A RETROSPECTIVE COHORT STUDY OF LYME DISEASE PATIENT OUTCOMES

BY

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A thesis submitted to the
Department of Biology
Mount Allison University
in partial fulfillment of the requirements for the
Bachelor of Science degree with Honours

April 22, 2020

Table of Contents

List of Tables and Figures

Tables:

Figures:

that had symptoms in; A. general, B. digestion, C. heart, D. vision, E. urinary, F. respiratory, G. thyroid, H. skin, I. neurological, J. muscle, joint and bones, K. blood, L. ears, nose and throat, and M. psychiatric symptom categories before and after the start or completion of treatment at the US Lyme disease clinic.

Acknowledgements

I would like to start by stating my sincerest thank you to Dr. Vett Lloyd for guiding me, inspiring me and giving me opportunities far beyond what I could have imagined in these past two years. Working in the Lloyd lab has given me skills that I will be able to take with me preceding my years at Mount Allison University and for that I am forever grateful. Additionally, I would like to extend many thanks to the other members of the Lloyd lab; Andrea, Alexandra, Caitlin, Naaman, Jessica and my sister Emma for offering their support in the lab and an extra special thank you to Kiana and Samantha for selflessly devoting their time to help assist in the data collection portion of this project. I would like to extend my gratitude to Susan Clark of the LoveJoy Health center, for the many hours she devoted to helping with this project. I would also like to thank Michelle and David Pellotte of Albion, Maine for graciously offering their accommodations during data collection.

I would like to extend my thanks to Dr. Diana Hamilton for assisting with the statistical analysis portion of this project. I would also like to thank Dr. Joshua Kurek for his role as my committee member in this project. I would like to take this opportunity to thank my parents Darya and Jeff Rogerson and my brother Joel Rogerson for their help in editing and supporting me throughout the course of this project. Finally, I would like to thank my friends and roommates; fellow B. Sc. Honours student, Jana Arsenault from the Hamilton lab, Sophia Patrick, Hallie MacEachern, Shaina Kennedy, Maddie Phillips, Natalie Rippey, Kiana Crawford and Hannah James, who I was lucky enough to have met during my first year at Mount Allison University and who have offered their endless support throughout the duration of this project.

Abstract

Lyme disease is a vector-borne illness caused by *Borrelia* spp. bacterium and spread primarily through the bite of a tick to humans and other mammalian hosts. Despite being a common disease prevalent in many regions of the world, there remains a considerable amount of uncertainty surrounding many aspects of the disease and consensus on the most appropriate and effective means of treating the illness remains to be achieved. Recommendations published by the Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society (ILADS), which are the primary guidelines followed by health care professionals treating Lyme disease, diverge in many of their key recommendations. Given this lack of consensus, surprisingly little research has been conducted on patient outcomes following different treatment approaches. In this study, patient outcomes from 210 Canadian Lyme disease patients seeking treatment at one US Lyme disease clinic following a treatment regimen conforming to the ILADS treatment guidelines were evaluated. It was found that the 201 of the 210 Lyme disease patients at the clinic responded positively to treatment and a significant ($P<0.05$) decrease in symptoms were observed over time. This study, along with related studies, may help to guide physicians to provide their patients with the most appropriate and effective means of care.

1.0 Introduction

Lyme disease is a zoonotic illness transmitted by ticks infected with pathogenic members of the *Borrelia* genus of spirochaetal phylum bacteria. One species, *Borrelia burgdorferi sensu stricto* (*B. burgdorferi ss*) causes the majority of Lyme disease cases in North America, however other members of the genus are also known to cause Lyme disease (Rudenko et al. 2011). *Ixodes scapularis* is the primary tick vector for *B. burgdorferi* in the midwestern and eastern regions of North America (Sperling and Sperling 2009). In the pacific regions of North America, *B. burgdorferi* is primarily transmitted by its sister species, *Ixodes pacificus* (*I. pacificus*) (Sperling and Sperling 2009). Ticks acquire *B. burgdorferi* by feeding on infected reservoir species such as small mammals (Tilly et al. 2008). In addition to infection through tick bites, some evidence exists for transmission through the placenta, by sexual intercourse and by exposure to the bacteria in the blood, urine or feces of infected organisms (Stricker and Middelveen 2015; Waddell et al. 2018; Aoki and Holland 1989); further research needs to be done to confirm and quantify non-tick vectored modes of infection. Climate change, shifting land use patterns and changes in distribution of reservoir hosts has led to an increase of tick populations in some areas of Canada (Gasmi et al*.* 2017; Rebman 2020). Therefore, Canada is experiencing an increase in number of Lyme disease cases being diagnosed. From 2009 to 2015 a six-fold increase in reported Lyme disease cases was observed (Gasmi et al*.* 2017). Additionally, it has been suggested, that the number of Lyme disease cases in Canada may be even greater than the numbers reported (Lloyd and Hawkins 2018). Evidence suggest Lyme disease is being under-reported in Canada due to failure of serological testing to detect infection and failure of physicians to serologically test patients and report cases (Lloyd and Hawkins 2018).

If treated with antibiotics in the early stages of the illness, progression of the infection is often avoided (Cameron et al. 2014). However, if not treated early, for an appropriate time course or if left untreated, serious multi-system manifestations can develop (Cairns and Godwin 2005). Although antibiotic treatment shortly after infection has proven to be effective in treating Lyme disease, failure has been reported in 10% - 35 % of patients who are unable to obtain early intervention (Johnson et al. 2018). Once the bacterium has entered into the host, it causes an infection in a localized region of the dermis at the site of the tick bite, known as early acute localized Lyme disease (Steere 2004). This stage lasts for several weeks while the bacterium multiples *in situ* (Asbrink and Hovmark 1988) and may be associated with the appearance of the erythema migrans rash (EM rash), otherwise known as the “bulls eye” or “target” rash, which is caused by an immune response to the bacteria (Dammin 1989). However, only 35% - 60% of Lyme disease patients develop the EM rash making diagnosis difficult (Cameron et al. 2014). Other signs of Lyme disease include common non-specific responses to infection such as constant fatigue, fever, aches in the muscles, headaches and nausea (Steere et al. 1986). If the infection is left untreated, the bacteria will continue to multiply and can navigate to new regions of the body through the blood or the lymph. This is the onset of the second stage of Lyme disease, described as early disseminated Lyme disease (Asbrink and Hovmark 1988). At this stage, symptoms previously described in early acute Lyme disease worsen with cardiac and arthritic symptoms starting to arise as the bacteria invades the vascular system and the connective tissues surrounding the joints (Steere 2004). Symptoms attributed to *B. burgdorferi* in the cardiac regions of the body include myocarditis, pericarditis, and atrioventricular heart block (Steere 2004). When the bacterium enters the tissues surrounding the joints in the body it can cause migratory joint pains and synovitis (Steere 2004). If the infection remains untreated for months to years after intial infection, late disseminated Lyme disease develops (Asbrink and Hovmark 1988). In this stage, the bacterium spreads to most organs and tissues of the body, including crossing the blood brain barrier to infect neural tissues, creating various severe multi-system manifestations including neurological symptoms such as migraines, dizziness, sleep disturbances, concentration issues, brain fog, and memory loss (Steere 2004).

To establish an infection in a mammalian host, *Borrelia* needs to evade the immediate host immune response and then establish a long-term infection. The spirochete employs multiple and sophisticated mechanisms to achieve both of these goals including active immune suppression, induction of immune tolerance, antigenic variation favoring evasion of the immune system and concealment of the spirochete in various tissues of the host; additional mechanisms likely remain to be elucidated (Rudenko et al. 2019). When the *Borrelia* spirochete detects the tick feeding, it moves from the midgut of the tick into the tick's salivary glands, where it is injected into the host's dermis as the tick feeds (Sultan et al. 2013, Ramamoorthi et al. 2005). The outer surface protein C (Osp C) of *B. burgdorferi* binds to the tick's salivary proteins (Salp15) causing an antigenic change in the bacterium favouring infection of the mammalian host (Ramamoorthi et al. 2005). Once in the host, the OspC-Salp15 complex can then evade immediate immune response by binding to the CD4 receptor on CD4+T cells inhibiting its activation and mitigating the immediate local immune response (Ramamoorthi et al. 2005; Anguita et al. 2002).

Resistance to the immune response and to antibiotic therapy is dependent on *B. burgdorferi's* adaptive ability (Rudenko et al. 2019). To be able to withstand the environmental and physiological changes associated with moving from an invertebrate (tick) to vertebrate (ie mammal) host, *B. burgdorferi* alters its level of gene expression in response to multiple factors such as temperature, pH, salts and nutrient content (Rudenko et al. 2019). There is evidence that a persistent *B. burgdorferi* infection can exist in a variety of mammalian hosts including, mice, rats, hamsters, guinea pigs, gerbils, dogs, monkeys and baboons (Stricker 2007; Hodzic et al. 2014). Clinical studies also provide evidence of persistent *B. burgdorferi* infection in humans (Priem et al. 1998; Breier et al. 2001; Berglund et al. 2002; Asch et al. 1994). Using various detection methods including microscopy, histopathological and molecular testing, one study found evidence of ongoing spirochetal infection despite antibiotic treatment cultured from body fluids and tissues from a randomly selected group of patients with persistent Lyme disease symptoms (Middelveen et al. 2018). Another study found similar results using immunoelectron microscopy and PCR to detect *Borrelia* in plasmas and cerebrospinal fluid from a group of Lyme disease patients experiencing persistent symptoms 4 to 68 months after antibiotic treatment (Honegr et al. 2004).

