POWV/DTV in people presenting with viral encephalitis who have had potential exposure to tick bites. The diagnosis is made by sending acute and convalescent serology and CSF testing. CSF findings are consistent with a viral picture including a mildly elevated WBC count (<500 per uL) with lymphocytic predominance; a mildly elevated protein, and normal glucose. The detection of the virus in CSF lacks sensitivity and confirmation of infection is often made by testing acute and convalescent serum for POWV/DTV specific antibodies. IgM can persist in serum for up to a year or more after arbovirus exposure. Thus, detection of IgM by itself is not sufficient for confirmation of acute infection but is consistent with an exposure at an undetermined

time. In addition, cross reactivity with other flaviviruses (dengue, Zika or West Nile virus can also occur). Infectious Diseases and Medical Microbiology can be consulted in suspect cases.

TREATMENT AND PREVENTION:

There is no vaccine or antivirals for POWV/DTV and treatment is supportive. The best preventative strategy is following recommendations to reduce and prevent tick bites when in areas of risk.

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Appendix A: Tick Identification

The two main ticks that are commonly found on humans in Nova Scotia are the *Dermacentor variabilis* (dog tick) and *Ixodes scapularis* (deer tick, black legged tick). Only *Ixodes* ticks have been found to transmit infection in Nova Scotia. In addition to *B. burgdorferi*, the bacterial agent that causes Lyme disease, blacklegged ticks are also capable of transmitting Powassan virus, *Anaplasma spp.* and *Babesia spp.* The last tick survey, done in 2016, found that 3.6-11.6% of black-legged ticks in Nova Scotia were infected with *Anaplasma phagocytophilum*, with infected ticks localized to the south shore region of Nova Scotia. While the number of cases of HGA have increased over the last year, we have only seen a few sporadic cases of *Babesia* infection and there have been no documented cases of Powassan infection.

Differentiating between *Dermacentor* and Ixodes ticks is important when assessing the need for prophylactic doxycycline after a tick bite. The freely available ***eTick*** is a tick identification platform that is available for identification of tick species within 24 hours at no cost.

The following are a few differentiating characteristics that can help clinicians and the public determine whether the tick they have removed is *Dermacentor* or *Ixodes* tick. Looking at the dorsal side of the tick (its back) the two types of ticks can be differentiated by whether the body has scalloped edges along their posterior end called festoons. As highlighted below (figure 3), *Dermacentor* ticks have a scalloped edge along the periphery of its back (almost like the dimples in a pie crust) whereas the *Ixodes* tick does not have festoons.

On the ventral side (its "stomach") the two can be differentiated by the appearance of its anal groove. *Dermacentor* ticks have an anal groove that extends as a straight line below the anal pore to the edge of their body whereas the *Ixodes* tick has an anal groove that forms an upside down "U" that extends from the edge of the body above and around the anal pore (figure 4).

The degree of engorgement is estimated by how swollen the tick is. If it is perfectly flat, it has not been feeding for long (probably less than 24 hours). A pictorial representation of engorgement that can be seen in adult and nymphal ticks: ***https://web.uri.edu/tickencounter/fieldguide/tick-growth-comparison-charts/***.

Analysis of the blacklegged tick for the presence of infection with *Borrelia burgdorferi*, *Anaplasma phagocytophilum* or *Babesia spp.* does not reliably predict the risk of developing Lyme disease after a bite and is not recommended for management decisions.

