5-2019

Treatment Options for Post Treatment Lyme Disease Syndrome

Barbara Bowman
University of North Dakota, barbara.bowman@und.edu

Treatment Options for Post Treatment Lyme Disease Syndrome

By

Barbara Bowman, PA-S

Bachelor of Science, College of St. Scholastica

1997

Contributing authors:

Russ Kauffman, MPAS, PA-C, Riann Collar, PA-S

Scholarly Project

Submitted to the Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Masters in Physician Assistant Studies

Grand Forks, North Dakota

May

2019

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

I would like to thank the UND PA staff and faculty for the continued support and dedication to the education of the PA students throughout the two-year program. I would like to thank my advisor, Professor Russ Kauffman, for his insight and direction throughout my PA education. I would like to thank all my preceptors who have helped guide my education and have provided good opportunities for hands on experience throughout my education. I would also like to thank Riann Collar (PA-S), Robert Frenchick (stats professor), and Sara Shuster (PharmD) for their input and guidance into my final scholarly project. Lastly, I would like to give a sincere thank you especially to my husband but also my family and friends for their support, patience, and encouragement through this challenging and rewarding endeavor.

ABSTRACT

With the high incidence of Lyme disease in the endemic areas of North America, it is important to appropriately diagnosis and treat this condition to prevent post treatment Lyme disease syndrome (PTLDS). Background information regarding Lyme disease is given. The purpose of this paper is to discuss the treatment options available for those patients that fit the case definition of PTLDS. A literature review was conducted using several different electronic databases finding peer reviewed research articles pertaining to the treatment options available for PTLDS. Extended antibiotic use is shown to be not beneficial in most cases. Alternative treatment options listed on the internet are shown to be not evidence based. Therefore, symptomatic treatment options seem to be the best positive outcome-based option available for providers to use. These options are discussed in detail throughout this paper. Though much more research is needed regarding the topic, this paper will give providers the information currently available that they will need to know when treating patients with PTLDS. Hopefully this will provide the patients with PTLDS the best outcome possible for improving their quality of life post Lyme disease.

Keywords: Lyme disease, PTLDS, chronic Lyme disease, chronic fatigue syndrome, and treatment outcomes

INTRODUCTION

Lyme disease is the most common vector borne illness in the USA, with over 300,000 new cases being reported every year (Rebman et al., 2017). Illness is caused by Borrelia burgdorferi (Bb) passed to humans by the Ixodes genus of the black legged deer tick. Lyme disease is endemic in the United States with most disease being acquired in the Northeast and upper Midwest states but can also be found along the Pacific coast. In these endemic areas it is important for family practice providers to educate their patients regarding prevention. This would include avoidance of exposure to ticks by using insect repellent and appropriate coverage of clothing. It would also include daily inspection of themselves, children, and pets when in areas of high prevalence such as the woods, brush, or tall grass. With a weak recommendation by DynaMed Plus, Lyme disease (2018), prophylactic antibiotic treatment of a single 200 mg oral dose of doxycycline can be given within 72 hours of tick removal if the Ixodes species tick is identified and was adherent for at least 36 hours.

According to DynaMed Plus, Lyme Disease (2018), when infected with Lyme disease, different clinical presentations exist including erythema migrans (EM), a localized skin reaction, which is the most common manifestation of Lyme disease and is alone diagnostic where no further testing is needed. Early disseminated disease may also present as carditis, typically atrioventricular conduction disturbances, or neuritis, such as cranial nerve palsy or meningitis. Late Lyme disease may present as arthritis involving a large joint or chronic neurologic disease such as peripheral neuropathy or encephalopathy.