The spirochete is able to evade detection by the host's immune system by embedding in the hosts extracellular matrix for reproduction and growth (Rudenko et al. 2019). When hostile environments are encountered, such as the presence of antimicrobials, biphasic killing is observed in which some of the bacterial population is killed while persisting subpopulations with pleomorphic phenotypes arise in the form of looped or ring-shaped bacteria, blebs, round bodies, spirochete colonies or biofilm aggregates (Rudenko et al. 2019). Thus short-term antibiotic therapy risks generating persisting subpopulations of *B. burgdorferi* that have the ability to alternate between active and inactive forms capable of causing a relapse (Rudenko et al. 2019). It has been suggested that different morphs of *B. burgdorferi* may react differently to various types of antibiotics and therefore, antibiotics that are typically used to treat Lyme disease may have different abilities to eliminate the bacterium (Rudenko et al. 2019; Zhang).

Detection of *B. burgdorferi* in humans remains challenging; the diagnosis is a clinical one supported by tick exposure history and laboratory testing. Symptoms can vary depending on the tissue or organ most heavily impacted, by patient genetic and immunological variability, as well as many other factors. This makes formulating a clinical diagnosis criterion for health care providers both challenging and subjective (Moore 2015). Misdiagnoses may be made due to typical features associated with Lyme disease being absent in some cases and the fact that many conditions may produce symptoms attributed to Lyme disease (Moore 2015). Typically, the initial diagnostic approach for health care providers is the appearance of the EM rash, but this sign does not present many Lyme disease patients, and is, additionally, only useful for some of the population (Boltri et al. 2002). Clinical diagnoses are supported by tick exposure history; however, ticks are stealth feeders and tick feeding is often not detected. Diagnosis is also supported by laboratory diagnostics. Indirect diagnostic techniques rely on serological detection of the human immune response to the *Borrelia* bacteria; either antibodies produced in the B cell response or T cell activation (Marques 2015). Antibody testing is by far the most common and the basis of the two-tiered diagnostic method recommended by the Centers for Disease Control and Prevention and currently used by health care professionals in the United States, Canada and in most European countries (Marques 2015). The two-tiered approach consists of detecting antibodies with an intial enzyme linked immunosorbent assay (ELISA) or a fluorescent antibody test (IFA) followed by a western blot test confirming specificity of the antibody response. Serological detection techniques suffer from a number of limitations. Differentiating between active infection and inactive infection using serological methods is not possible (Tylewska-Wierzbanowska and Chmielewski 2002). Further, the commercial western blots, and to a lesser extent, are optimized to detect only one strain of one species of *B. burgdorferi (*Tylewska-Wierzbanowska and Chmielewski 2002). This strain is a lab-adapted strain that may not even exist currently in nature, and is only one species among many pathogenic *Borrelia* species. Additionally, some patients may not mount an immune response to the bacterium throughout the entire course of their illness (Tylewska-Wierzbanowska and Chmielewski 2002). These limitations to both the sensitivity and specificity of these tests provide as much controversy as help to Lyme disease patients (Marques 2015).

Direct diagnostic techniques for Lyme disease include directly detecting the bacteria by bacterial culture, usually in combination with polymerase chain reaction (PCR) for molecular confirmation of the spirochete via DNA sequence analysis (Marques 2015). *B. burgdorferi* spirochetes can be cultured from blood, skin, urine and human vaginal and seminal secretions (Lebech 2002; Middelveen et al. 2015). The direct culture method identifies active infection by viable *B. burgdorferi* spirochetes and can detect more than a single strain of *Borrelia* bacterium as many species of *Borrelia* sp. bacterium can grow in culture (Lebech 2002). While direct, this method is not typically used clinically due to the slow-growing nature of the *B. burgdorferi* spirochetes (Marques 2015). Additionally, it has been observed that sensitivity using a culture method is quite low (Marques 2015). Despite these constraints, a direct culture method remains the gold standard to confirm diagnosis of Lyme disease as this technique overcomes many of the limitations experienced by indirect detection methods (Lebech 2002).

If diagnosed with Lyme disease, health care providers typically prescribe antibiotics. It has been observed that antibiotics are most effective if administered during the early stages of the infection and the efficacy of antibiotics tends to decrease as the dissemination of *B.*

burgdorferi occurs (Steere 1980). Two primary treatment guidelines exist for the management of Lyme disease: guidelines published by the Infectious Disease Society of America (IDSA) and guidelines published by the International Lyme and Associated Disease Society (ILADS). The majority of health care providers in Canada follow guidelines suggested by the IDSA, although a more conservative version of these guidelines is endorsed by the Association of Medical Microbiology and Infectious Disease Canada. A number of recommendations differ between the ILADS and the IDSA published guidelines and therefore, a consensus has yet to be agreed upon by the medical community (Cameron 2009; Cameron et al. 2014). The following table adapted from the Supplementary Appendix I by Cameron et al., highlights the major differences between the IDSA and the ILADS treatment guidelines (Table 1.0) (Cameron et al. 2014).

Table 1.1: Comparison of IDSA and ILADS recommendations for treatment of Lyme disease (Cameron et al. 2014)

	IDSA	ILADS
Ixodes species bite	A single 200 g dose of oral doxycycline if: • Tick was attached for 36 hours. • Tick infection rate is >20% in area bite occurred. • Treatment can begin 72 hours after bite.	Prophylaxis with doxycycline 100-200 mg twice daily for at least 20 days.
EM Rash	• Doxycycline for 10-21 days Or • Amoxicillin or cefuroxime for 14-21 days	A minimum of 4-6 weeks of amoxicillin, cefuroxime, or doxycycline.
Persistent-post treatment symptoms	No antibiotics	4-6 weeks of retreatment with antibiotics selection based on several factors; Reassessment after retreatment and subsequent modifications of antibiotics or discontinuation of treatment

The IDSA defines Lyme disease as an uncommon infection that is contracted only in geographically defined areas of the world. They state that the disease is easily diagnosed and treated at its early stages by accurate laboratory testing measures and short-term use of antibiotics. Additionally, the IDSA states that no valid evidence-based studies exist proving the presence of a persistent *B. burgdorferi* infection and names the illness after this treatment regime, post-treatment Lyme disease syndrome, a condition attributed to an autoimmune response (Wormser et al. 2006). Evidence to support treatment recommendations by the IDSA includes a limited number of randomized clinical trials. One of the major studies was a randomized clinical trial on 482 subjects who had previously been bitten by *I. scapularis* within 72 hours and administered a single 200 mg dose of doxycycline (Nadelman et al. 1997). It was concluded that the efficacy of the treatment was 87% after observing formation of the EM rash after only 6 weeks following the tick bite (Nadelman et al. 1997). Another clinical trial done by Klempner (2002) on a group of patients previously treated for Lyme disease who were still experiencing symptoms, found that after administering ceftriaxone for 30 days followed by doxycycline for 60 days there was no significant difference in improvement between the control and experimental group (Klempner 2002).

The ILADS defines Lyme disease as a common infection that can be contracted in many regions of the world. The ILADS recognizes evidence of the existence of a persistent *B. burgdorferi* infection and therefore, bases its recommendations on literature supporting the hypothesis that a persistent *B. burgdorferi* infection may be causing symptoms of long durations in patients untreated and previously treated for Lyme disease (Cameron et al. 2014). The ILADS argues that no evidence-based literature currently exists to support the hypothesized autoimmune response producing Lyme disease symptoms of long durations following treatment and thus considers the concept of post-treatment Lyme disease syndrome discreditable (Stricker and Johnson 2007). The ILADS supports an open-ended treatment approach for treating those with Lyme disease, which is individualized for each patient. Evidence for the guidelines suggested by the ILADS is also based on a limited number of randomized controlled trials. One of the largest studies to support ILADS guidelines was conducted on 277 Lyme disease patients who were treated with tetracyclines for an average of 4 months. In this study, 33% of patients improved after 2 months of treatment and after 3 months of treatment 61% of patients showed high improvement (Donta 1997). This may suggest that a longer treatment duration may result in increased improvement in these patients (Donta 1997). A study by Cameron (2008) concluded that a significant difference in quality of life was observed after 90 days of amoxicillin was administered to Lyme disease patients experiencing persistent symptoms after initial treatment (Cameron 2008). ILADS notes that limitations for these studies exists and therefore, highlights the need for research to establish effective treatment regimens for treating known tick bites, EM rashes and persistent disease (Cameron et al. 2014).

It has been found that a large number of Canadian Lyme disease patients are dissatisfied with their treatment in Canada and therefore are seeking treatment options internationally, specifically in regions of the United states, where they are able to receive treatment following ILADS treatment guidelines (Boudreau et al. 2018). Despite Lyme disease being the most common tick-vectored disease in the western hemisphere, with the number of cases projected to increase in the future, evidence for the best approach to treating Lyme disease remains sparse. Similarly, the few studies that exist on Lyme disease treatment present conflicting results. Studies on the treatment recommendations for Lyme disease suggested by both the IDSA and the ILADS are limited by variability in enrollment criteria, intervention and outcomes measures. There is a critical need for evidence-based research to guide physician treatment regimens in Canada. The aim of this research is to evaluate the efficacy of a treatment approach involving long-term multiple antimicrobials by examining patient outcomes from one specialized US Lyme disease clinic treating patients following ILADS treatment guidelines. We analyzed data from symptom charts of 210 Canadian Lyme disease patients receiving treatment at this US Lyme disease clinic. Aggregate demographic data and the change in the number and nature of symptoms over time was assessed.

2.0 Materials & Methods

2.1.0 Participants and setting

All subjects in this study were residents of Canada who are currently ongoing or have previously received treatment, between the years of 2008 and August of 2019, at the Lovejoy Health Center, a specialized Lyme disease medical clinic, by Dr. Richard Dubocq. The Lovejoy health centre opened in 1978 and started treating American Lyme disease patients in 2000 and Canadian Lyme disease patients in 2008. Patients included in this study were either referred by a Canadian physician or they were self-referred. All patients in this study were given a clinical diagnosis of chronic Lyme disease with a long-standing duration of symptoms and/or likely tick exposure and/or supportive laboratory diagnostics by the treating physician. Some patients had other diagnoses by healthcare providers in Canada. Some had had treatment for Lyme disease varying from a single dose of doxycycline to several months of oral antibiotics, others had not previously been treated for Lyme disease. Permission for secondary use of anonymous data from patients currently and previously treated for Lyme disease at this clinic was approved by the Mount Allison University Research Ethics Board (Research Ethics Protocol #102622). Information collected included patient's age, gender, symptoms, and health history. All data was collected by the physician's research assistants in the summer of 2019, with no known exclusions.

