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Association of Medical Microbiology and Infectious Disease Canada
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AMMI Canada Position Statement on the Diagnosis and Treatment of People with Persistent Symptoms That Have Been Attributed to Lyme Disease

Summary:

Individuals with ongoing symptoms that have been attributed to Lyme disease based on alternative serologic criteria or clinical criteria alone experience very real and sometimes debilitating symptoms. They often feel abandoned when physicians cannot provide them with the diagnosis or management plan. However, the cause of these symptoms is often not clear. Symptoms such as body pain, fatigue and difficulty concentrating are not specific for any one cause. AMMI Canada supports evidence guided care for people with persistent symptoms attributed to Lyme disease in a compassionate and comprehensive manner. However, AMMI Canada cannot support recommendations for prescribing prolonged courses of antibiotics for this situation. The data show that prolonged antibiotic therapy does not alter patient outcomes, but can lead to potentially severe adverse reactions, as well as the development of, and infection with, antibiotic-resistant organisms (Klempner et al., 2013; Marzec et al., 2017). AMMI Canada is dedicated to an evidence-based approach to treating people with all types of infections and to assisting their physicians through enhancing education and research.

1. Background

Lyme disease can occur when an infected tick injects an individual with bacteria belonging to the *Borrelia burgdorferi* (*Bb*) *sensu lato* species complex. In most cases, a rash occurs early during infection. However, if this is absent, missed or untreated, the bacterium can spread elsewhere in the body leading to other manifestations such as arthritis, meningitis, neuropathy and carditis. Lyme causing Borrelia are reliably killed with recommended doses of antibiotics. However, some patients with Lyme disease will continue to have symptoms after treatment that can take months to resolve (Wormser et al., 2015; Wills et al., 2016). Although more research is needed, at this time there are no studies in humans that prove the bacteria that causes Lyme disease causes chronic infection upon completion of antibiotic treatments as recommended by the Infectious Disease Society of America, AMMI Canada, the CDC in the US or the National Institute for Health and Care Excellence in the UK. (Feder et al., 2007; Lantos et la., 2014, Lantos, 2015; Oliveira and Shapiro, 2015).

There are individuals with ongoing symptoms attributed to Lyme disease, based on alternative serologic criteria or clinical criteria alone that are suffering with very real and often debilitating symptoms. However, the cause is often not clear, or the symptoms can be attributed to another diagnosis (Lantos et al., 2015; Nelson et al., 2015; Haddad et al., 2018). Symptoms such as body pain, fatigue and difficulty concentrating are non-specific and are commonly found in the general population, after other infectious diseases (Hickie et al., 2006), and with other diagnoses. (Sharpe and Wilks, 2002; Ricci et al., 2007; Patrick et al., 2015; Dahlhamer et al., 2018). Using data from the 2014 Canadian Community Health Survey and the 2012 Canadian Community Health Survey-Mental Health it is estimated that 1.3 million adults in Canada aged 25 or older live with medically unexplained physical symptoms (Park and Gilmour 2017).

AMMI Canada supports compassionate and evidence guided comprehensive care for patients with persistent symptoms that have been attributed to Lyme disease. AMMI Canada believes it is of the utmost importance to identify what treatments improve outcomes with well-designed clinical trials, and that it is always important to support patients who are suffering from prolonged symptoms, regardless of the cause.

2. **Ensuring Best Practice using Published Evidence**

Guidelines for the prevention, diagnosis and treatment of Lyme disease which rigorously reviewed all of the available evidence and have been external peer-reviewed were produced by the Infectious Disease Society of America (IDSA) and are endorsed by AMMI Canada (Wormser et al., 2006). Although published in 2006, the recommendations are similar to those in recently published evidence-based guidelines and position papers produced in Europe in 2018 including:

- UK National Institute for Health and Care Excellence (NICE) –Last updated October 18, 2018
- The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study group for Lyme borreliosis [Dessau et al., 2018]

In 2006, the Attorney General for the State of Connecticut in the United States, launched an investigation into the development process of IDSA's Lyme disease guidelines. There was a concern that the guidelines process was tainted by commercial conflicts of interest and the suppression of scientific evidence. The IDSA and the Connecticut Attorney General's office agreed to retain an independent panel to review all of the IDSA guidelines. This special, independent panel, reported in 2010 that all of the IDSA recommendations were sound, and that there were no conflicts of interest from their contributors (Lantos et al., 2010; https://www.idsociety.org/public-health/lyme-disease/lyme-disease/chronic-lyme-disease-video/). As part of their routine practice, IDSA is in the process of updating these guidelines (in collaboration with multiple other specialty societies including representation from AMMI Canada) using GRADE criteria for quality of evidence.