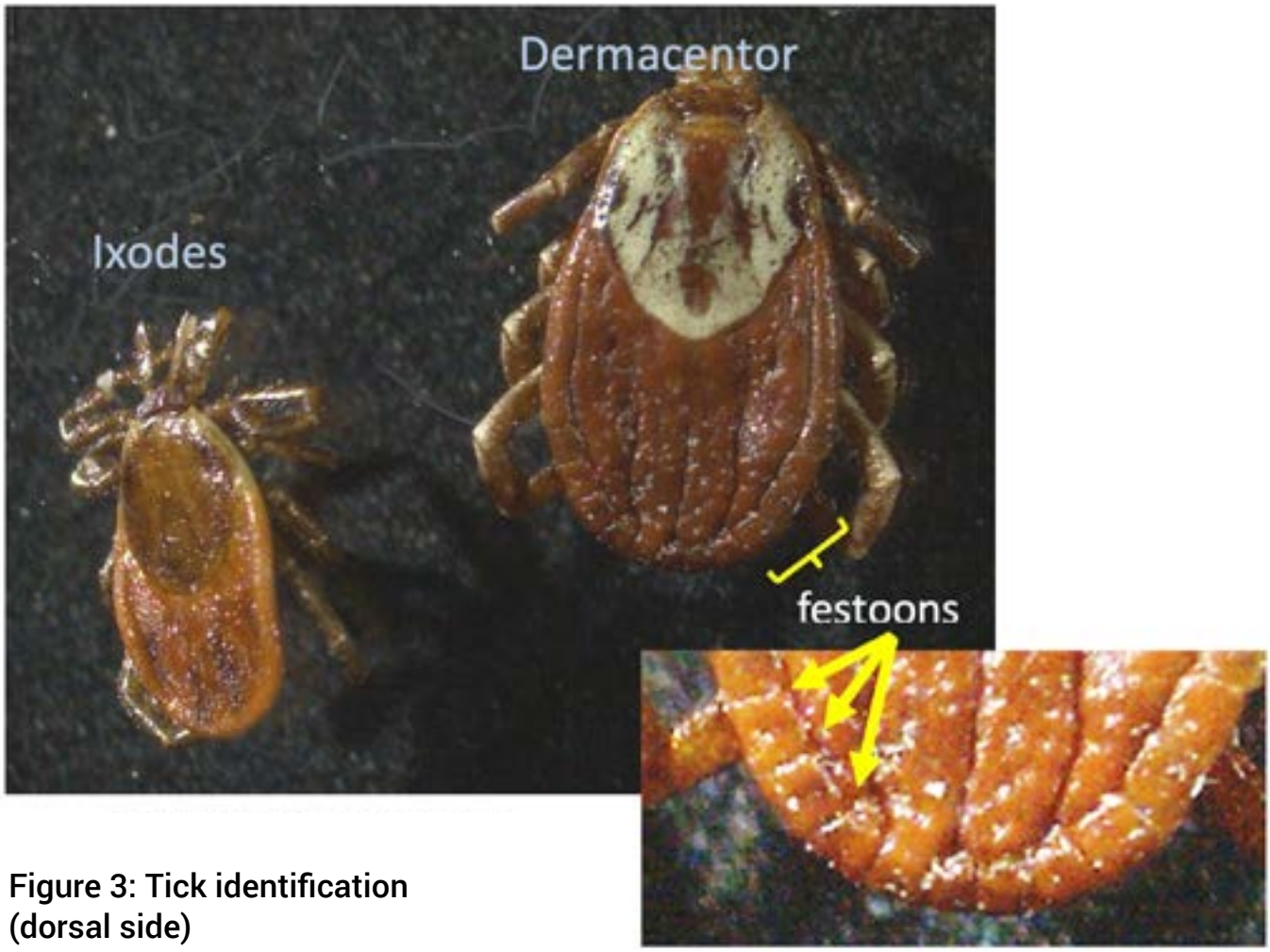

Figure 3: Tick identification (dorsal side)

Source: *NS Microbiology Laboratory*

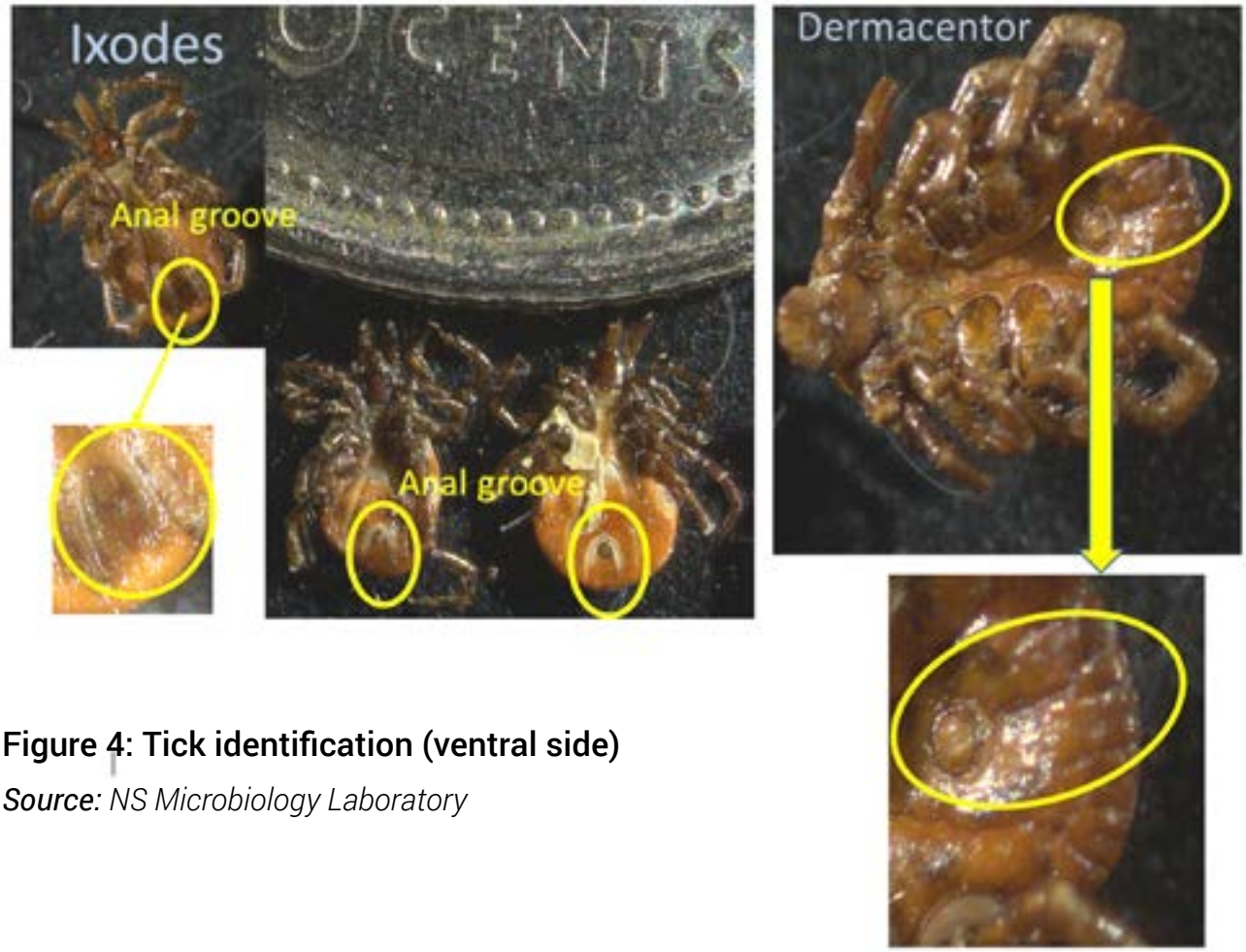

Figure 4: Tick identification (ventral side)

Source: *NS Microbiology Laboratory*