2.2.0 Study design

Symptom charts (Table. 2.1) consisting of specific symptoms in various categories were completed by each patient at each consultation, which occurred at 3-month intervals. A total of 43 multi-system symptoms of Lyme disease were measured (Table 2.1).

Patients included in this analysis were those who had at least two consultations at the clinic between 2008 and August 2019; those with only one consultation included those who were not given a diagnosis of Lyme disease and/or chose not to pursue treatment at the clinic for, presumably, diverse but undocumented reasons. The multiple consult subset of patients was then further divided into groups based on the number of consultations the patients had at the clinic.

a) *Patients with 1 clinic visit.* This subset of patients had one consultation at the clinic before ceasing their treatment
b) *Patients with 1 clinic visit ongoing treatment.* This subset of patients had one consultation at the clinic within 4 months of the date data collection presuming their treatment at the clinic was ongoing.
c) *Patients with short treatment duration.* This subset of patients had either 2 or 3 consultations at the clinic before ceasing their treatment.
d) *Patients ongoing treatment < 1 year.* This subset of patients had either 2 or 3 consultations at the clinic with their most recent consultation within one year prior to data collection. These patients were at the beginning stages of their treatment at the clinic.
e) *Patients ongoing treatment >1 year.* This subset of patients was at the clinic for more than one year with their most recent consultation at the clinic within one year prior to data collection. These patients were nearing the end stages of their treatment at the clinic.
f) *Patients completed treatment.* These patients were those who had completed treatment at the clinic and therefore, had no consultations at the clinic for at least one year prior to data collection.

In order to determine patient's outcomes at the clinic, response to treatment was determined by change in number of symptoms, totalled and in each category, at initial visit, subsequent and most recent/final visit to the clinic in the patient groups that had more than one consultation at the clinic. Change in number of symptoms at first consultation compared to most recent consultation to the clinic was calculated using the following equation:

= Number of symptoms at most recent visit – Number of symptoms at initial visit

High responders, with the greatest change, were represented by data points less than -10 (Δ > 10 symptoms) , moderate responders were represented by data points ranging from -9 to 0 (Δ 0-9 symptoms), non-responders were represented by data points at zero (Δ 0 symptoms), and patients who were worse after treatment were represented by positive data points (Δ + symptoms).

In order to determine if each body system was differentially affected by treatment, change in number of patients that had each symptom at first visit compared to most recent visit to the clinic was calculated for all patients in the study who had at least two consultations at the clinic. The following equation was to calculate change in number of patients with each symptom:

= Number of patients with symptom at their most recent visit – Number of patients with symptom at their initial visit

Symptoms that had the greatest change in number of patients displaying the symptom after the start or completion of treatment were categorized into a high response group and were represented by data points less than -20 (Δ > 20 patients), symptoms that responded moderately after the start or completion of treatment were represented by data points ranging from -20 to -10 (Δ 10-20 patients), symptoms that slightly responded after the start or completion of treatment were represented by data points ranging from -9 to 0 (Δ 1-9 patients), symptoms that did not respond to treatment were represented by data points at zero (Δ 0 patients) , and symptoms that were worse after start of treatment were represented by positive data points (Δ + patients).

2.2.1 Statistical analysis

In order to determine if symptom number was changing over time, measured in consultations, for each of the patient groups with more than one consultation, a generalized linear mixed model was made using R software (Version 3.6.2, "Dark and Stormy Night"). Generalized linear mixed models work well with unbalanced repeated measures and longitudinal data as it assumes a continuous outcome variable that is related to a set of explanatory variables following a linear trend (Cnaan et al. 1997). This method also allows for lack of independence between observations, as is true for repeated measures studies, making it the optimal approach to analyze trends in multiple observations on a single subject with flexibility (Cnaan et al. 1997). The Poisson distribution is useful to model count data such as the measures used in this study, because it specifies probability for only integer values (Zeileis et al. 2008).

Table 2.1: Symptoms recorded by patients at each consultation to the US Lyme disease clinic.

Category	**Symptoms**	
General wellness	Weight fluctuations Fatigue	Night sweats Chills
Vision	Vision problems	Eye pain
Digestion	Ingestion/Heart burn Nausea/Vomiting	Vomiting blood Blood in stool
Heart/Circulation	Chest pain Palpitations	Ankle swelling
Urinary	Blood in urine Pain when urinating Weak urine flow	Frequently urinating Urinary leaking
Thyroid/Endocrine	Hot flashes Frequent thirst	Hair changes
Skin	Lesions Itching/rash	Color changes
Lungs/Breathing	Shortness of breath Wheezing	Frequent cough
Blood/Lymph	Bruise easily	Difficulty to stop bleeding
Neurological	Weakness in extremities Dizziness	Difficulty with balance Memory loss
Ear, Nose, Throat	Trouble hearing Sinus trouble	Nosebleed
Muscles, Joints, Bones	Joint pain Muscle pain	Back pain
Psychiatric	Panic Attacks Anxious	Depressed Feeling major stress

Results

3.1.0 Participant demographics

The majority of the 210 participants in this study were from Atlantic provinces of Canada with a large portion being from New Brunswick (N=128) and Nova Scotia (N=68). Participants in this study were also from Quebec (N=8), Prince Edward Island (N=3), Ontario (N=2), Newfoundland (N=1), and Manitoba (N=1). Patient's demographic and clinical data included age, sex, presence of comorbidity, history of health and tick exposure history, which are detailed in Table 3.1.

At the time of data collection, August 2019, there were 210 Canadian patients who were currently or had previously received treatment from the US Lyme disease clinic (Figure 3.1). Since the year 2013, there had been a steady increase in number of Canadian patients seeking treatment from the clinic (Figure 3.1).

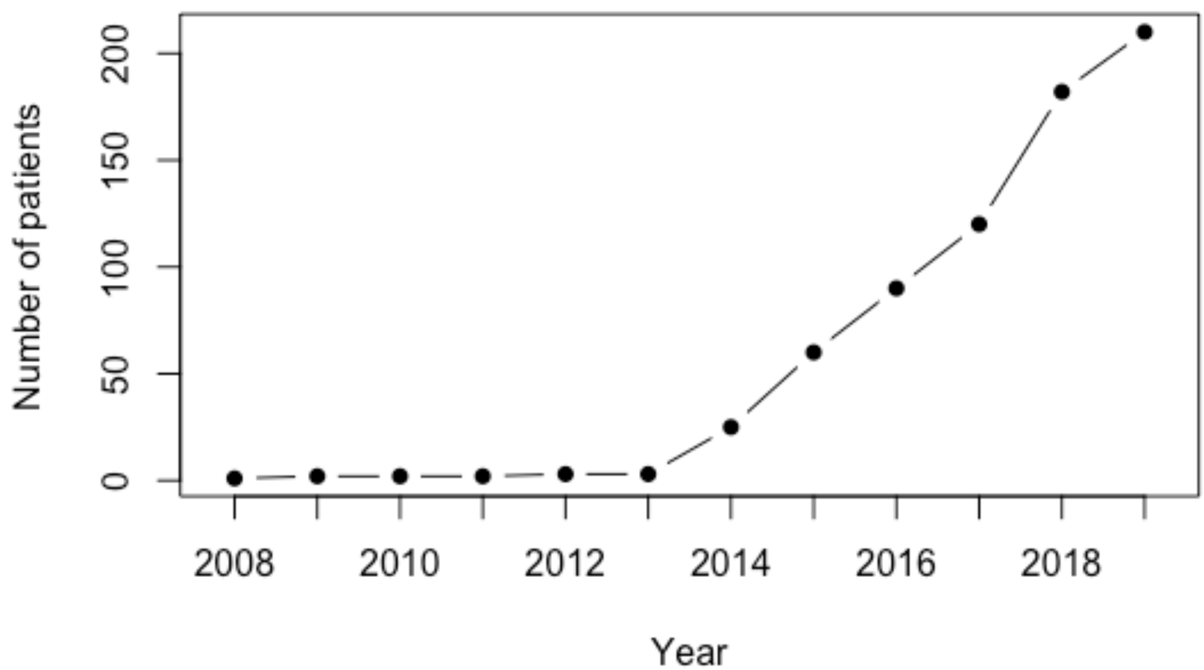


Figure 3.1: Number of Canadian patients at US Lyme disease clinic seeking care at the clinic from 2008 to August 2019.

Patients received care at the clinic for varying lengths of time. At the time of data collection, some patients had completed treatment (31%), most were still undergoing treatment (41%) and some had not pursued treatment past the first or first few consultations (28%) (Figure 3.2). There was a greater number of females (62%) than males (38%) receiving treatment at the clinic (Figure 3.2).