In patients with symptoms other than EM, 2-tiered serologic testing can be performed by the laboratory, but this testing is not without complications of its own. Serologic testing has evolved over the years, improving sensitivity of the enzyme-linked immunosorbent assays (ELISA) as the way to screen for Lyme disease but it has been found that as many as 50% of patients will test seronegative in the early course of the illness (Halperin, 2015). Western blot should not be ordered on patients who are seronegative. Western blot provides specificity if the screening test comes back positive but can be difficult to interpret. Patients with disease of more than 1-month or 2-month duration should be IgG seropositive, so IgG blots provide the most reliable information (Halperin, 2015). According to DynaMed Plus, Lyme disease (2018), do not retest patients who report persistent symptoms to determine if antibody titers have increased or decreased because seroreactivity does not correlate with ongoing symptoms. Increased titers often persist in most patients for at least months after treatment of early infection, and for years after treatment of late infection. Rebman, Crowder, Kirkpatrick, and Aucott (2015) conducted a prospective cohort study which highlighted and supported the difficulty in relying on serologic testing to confirm prior exposure not only in early disease but also in identification of later cases of antibiotic-refractory symptoms of post-treatment Lyme disease syndrome (PTLDS).

Guidelines have been set up for the initial treatment regimen of Lyme disease with strong recommendation by DynaMed Plus, Lyme disease (2018). Doxycycline is the antibiotic of choice for EM, Lyme arthritis, and cranial nerve palsy. Hospitalization and IV ceftriaxone are often required for Lyme carditis and neurologic Lyme disease other than cranial nerve palsy. Dose and duration are specified for the different types of symptoms. Providers need to make

sure to differentiate the presentations of Lyme disease as early as possible and treat appropriately. Misdiagnosis or inappropriate treatment may lead to an increase in likelihood of developing persistent symptoms following treatment.

Statement of the Problem

Primary care providers still struggle to appropriately diagnosis and treat Lyme disease. Even though treatment guidelines have been established for prophylaxis and initial treatment of Lyme disease, controversy continues within the medical field questioning if long term symptoms such as fatigue, pain, joint and muscle aches, memory and concentration deficits after Lyme treatment do truly exist. Feng et al. (2017) have estimated that approximately 10-20% of patients continue suffering from chronic symptoms described as PTLDS following the standard antibiotic treatment of 2-4 weeks for early or late Lyme disease. The question remains that even if these symptoms are a direct or indirect consequence of Lyme disease, how can providers appropriately treat these patients.

Statement of the Research Question

In patients who were treated appropriately for Lyme disease but develop PTLDS, does extended course antibiotic therapy versus symptomatic treatment versus alternative treatments help relieve PTLDS symptoms most effectively?

LITERATURE REVIEW

A comprehensive search was performed using several electronic databases including DynaMed Plus, PubMed, Clinical Key, and CINAHL. Specific key words used in the search for this

topic included Lyme disease, PTLDS, chronic Lyme disease, chronic fatigue syndrome, and treatment outcomes. A review of the literature yielded several high-quality randomized control trials, prospective cohort studies, and case control studies published primarily within the past 5 years. Two articles going back to 2001 and 2007 were included because it is important to establish how long the struggle of treating Lyme Disease and PTLDS has existed. The articles also show how there have not been many advances made in diagnosis or treatment throughout the years. Studies were limited to those which provided good background information and high levels of evidence regarding treatment options that have been studied thus far and did not include conflict of interest.

Evidence of PTLDS

The Infectious Diseases Society of America proposed a case definition for PTLDS in 2006 as:

> – An adult or child with a documented episode of early or late Lyme disease fulfilling the case definition of the Centers for Disease Control and Prevention
> – Treatment with a generally accepted treatment regimen, with resolution or stabilization of the objective manifestation(s) of Lyme disease
> – Onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a 6 month period after completion of antibiotic therapy:
> • Fatigue
> • Widespread musculoskeletal pain
> • Complaints of cognitive difficulties
> • Subjective symptoms are of such severity that, when present, they result in substantial reduction in previous levels of occupational, educational, social, or personal activities. (Nemeth et al., 2016, Table 1)