In the opinion of AMMI Canada, the best approach to health guidelines is always a rigorous scientific review of evidence.

While there are alternate views on the diagnosis and treatment of Lyme disease, not all are supported by the most recent evidence based guidelines published by the UK National Institute for Health and Care Excellence (NICE) in 2018.

3. **Laboratory testing is accurate in late Lyme disease**

Numerous studies have shown that the performance characteristics of serologic testing for Lyme disease depends on the stage of infection (Moore et al., 2016). A systematic review in 2016 shows that the two-tier test currently recommended by the Centres for Disease Control (CDC) and the Canadian Public Health Laboratory Network (EIA followed by immunoblot using CDC interpretive criteria) is insensitive in early localized Lyme disease missing up to 50% of cases. However, testing

performs very well in late Lyme disease where sensitivity approaches 100% (Waddell et al. 2016). Therefore, people with months to years of symptoms who test negative using the CDC interpretive criteria should be investigated for other causes of their symptoms.

Concordant with the NICE guidelines (2018), AMMI Canada recommends that Lyme disease testing be done in accredited laboratories that participate in proficiency programs and use validated methods ("Validation should include published evidence on the test methodology, its relation to Lyme disease and independent reports of performance") (NICE 2018)

Given the high rate of false positive results (some as high as 50%) (Fallon et al, 2014), the use of laboratories that do not use FDA or Health Canada approved tests or use alternative interpretive criteria is not recommended.

AMMI Canada supports ongoing research to develop newer methods and testing strategies that will improve the sensitivity of detecting early infection while maintaining specificity to ensure accuracy. As new data develops, they will be taken into consideration to inform recommendations in the future.

4. **Long Term Antibiotic Treatment Does Not Improve Persistent Symptoms Attributed to Lyme disease**

Well-designed studies have shown that long-term antibiotic treatment – beyond standard recommended treatment – is of no more benefit to the patient than a placebo, but caused significant adverse events in up to 26% of participants including *Clostridioides difficile*, intravenous catheter site infections (when intravenous catheters are used for medication delivery), and significant allergic reactions (Patel et al., 2000; Fallon et al., 2008; Holzbauer et al., 2010;Klempner et al., 2013; De Wilde et al., 2017; Marzec et al., 2017).

Furthermore, focusing care on unproven treatments can result in delays in conducting other investigations, identifying the correct diagnoses, and initiating evidence-based treatment to optimize patient wellbeing (Lantos et al., 2015; Nelson et al., 2015; Haddad et al., 2018).

5. **Providing Comprehensive Care to Patients with Complex Chronic Health Conditions**

Many health care providers provide excellent care for people with complex chronic symptoms. However, some people with persistent symptoms, with or without a defined etiology, may have a difficult time getting adequate care and feel poorly served by the health care system. AMMI Canada does not support the use of prolonged antimicrobials to treat patients with persistent symptoms that have been attributed to Lyme disease. Instead, AMMI Canada strongly encourages evidence guided care of these patients in a compassionate and comprehensive manner to identify the underlying cause and an approach to help alleviate symptoms.

AMMI Canada applauds provinces and health authorities that support clinics modeling comprehensive care for patients with persistent symptoms attributed to Lyme disease, such as the Complex Chronic Diseases Program at BC Women's Hospital. AMMI Canada strongly encourages this approach and encourages other provinces to make these models of care a priority throughout Canada.

6. Conclusion

There is no doubt that individuals with ongoing symptoms that have been attributed to Lyme disease based on alternative serologic criteria or clinical criteria alone, are suffering with very real and often debilitating symptoms. AMMI Canada supports the call for research to better define 1) the epidemiology of persistent symptoms attributed to Lyme disease, 2) the cause of these symptoms, and 3) effective management strategies, through well designed research studies.

In addition, AMMI Canada supports enhancing educational efforts for health care workers and the public on where Lyme disease is present in Canada, its symptoms and signs and how to diagnose and treat *Borrelia* infections that cause Lyme disease.

Endorsement: The Position statement is endorsed by:

- Association des Medecins Microbiologistes Infectiologues du Quebec
- Canadian Association for Clinical Microbiology and Infectious Diseases
- Canadian Neurological Society
- Canadian Paediatric Society
- Public Health Physicians of Canada

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