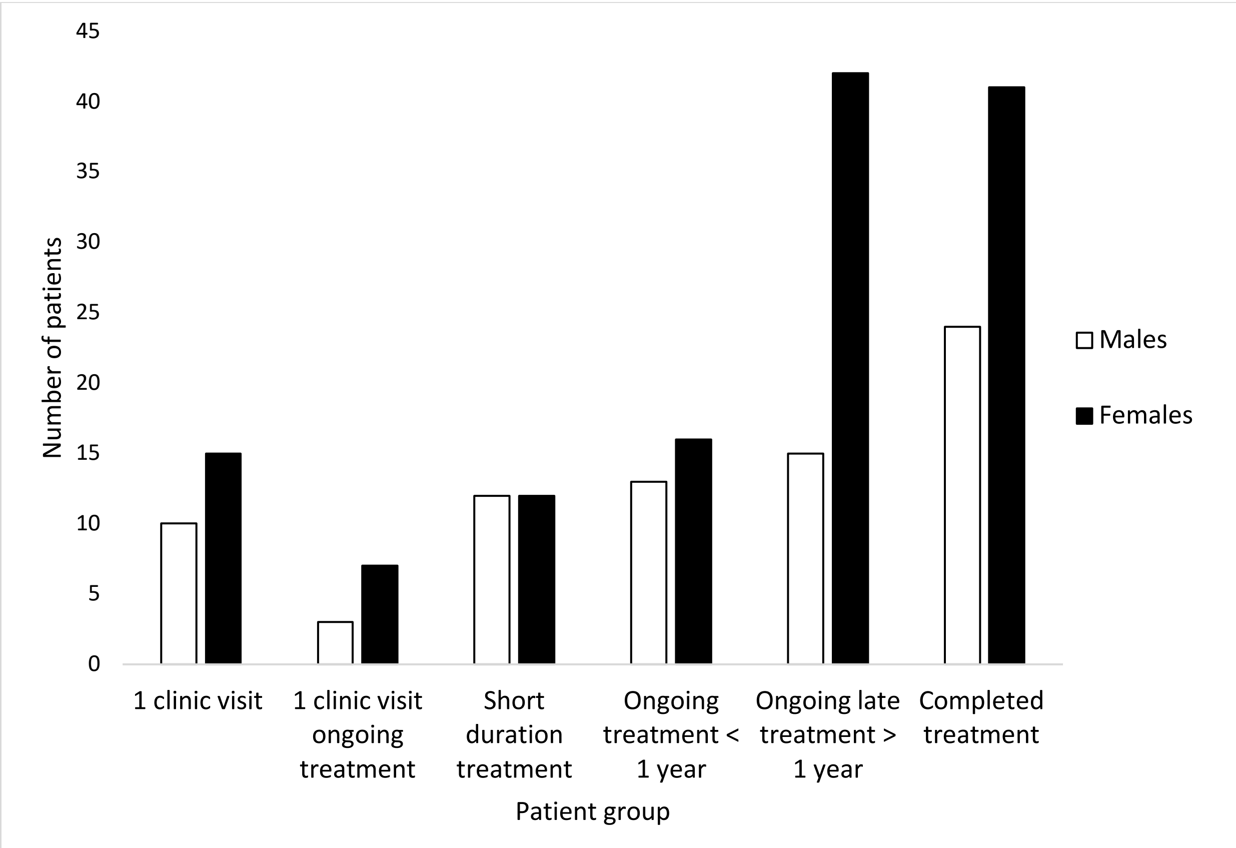


Figure 3.2: Treatment status of Canadian patients at the US Lyme disease clinic from 2008 to August 2019.

Table 3.1: Demographic characteristics of 210 Canadian patients treated at one US Lyme disease clinic.

	Patients	
Variable	No.	%
Age, years		
<60	116	55.2%
>60	94	44.8%
Sex		
Male	86	41.0%
Female	124	59.0%
Presence of comorbidity		
Anemia	40	19.0%
High blood pressure	52	24.8%
Heart murmur	23	11.0%
Asthma	24	11.4%
Diabetes	15	7.14%
IBS	78	37.1%
Yellow jaundice	9	4.29%
Seizures	13	6.19%
Nervous condition	28	13.3%
Gout	9	4.29%
Arthritis	64	30.4%
Migraines	96	45.7%
History of health		
Heart attack	11	5.23%
Stroke	7	3.33%
Pneumonia	47	22.4%
Ulcer	18	8.57%
Hernia	19	9.05%
Cancer	27	12.4%
Blood clot	9	4.29%
Kidney infection	47	22.4%
Kidney stones	42	20.0%
Fractures	63	30.0%
Tick exposure history		
Known tick bite	56	26.7%
EM rash	46	21.9%

3.1.1 Symptoms observed

Number of patients who had each symptom in each body system were totaled to determine the most commonly observed symptoms upon presentation to the clinic. Back pain, dizziness, muscle pain, joint pain and fatigue were the five most commonly observed symptoms (Figure 3.3).

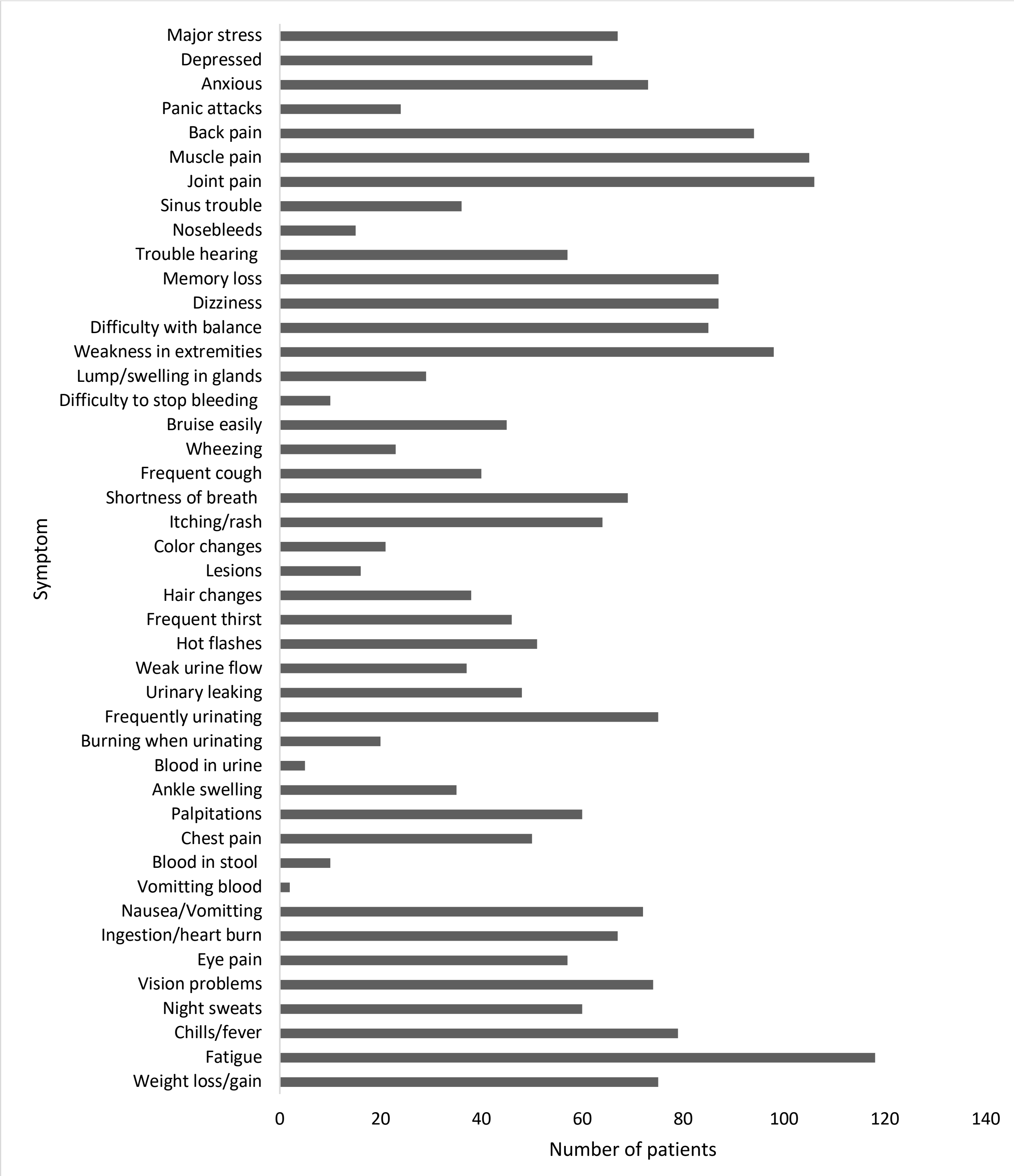


Figure 3.3: Number of patients with each symptom at their initial visit to the US Lyme disease clinic (N=210).

3.2.0 Determination of patient response to treatment

In order to analyze patient's response to treatment, the change in the number of symptoms between the patients' intial visit to the clinic and their last or most recent visit was calculated for each of the four patient groups.

All patients in the short duration treatment group responded to treatment, to a greater or less extent (Figure 3.4, A.), on average to a lesser extent than those treated for longer durations. In the group of patients in ongoing treatment for <1 year at the clinic, the majority of patients were responding positively to treatment at the time of data collection, although 2 patients (1 male and 1 female) (6.9%) responded negatively (Figure 3.4, B.). In the group of patients in the ongoing treatment >1 year group, the majority of patients were responding positively at the time of data collection, although 4 patients (2 males and 2 females) (7%) responded negatively (Figure 3.4, C.). There was 1 patient (female) (1.7%) who had the same number of symptoms as upon initial presentation, although the symptoms were not identical. Among patients who completed long-term treatment at the clinic, the majority of patients responded positively, while 2 patients (females) (6.1%) responded negatively to treatment (Figure 3.4, D.).