A recent study was published by Rebman et al. (2017) that characterized a case series of patients with well-documented PTLDS comparing them to a sample of healthy control subjects. This case series study included 61 participants which were physician-referred or self-referred

and met the case definition of PTLDS. The normal control group consisted of 26 healthy control participants that did not have a clinical history of Lyme disease or current antibodies to Bb. All participants in the study were evaluated by physical exam, clinical laboratory testing, standardized questionnaires, and a 36-item current symptom list. Comparison was made between the control group and all participants with PTLDS. Rebman et al. (2017) found that 59% of the participants with PTLDS were misdiagnosed initially or had delayed initial diagnosis of Lyme disease proving the importance of proper and timely diagnosis and treatment. A case series study provides low evidence about therapeutic effectiveness, but this study was a first for comparing patients with rigorously defined PTLDS to the non-Lyme infected control group. All participants, including the normal controls, were taken from an appropriate endemic area for Lyme disease. The studies confounding effect brings to attention that there is no definitive biomarker for Bb infection or PTLDS. This causes uncertainty that symptoms are attributable to PTLDS and not other co-morbidities. The authors did try to address this by following the same exclusionary criteria for all participants. The physical exams and laboratory testing provided by Rebman et al. (2017) showed few abnormalities with the most notable exception being 32.2% diminished vibratory sensation on physical exam among the participants with PTLDS. Therefore, standardized questionnaires were utilized to measure symptoms. The results showed significantly greater fatigue, pain, sleep disturbance, depression and lower quality of life occurred in the patients with PTLDS (p<0.001) (Rebman et al., 2017). This study hopes to provide a pattern of symptoms that can be used as a tool for the diagnosis for PTLDS. It also hopes to provide a well-validated symptom survey that can be used to monitor treatment since laboratory testing has been shown to be unreliable.

Identifying the cause of PTLDS may be beneficial in establishing treatment guidelines. One hypothesis is that the existence of PTLDS occurs because the Bb spirochetes or spherules from the spirochetes remain in this subset of patients even after treatment. Middelveen et al. (2018) performed a case-control study where 12 subjects were randomly chosen from the North American patient population. All were either clinically diagnosed with Lyme disease or tested positive for serological testing prior to the study. All patients had been treated with antibiotics and symptomatic patients who remained on antibiotics were also included in the study. Ten healthy subjects who tested negative for serologic testing were used as controls. All 12 positive case studies were described in detail for symptoms and sample types were taken for culture from all participants. The study confirmed the presence of live Borrelia spirochetes with positive cultures in these patients who were treated with antibiotics but remained symptomatic. In contrast, all the control subjects were negative for Borrelia spirochetes. These positive results are shown in Table 1.

Middelveen et al. (2018) clearly defines and describes the cases well. A problem with this study group was that it defined a very small percent of the population and the study admits to some of the subjects not being from an endemic area. The control subjects were randomly selected, and all appropriately tested. The control group was selected from the same population as the study group. Study measures were not identical as different culture specimens were sampled depending on the subjects. It was not explained how the type of culture specimen collected per patient was determined. The specimen types varied between whole callus, blood culture, vaginal, or seminal cultures. The study measures were objective.

These results mirror studies performed on non-human primates previously. Clinical studies on a larger scale with human participants are needed to confirm these findings.

Table 1. Summary of Microscopy Results from Patient Culture Samples

Case #	Sample Type	Darkfield	Dieterle	Bb Immunostain
Case 1	whole callus blood culture	N/A spirochetes	spirochetes N/A	positive, spirochetes N/A
Case 2	blood culture vaginal culture	spherules spirochetes	spherules spirochetes	positive, spherules positive, spirochetes, biofilm
Case 3	blood culture seminal culture	spirochetes/spherules spirochetes	spirochetes/spherules spirochetes	positive spirochetes/spherules positive, spirochetes
Case 4	blood culture vaginal culture	spirochetes/spherules spirochetes	spirochetes/spherules spirochetes	positive spirochetes/spherules positive, spirochetes
Case 5	blood culture vaginal culture	spherules spirochetes	spherules spirochetes	positive, spherules positive, spirochetes
Case 6	blood culture seminal culture	spherules spirochetes	spherules spirochetes	positive, spherules positive, spirochetes
Case 7	vaginal culture	spirochetes	spirochetes	positive, spirochetes
Case 8	seminal culture	spirochetes	spirochetes	positive, spirochetes
Case 9	vaginal culture	spirochetes	spirochetes	positive, spirochetes
Case 10	seminal culture	spirochetes	spirochetes	positive, spirochetes
Case 11	vaginal culture	spirochetes	spirochetes	positive, spirochetes
Case 12	blood culture skin culture	spherules spirochetes	spherules spirochetes	positive, spherules positive, spirochetes

N/A, not available.