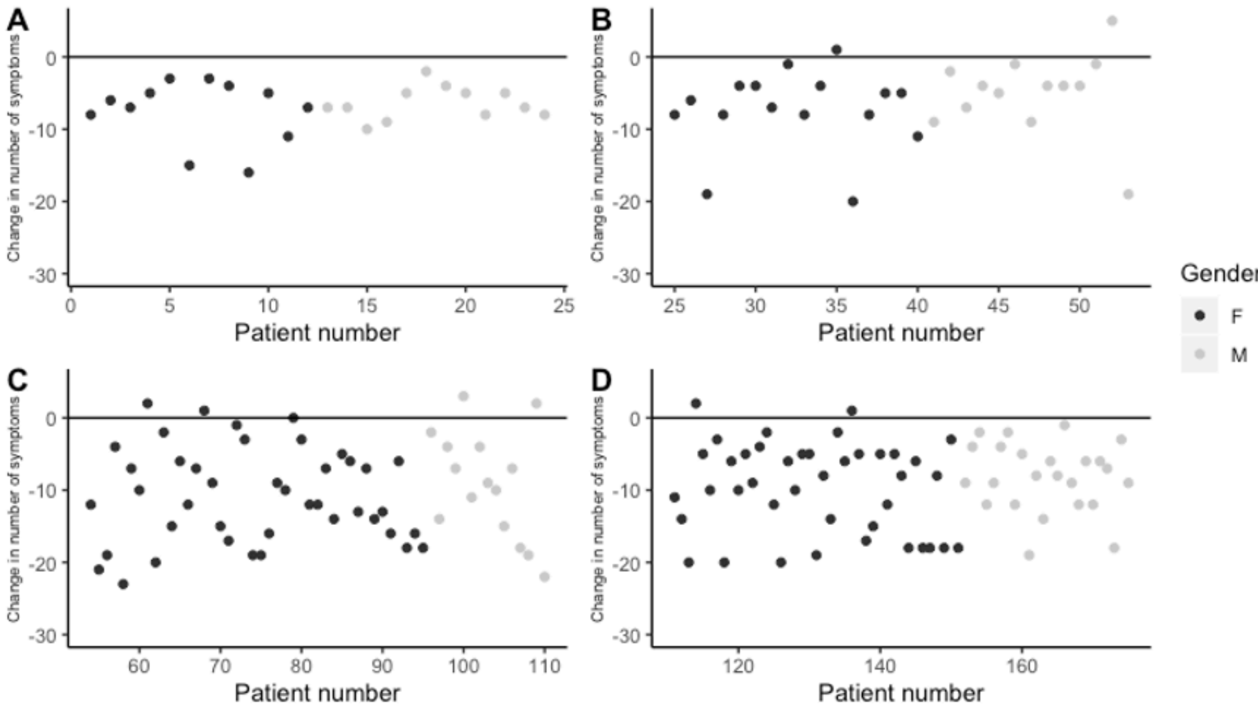


Figure 3.4: Change in number of symptoms reported at initial visit to the clinic compared to most recent recorded visit to the clinic in; A. patients with short duration treatment, B. patients ongoing treatment < 1 year, C. patients ongoing treatment > 1 year, and D. patients who completed treatment at the US Lyme disease clinic.

When comparing the response of patients to treatment in each group, it was found that the majority of patients were high responders (Δ > 10 symptoms) or moderate responders (Δ 1-9 symptoms) in both males and females (Figure 3.5). When comparing the response of patients to treatment between genders it was found that a greater percentage of females were high responders in each patient group (Δ > 10 symptoms) compared to males (Figure 3.5).

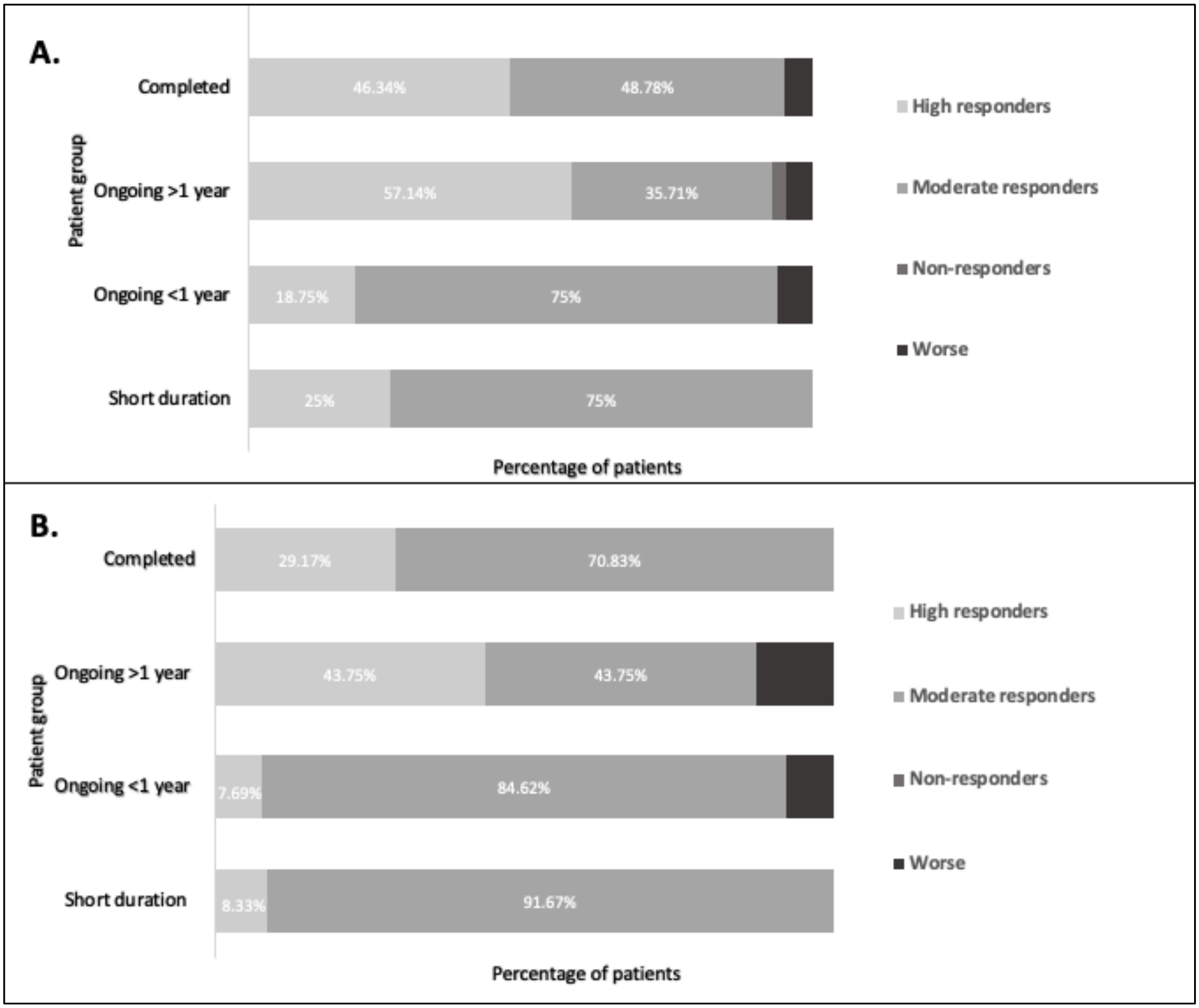


Figure 3.5: Percentage of males (A.) and females (B.) who were high responders (Δ > 10 symptoms), moderate responders (Δ 1- 9 symptoms), non-responders (Δ 0 symptoms) and worse (Δ + symptoms) after the start of treatment in patients with short duration treatment, patients ongoing <1 year of treatment, patients ongoing >1 year of treatment and patients who completed treatment at the US Lyme disease clinic.

3.3.0 Determination of average change in symptom number over time

To assess variation in number of symptoms between visits to the clinic and variation in number of symptoms between genders in each of the four patient groups, a generalized linear mixed model analysis was used. In patients in the short duration treatment group at the US Lyme disease clinic a downward trend in mean number of symptoms was observed in both males and females (Figure 3.6, A.). This difference in the number of symptoms between visits was significant ($P<0.001$) (Figure 3.6, A.). On average, females had a greater number of symptoms at each clinic visit than males in this patient group, however, this difference was not significant ($P=0.28$) (Figure 3.6, A.). Similarly, a continuous downward trend in number of symptoms was observed in both males and females in the patient group ongoing treatment for <1 year at the clinic (Figure 3.6, B.). The difference in mean number of symptoms was significant ($P<0.001$) (Figure 3.6, B.). Females in this patient group, had a greater number of symptoms at visit one and visit two compared to males in this patient group, the difference was not significant ($P=0.23$) (Figure 3. 6, B.).

In patients in the ongoing treatment at the clinic for >1-year group, a continuous downward trend in number of symptoms was observed in both males and females over visits to the clinic, which was also determined to be significant ($P<0.001$) (Figure 3.6, C.). A continuous downward trend in mean number of symptoms was observed in both males and females over visits to the clinic in patients who completed treatment (Figure 3.6, D.). Differences in mean number of symptoms at each visit was determined to be significant ($P<0.001$) (Figure 3.6, D.) Females in this patient group had a greater number of symptoms in the majority of visits compared to males, however, differences were not significant ($P=0.11$) (Figure 3.6, D.).

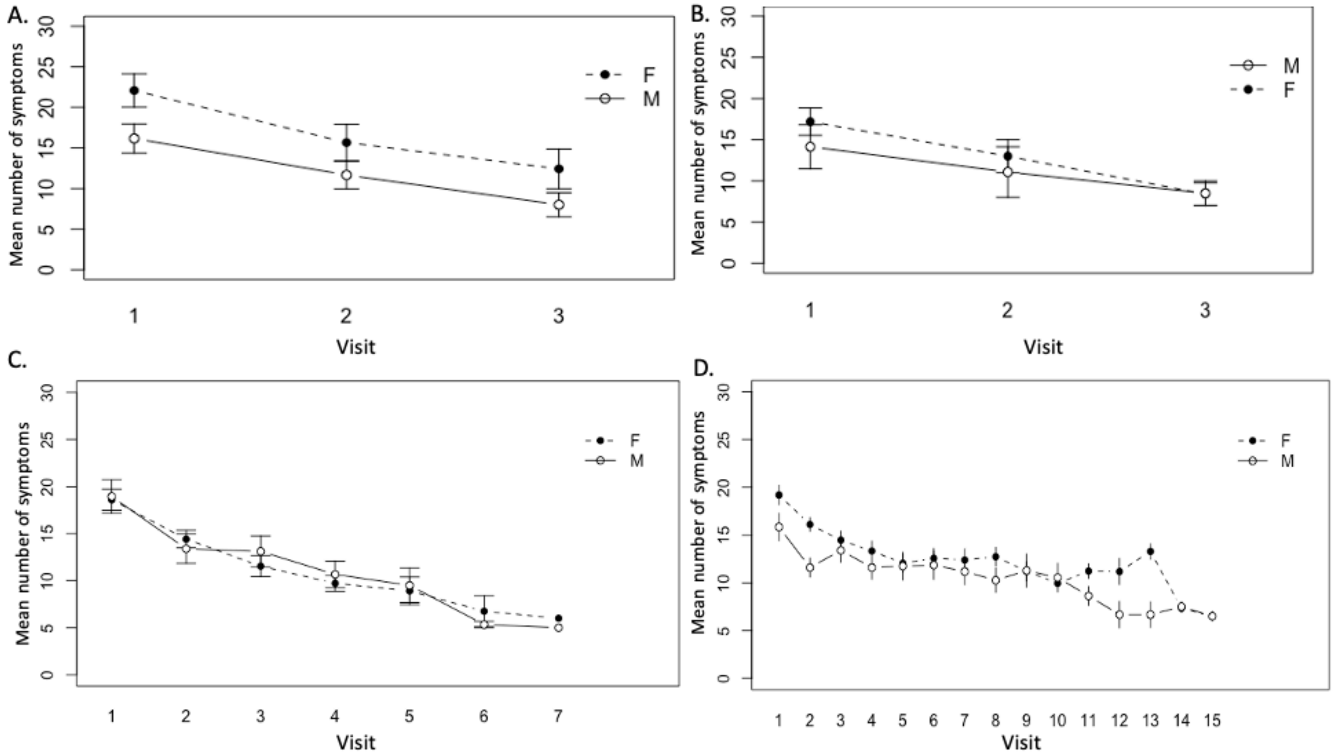


Figure 3.6: Mean number of symptoms over visits to the US Lyme disease clinic in; A. patients with short duration treatment (F=12, M=12), B. patients ongoing treatment <1 year (F=16, M=13), C. patients ongoing treatment >1 year (F=42, M=15), and D. patients who completed treatment (F=41, M=24) at the US Lyme disease clinic.

3. 4. 0 Effect of treatment on specific symptoms

In order to determine if 43 total symptoms from 13 body systems were differentially affected by treatment, change in number of patients (N=175) who had each symptom before and after the start or completion of treatment was calculated. Out of 43 symptoms, 26 symptoms responded highly to treatment (Δ > 20 patients), 9 symptoms responded moderately to treatment (Δ 10-20 patients), 8 symptoms slightly responded to treatment (Δ 1-9 patients), no symptoms failed to respond to treatment (Δ 0 patients), and 1 symptom got worse after the start or completion of treatment (Δ + patients) (Figure 3.7).

The five most commonly observed symptoms were highly responsive (Δ > 20 patients) to treatment at the clinic (Figure 3.9).

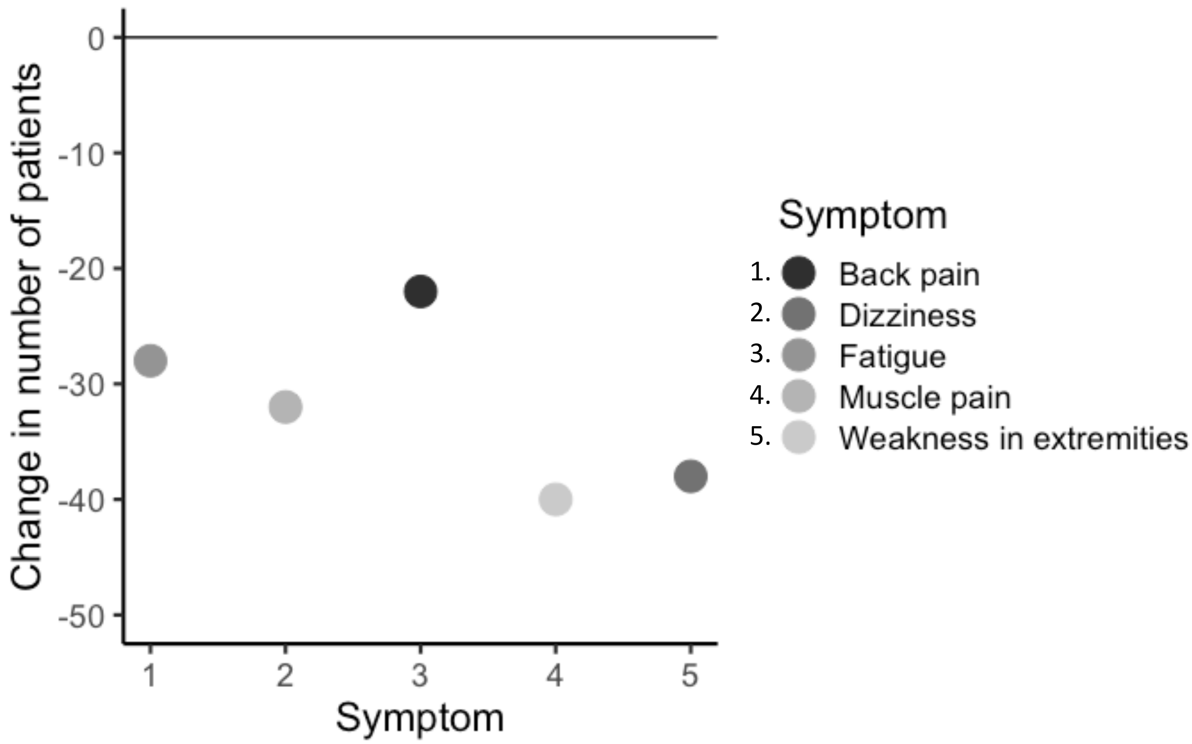


Figure 3.7: Change in number of patients (N=175) within all patient groups, that had the most commonly observed symptoms before and after the start or completion of treatment at the US Lyme disease clinic.

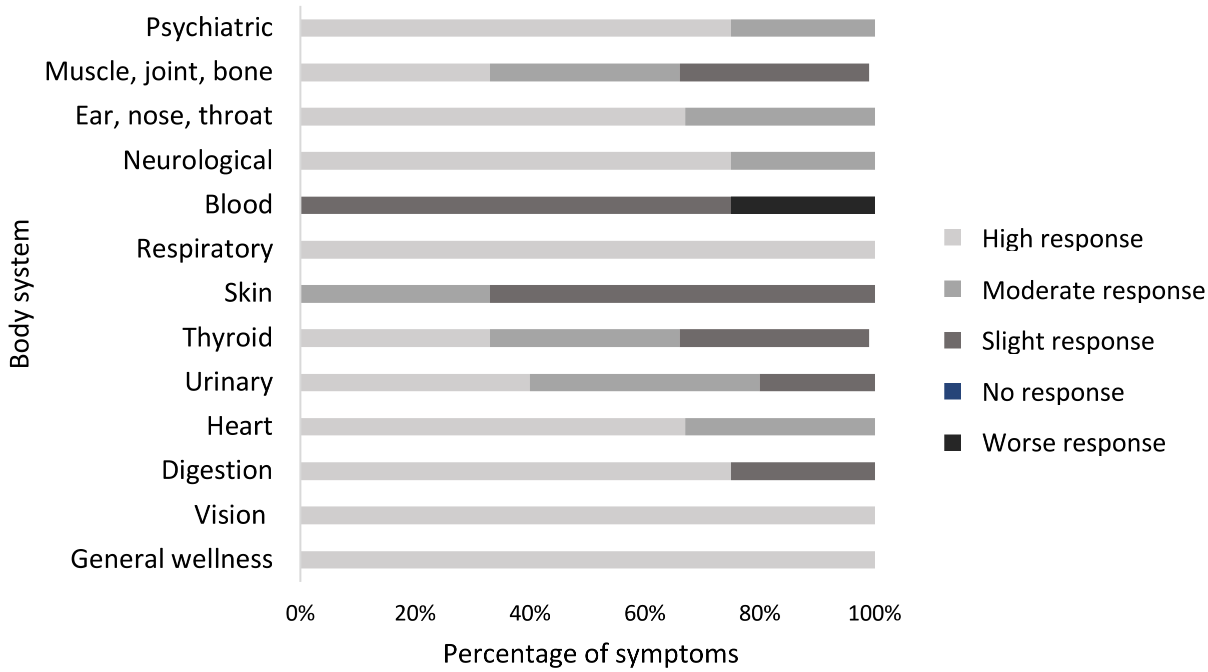
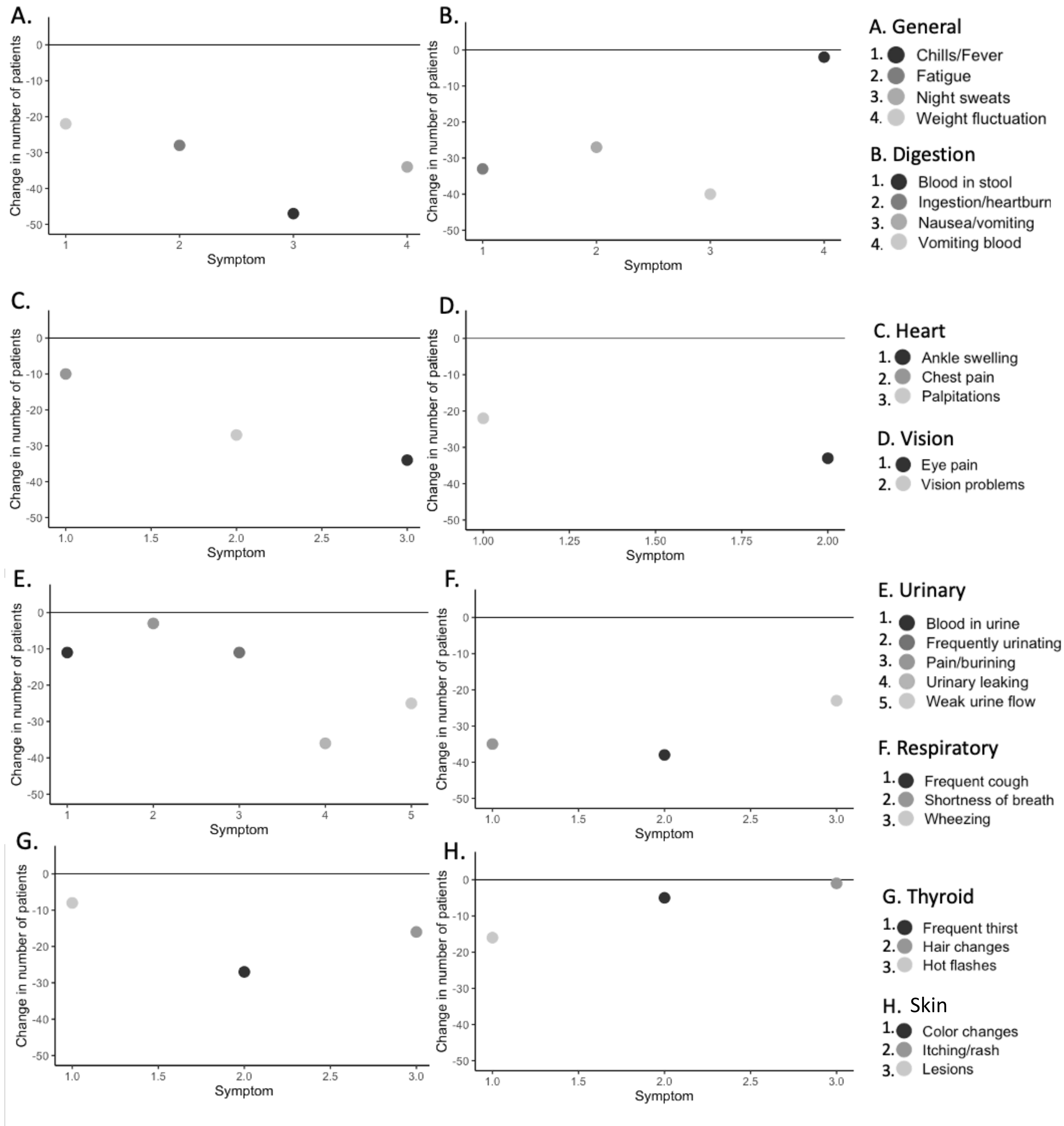