Note. Adapted from "Persistent Borrelia infection in patients with ongoing symptoms of Lyme disease", by Middelveen, M., Sapi, E., Burke, J., Filush, K. R., Franco, A., Fesler, M. C., & Stricker, R. B., 2018, *Healthcare, 6*(2), pii:E33. Copyright 2018 by the authors.

Treatment of PTLDS with Extended Use of Antibiotics

Studies going back to 2001 prove that extended use of intravenous and oral antibiotics for greater than 90 days does not improve symptoms more than placebo groups. Klempner et al. (2001) conducted a randomized control trial to determine if long term antibiotic use was beneficial in improving health-related quality of life in patients previously diagnosed and treated for Lyme disease. The study included 78 patients who were still seropositive for IgG

antibodies to Borrelia burgdorferi and the control group included 51 patients who were seronegative. Patients were randomly selected on a 1:1 ratio to receive IV ceftriaxone for 30 days and then oral doxycycline for 60 days or placebo IV dextrose solution and placebo oral capsules for same amount of time. Using the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) it was determined that considerable impairment of health-related quality of life was seen in both groups. Table 2 shows that the criteria evaluated produced very similar confidence intervals of 95% across both groups. This shows that there was no statistical difference between the patients receiving extended antibiotics and those who did not.

Table 2. Clinical Responses at 180 Days

TABLE 2. CLINICAL RESPONSES AT 180 DAYS.*

SF-36 OUTCOME CATEGORY	SEROPOSITIVE PATIENTS				SERONEGATIVE PATIENTS				ALL PATIENTS			
	ANTIBIOTIC GROUP (N=35)	PLACEBO GROUP (N=35)	DIFFERENCE IN RISK	P VALUE	ANTIBIOTIC GROUP (N=22)	PLACEBO GROUP (N=23)	DIFFERENCE IN RISK	P VALUE	ANTIBIOTIC GROUPS (N=57)	PLACEBO GROUPS (N=58)	DIFFERENCE IN RISK	P VALUE
	no. (%)		% (95% CI)		no. (%)		% (95% CI)		no. (%)		% (95% CI)	
Physical component				0.96				0.34				0.55
Improved	11 (31)	10 (29)	3 (−19 to 24)		9 (41)	5 (22)	19 (−7 to 46)		20 (35)	15 (26)	9 (−8 to 26)	
Unchanged	16 (46)	17 (49)			9 (41)	11 (48)			25 (44)	28 (48)		
Worse	8 (23)	8 (23)	0 (−20 to 20)		4 (18)	7 (30)	−12 (−37 to 13)		12 (21)	15 (26)	−5 (−20 to 11)	
Mental component				0.46				0.71				0.87
Improved	11 (31)	16 (46)	−14 (−37 to 8)		8 (36)	6 (26)	10 (−17 to 37)		19 (33)	22 (38)	−5 (−22 to 13)	
Unchanged	16 (46)	12 (34)			9 (41)	12 (52)			25 (44)	24 (41)		
Worse	8 (23)	7 (20)	3 (−16 to 22)		5 (23)	5 (22)	1 (−23 to 25)		13 (23)	12 (21)	2 (−13 to 17)	
Total				0.96				0.58				0.90
Improved	13 (37)	14 (40)	−3 (−26 to 20)		10 (45)	7 (30)	15 (−13 to 43)		23 (40)	21 (36)	4 (−14 to 22)	
Unchanged	10 (29)	9 (26)			6 (27)	8 (35)			16 (28)	17 (29)		
Worse	12 (34)	12 (34)	0 (−22 to 22)		6 (27)	8 (35)	−8 (−34 to 19)		18 (32)	20 (34)	−3 (−20 to 14)	