Figure 3.8: Percentage of symptoms in each body system that responded highly (Δ > 20 patients), moderately (Δ 10-20 patients), slightly (Δ 1-9 patients), no response (Δ 0 patients), or a worse (Δ + patients) response in patients before and after the start or completion of treatment in patients with two or more consultations (N=175) at the US Lyme disease clinic.

In the symptom category of "general wellness", all symptoms were observed to be highly responsive to treatment at the clinic (Δ > 20 patients) (Figure 3.8, A.). The majority of symptoms in the "digestion" symptom category were observed be highly responsive to treatment (Δ > 20 patients), while one symptom was observed to only respond slightly to treatment (Δ 1-9 patients) (Figure 3.8, B.) Symptoms in the "heart" symptom category, were observed to be highly or moderately responsive to treatment (Δ > 20 patients or Δ 10- 20 patients) (Figure 3.8 C.). All symptoms in the symptom category "vision" were observed to be highly responsive to treatment (Δ > 20 patients) (Figure 3.8, D.). In the "urinary" symptom category, the majority of symptoms were observed to be highly or moderately responsive to treatment (Δ > 20 patients or Δ 10- 20 patients), while one symptom was observed to only slightly respond to treatment (Δ 1- 9 patients) (Figure 3.8, E.). All symptoms in the "respiratory" symptom category were highly responsive to treatment (Δ > 20 patients) (Figure 3.8, F.). Similarly, all symptoms in the "thyroid" symptom category were observed to either highly respond or moderately respond to treatment (Δ > 20 patients or Δ 10- 20 patients) at the clinic (Figure 3.8, G.). In the “skin” symptoms category, one symptom was highly responsive to treatment (Δ > 20 patients) while the others only slightly responded (Δ 1- 9 patients) (Figure 3.8, H.). In the “neurological” symptom category, symptoms were either highly responsive (Δ > 20 patients) to treatment or moderately responsive (Δ 10- 20 patients) (Figure 3.8, I.). In the “muscle, joint and bone” category, the majority of symptoms were highly responsive (Δ > 20 patients) to treatment, while one symptom was only slightly responsive (Δ 1- 9 patients) (Figure 3.8, J.). In the “blood” symptom category, some symptoms were moderately or slightly responsive to treatment (Δ 10- 20 patients or Δ 1- 9 patients), while one symptom was observed to get worse (Δ + patients) (Figure 3.8, K.). In the “nose, ears and throat” symptom category all symptoms were moderately responsive to treatment (Figure 3.8, L.). In the “psychiatric” symptom category, symptoms were either highly or moderately responsive to treatment (Δ > 20 patients or Δ 10- 20 patients) (Figure 3.8, M.).


A.
B.
C.
D.
E.
F.
G.
H.
Change in number of patients
Symptom
A. General
1. Chills/Fever
2. Fatigue
3. Night sweats
4. Weight fluctuation
B. Digestion
1. Blood in stool
2. Ingestion/heartburn
3. Nausea/vomiting
4. Vomiting blood
C. Heart
1. Ankle swelling
2. Chest pain
3. Palpitations
D. Vision
1. Eye pain
2. Vision problems
E. Urinary
1. Blood in urine
2. Frequently urinating
3. Pain/burining
4. Urinary leaking
5. Weak urine flow
F. Respiratory
1. Frequent cough
2. Shortness of breath
3. Wheezing
G. Thyroid
1. Frequent thirst
2. Hair changes
3. Hot flashes
H. Skin
1. Color changes
2. Itching/rash
3. Lesions

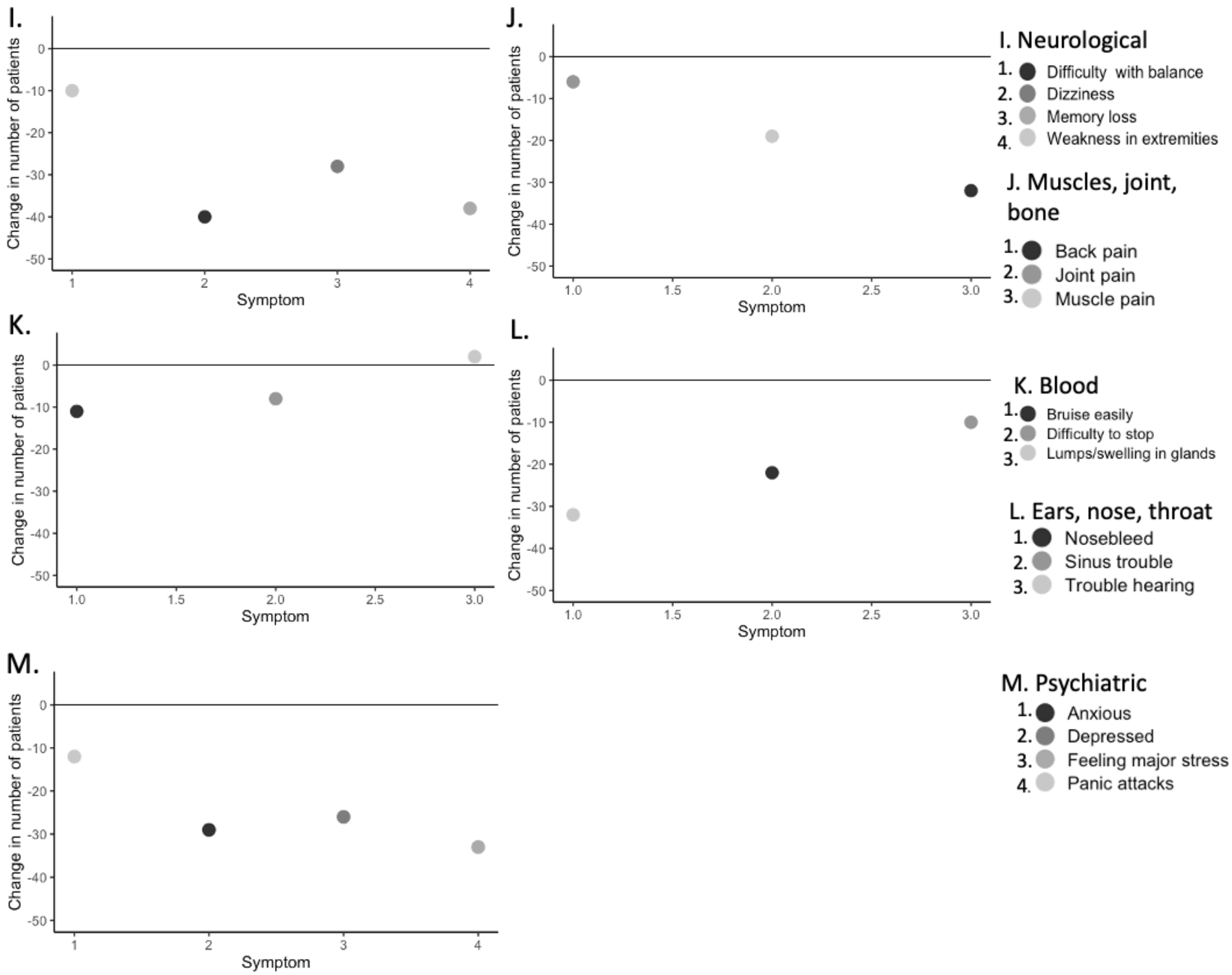


Figure 3.9: Change in number of patients (N=175) within all patient groups, that had symptoms in; A. general, B. digestion, C. heart, D. vision, E. urinary, F. respiratory, G. thyroid, H. skin, I. neurological, J. muscle, joint and bones, K. blood, L. ears, nose and throat, and M. psychiatric symptom categories before and after the start or completion of treatment at the US Lyme disease clinic.

4.0 Discussion

This study focused on determining the responses of Lyme disease patients with a clinical diagnosis of chronic Lyme disease to a treatment regimen based on ILADS treatment guidelines. Patients included in this study either had not been treated for tick-vectored diseases or antibiotic treatment of short duration had taken place but wellness had not been restored to the patient's satisfaction. As an alternative to treatment regimens offered in Canada, which are generally based on the IDSA treatment guidelines, some Canadian patients seek treatment regimens based on ILADS treatment guidelines, which are more readily available in the United States than in Canada (Beaudreau et al.). In this study, patient outcomes for 210 Canadian patients seeking treatment at a single specialized Lyme disease medical clinic in the United States that offers treatment following the ILADS treatment guidelines, from 2008 to August 2019, were evaluated. Patient outcomes were determined by compiling the number and type of symptoms reported by each patient at each visit to the clinic. It was found that 201 of 210 patients in this study responded positively to treatment with significant decreases in number symptoms over time.

4.1.0 Patients overall response to treatment

After calculating the change in number of symptoms patients had at their initial and most recent visit to the clinic, the majority of patients were found to respond positively to treatment and symptoms significantly decreased through time. There was a significant decrease in number of symptoms over visits to the clinic in each of the patient groups with more than one consultation. In each of the patient groups, the average number of symptoms decreased to approximately 5 symptoms at last or most recent visit to the clinic; no patients reported zero symptoms at completion of treatment. Additionally, in this study there were 4.3% of patients, 5 females and 3 males, who got worse after the start of treatment. This might be attributed to variability in the progression of the illness, treatment side effects, pre-existing comorbidities or new conditions.

As this was a retrospective patient outcome study, there was no control patient population that was untreated so it is not formally possible to distinguish the possibility that treatment was responsible for the reduction in symptoms as opposed to symptoms resolving over time. Although relatively few studies monitor disease progression in known but untreated Lyme disease patients, one study, looking at 13 untreated Lyme disease patients with persistent symptoms for greater than 12 weeks, found that patients continued to have symptoms with no relief for a period of 3 months to 5 years after initial onset of symptoms (Aucott et al. 2012). In another study looking at 55 untreated Lyme disease patients with persistent symptoms for an average of 6 years, it was found that 80% of the patients in this cohort, experienced continual symptoms over time (Steere 1987). These findings support the widely accepted observation that, if left untreated, Lyme disease will continue to cause multisystem manifestations in patients that will not be resolved without intervention.

In patients with short duration treatment and patients who were ongoing treatment at the clinic for <1 year, the majority of these patients moderately responded (Δ 1- 9 symptoms) to treatment, while a smaller percentage of patients in this group were high responders (Δ > 10 symptoms). When comparing these results to the patient group who had been undergoing treatment for >1 year at the clinic and the patient group that completed treatment, it was found that a greater percentage of patients in these groups were high responders (Δ > 10 symptoms). It is difficult, however, to make general comparisons between the groups due to differences in number of patients between the groups (Short duration treatment group, N= 24; ongoing treatment <1 year group, N= 29; ongoing treatment >1 year group, N= 57; completed treatment group, N=65). Further, patients will have had a different number and type of symptoms at their initial visit to the clinic, which would necessarily affect or alter the number of symptoms that could change over time and treatment. However, with these caveats, the results presented here indicate that longer treatment durations with the protocol used at this clinic may have better symptom outcomes compared to shorter treatment durations.

When comparing the results of this study to previous studies that used similar treatment regimens, comparable results were observed. A study conducted in 1997 on 277 Lyme disease patients using long-term tetracycline therapy found a larger percentage of patients whose conditions improved after longer durations of the treatment compared at their state at earlier on in the treatment (Donta 1997). Similarly, a study comparing results from a group of 30 Lyme disease patients treated with antibiotics for 14 days and a group of 30 Lyme disease patients treated with antibiotics for 100 days, found that a greater percentage of patients showed good or excellent treatment response in the group of patients treated for 100 days with a low rate of clinical relapse compared to the group of patients treated for 14 days (Oksi et al. 1998).

4.2.0 Gender-based differences in presentation and recovery

In this study, there were more females than males seeking treatment. On average, females in these two groups had a greater mean number of symptoms at each visit to the clinic although, the difference between genders was not significant. The Public Health Agency of Canada (PHAC) and other public health agencies report a greater percentage of males with Lyme disease than females (Gasmi et al. 2017). It has been found, however, that males are more likely to present with positive Lyme disease test results compared to females (Lee-Lewandrowski et al. 2019), which might lead to under-detection of Lyme disease in females, leading to earlier and more successful treatment. There is also extensive literature that indicates that females are more likely to seek healthcare than males (Bertakis et al. 2000; Verhaak et al. 2005; Thompson et al. 2016). Jarefors (2006) found that females with Lyme disease had significantly higher spontaneous secretions of cytokines compared to males, which is indicative of a greater inflammatory response and potentially inflammation-related symptoms. An intensified inflammatory response to *B. burgdorferi* may also influence the female response to treatment. The gender-based differences in the patient population presenting with chronic Lyme disease is deserving of wider and further study.

Females were not only presenting at the clinic in greater numbers than males, it was also observed that females appeared to respond better to treatment. A greater percentage of females were high responders compared to males in each patient group of this study, with the caveat that males were under-represented in this study and the sample size for both genders is relatively low. This finding differed from previous studies, where females were found to be less likely to respond positively to long-term treatment compared to males (Donta 1997). Not withstanding this difference, males and females were approximately equally represented in the group of patients with short duration treatment and in the group of patients with ongoing treatment <1 year at the clinic. In the patients who had completed treatment at the clinic, similar results were observed compared to patients ongoing treatment >1 year at the clinic. Further, trends in number of symptoms over visits at the clinic were similar in in both males and females.

4.3.0 Response to treatment at the body systems level

The most commonly observed symptoms of the patients in this study included back pain, dizziness, fatigue, muscle pain and weakness in the extremities. This finding corresponds with those in other studies; fatigue, joint pain, difficulty in focusing, muscle pain and memory were rated among the most severe in a cohort of Lyme disease patients (Rebmen 2020). After calculating the change in number of patients with each symptom before and after treatment, it was found that the majority of symptoms improved in most of the symptom categories, including among the most commonly observed symptoms. One exception to the overall general improvement was in the In the "blood" symptom category, the symptoms "lumps and swelling", which was reported by a greater number of patients during or at completion of treatment compared to the initial visit. Lumps and swelling may be an adverse effect to the treatment regimen or this may be a result of the natural progression of the illness. It has been found that *B. burgdorferi* may accumulate in the lymph nodes as an evasion strategy when confronted with hostile environments such as antibiotic pressures inside the host (Tunev et al. 2011). Accumulation in the lymph nodes may cause swelling and lumps, therefore this symptom may be attributed to the use of antibiotics. In all cases, it is important to note that these are averages and don't represent the experiences of every patient or their state of wellness at all times, merely those at the time they reported the symptoms.

To extend this study, it would be valuable to obtain the perspective and experiences of patients with their treatment at this Lyme disease clinic and other healthcare providers. Additionally, in order to assess both the accuracy of diagnosis and the efficacy of the treatment regimen, culture of *Borrelia* could be attempted from a subset of Lyme disease patients at the clinic from each of the patient groups. It would also be valuable to follow the patients at this clinic over a number of years following treatment completion to assess the stability and completion of their recovery.

4.4.0 Limitations of the study

In this study, as in most treatment outcome studies, the patient population is diverse. Lyme disease affects all ages and genders (Johnson et al. 2018) and retrospective cohort studies are additionally limited in the level of control the researchers have over variables that are measured (Sedgwick 2014). Heterogeneity can exist in severity of the disease among different individuals, which may impact both the patient's relative adherence and responses to treatment. Similarly, patients' background, prior healthcare and comorbidities will affect their health. Further, patients may have different levels of vulnerability to adverse side effects from the treatment. Finally, In Lyme disease, delays in diagnosis would also have a significant impact on disease severity and response to treatment (Johnson et al. 2018). To, marginally, counter this heterogeneity, this study was conducted on patients seeking treatment from only one US Lyme disease clinic and patients were treated by only one physician at the clinic, nevertheless, patient treatment varied by patient so this also introduces variability in response. Additionally, all data used in this study was primarily patient reported and there is a level of subjectivity that should be considered that would be expected to add to variability. The influence of these factors, in particular in whether the results of this study can be extended to other Lyme disease patients undergoing similar treatment regimens elsewhere, is an important area requiring further study.

4.5.0 Conclusions and significance of the research project

Ongoing disputes within the medical community concerning most aspects of Lyme disease have resulted in fewer studies on this illness in comparison to other infectious diseases, despite Lyme disease being an illness commonly observed in many regions of the world, (Johnson et al. 2018). The findings presented in this study show that treatment at this Lyme disease clinic in the USA was effective in relieving symptoms in Canadian patients. More research is needed on patient responses to treatment following both of the treatment guidelines developed to help best guide physician's treatment regimens. This study provides insight into the response of a cohort of Lyme disease patients treated following ILADS treatment guidelines as practiced by one physician. In the future, this and related studies may help to guide physicians to providing the most effective care for their patients. The lack of this information has resulted in uncertainty for both patients and those treating them (Rebmen 2020), a situation that needs to be resolved as the number of infections increase.

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