*Patients were considered to be seropositive if they had a Western blot indicating substantial levels of serum IgG antibodies to *Borrelia burgdorferi* at the time of enrollment in the study; patients were considered to be seronegative if they had a negative Western blot. The antibiotic treatment regimen for those in the antibiotic group was intravenous ceftriaxone (2 g per day) for 30 consecutive days, followed by oral doxycycline (200 mg per day) for 60 consecutive days. The difference in risk is the proportion of patients with improved or worse scores in the antibiotic group minus the proportion with improved or worse scores in the placebo group. P values were derived by the chi-square test for the comparison of the antibiotic group with the placebo group across the three outcome categories of "improved," "unchanged," and "worse." SF-36 denotes Medical Outcomes Study 36-item Short-Form General Health Survey, and CI confidence interval.

Note. Adapted from "Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease", by Klempner, M. S., Linden, T. H., Evans, J., Schmid, C. H., Johnson, G. M.,

Trevino, R. P.,…Weinstein, A. W., 2001, *New England Journal of Medicine, 345*(2), 85-92. Copyright 2001 by the Massachusetts Medical Society.

This article by Klempner et al. (2001) also demonstrates how long the problem has persisted. Recruitment for the study began in 1997. Standardized questionnaires were used to determine clinical response. The problem is that results could be affected by subjective views of the patients. Not only was extended antibiotic use addressed but adverse events were evaluated and graded according to scales derived from the Common Toxicity Criteria of the National Cancer Institute. Rash, diarrhea, and vaginal pruritis were more common in the extended use antibiotic groups. No deaths occurred. The primary analysis was an intention-to-treat. The study was completed by 107 patients out of 129 (83%) (Klempner et al., 2001). Any participant completing at least 75% of the prescribed medication was still included.

In a more recent study, similar observations and conclusions were made. According to Berende et al. (2016) a randomized, double-blind, placebo-controlled trial that included 280 participants was conducted. The 280 participants were divided into groups of 86 receiving doxycycline, 96 receiving clarithromycin plus hydroxychloroquine, and 98 in the placebo group. This study showed that prolonged antibiotic treatment of either doxycycline or clarithromycin-hydroxycholorquine after an initial dose of ceftriaxone did not lead to a better quality of life than the group that received the placebo. The outcomes were measured by using the RAND SF-36 Health Status Inventory with mean scores of 35.0 across all three groups. Table 3 reflects that the poor quality of life of these patients remained across all three groups after the treatment. In all study groups, the SF-36 physical-component summary score increased significantly from baseline over the study period (p=<0.001) (Berende et al., 2016). An

incidental finding was also found to include that 68.6% of the participants experienced drug-related adverse events.

Table 3. Treatment Effect at the End of the Treatment Period in the Modified Intention-to-Treat Population

Table 2. Treatment Effect at the End of the Treatment Period in the Modified Intention-to-Treat Population.*

Outcome	Doxycycline Group (N=86)	Clarithromycin–Hydroxychloroquine Group (N=96)	Placebo Group (N=98)	P Value†	Doxycycline Group vs. Placebo Group	Clarithromycin–Hydroxychloroquine Group vs. Placebo Group
	score (95% CI)				*difference in score (95% CI)‡*	
Primary outcome: SF-36 physical-component summary§	35.0 (33.5 to 36.5)	35.6 (34.2 to 37.1)	34.8 (33.4 to 36.2)	0.69	0.2 (−2.4 to 2.8)	0.9 (−1.6 to 3.3)
Secondary outcomes						
RAND SF-36§						
Mental-component summary	40.2 (38.6 to 41.9)	40.5 (38.9 to 42.1)	40.1 (38.6 to 41.7)	0.94	0.1 (−2.7 to 2.9)	0.4 (−2.3 to 3.1)
Global-health composite	36.1 (34.5 to 37.8)	36.6 (35.1 to 38.1)	36.0 (34.5 to 37.5)	0.85	0.1 (−2.6 to 2.9)	0.6 (−2.1 to 3.2)
Physical-functioning scale	41.9 (40.5 to 43.3)	42.1 (40.8 to 43.4)	41.0 (39.7 to 42.3)	0.44	0.9 (−1.4 to 3.2)	1.1 (−1.1 to 3.4)
Role–physical scale	33.6 (31.6 to 35.6)	34.4 (32.5 to 36.3)	33.9 (32.0 to 35.8)	0.84	−0.3 (−3.7 to 3.1)	0.5 (−2.8 to 3.8)
Bodily pain scale	39.1 (37.5 to 40.7)	40.5 (39.0 to 41.9)	39.4 (37.9 to 40.9)	0.42	−0.3 (−2.9 to 2.4)	1.1 (−1.5 to 3.6)
General-health scale	37.1 (35.6 to 38.6)	38.4 (37.0 to 39.8)	37.5 (36.2 to 38.9)	0.41	−0.4 (−2.9 to 2.0)	0.9 (−1.5 to 3.3)
Mental-health scale	45.1 (43.8 to 46.4)	45.2 (43.9 to 46.4)	45.1 (43.9 to 46.4)	1.00	0.0 (−2.3 to 2.2)	0.0 (−2.1 to 2.2)
Role–emotional scale	44.7 (42.4 to 47.0)	41.4 (39.2 to 43.6)	42.6 (40.4 to 44.8)	0.11	2.1 (−1.7 to 6.0)	−1.2 (−5.0 to 2.6)
Social-functioning scale	36.3 (34.2 to 38.4)	38.5 (36.6 to 40.5)	37.5 (35.6 to 39.5)	0.32	−1.2 (−4.7 to 2.3)	1.0 (−2.4 to 4.4)
Vitality scale	42.5 (40.9 to 44.0)	42.4 (41.0 to 43.9)	41.9 (40.5 to 43.4)	0.85	0.5 (−2.0 to 3.1)	0.5 (−2.0 to 3.0)
Checklist Individual Strength¶						
Total score	88.7 (84.4 to 92.9)	87.1 (83.0 to 91.1)	88.4 (84.4 to 92.4)	0.84	0.3 (−6.9 to 7.4)	−1.3 (−8.3 to 5.6)
Fatigue-severity scale	39.4 (37.3 to 41.5)	38.6 (36.6 to 40.5)	38.3 (36.3 to 40.2)	0.73	1.1 (−2.4 to 4.6)	0.3 (−3.1 to 3.7)

* All study groups first received a 2-week course of ceftriaxone before the randomized 12-week course of study drug or placebo. P values were derived by analysis of covariance. All scores are adjusted for sex and baseline SF-36 physical-component summary score.
† Bonferroni correction was used for pairwise comparisons among the three study groups.
‡ Group differences should exceed 2 to 4 T-points (exact number of points varies for each scale) to indicate minimally important differences on all RAND SF-36 scales.[14]
§ The ranges of the RAND SF-36 scores were as follows: RAND SF-36 physical-component summary, 15 to 61; mental-component summary, 11 to 66; global-health composite, 8 to 65; physical-functioning scale, 16 to 58; role–physical scale, 26 to 56; bodily pain scale, 20 to 60; general-health scale, 20 to 64; mental-health scale, 16 to 66; role–emotional scale, 19 to 54; social-functioning scale, 12 to 57; and vitality scale, 26 to 70. For all scales, higher scores indicate better quality of life.
¶ Scores on the Checklist Individual Strength range from 20 to 140 for the total score and from 8 to 56 for the fatigue-severity scale. For both scales, higher scores indicate more fatigue.

Note. Adapted from "Randomized trial of longer-term therapy for symptoms attributed to Lyme disease", by Berende, A., ter Hofstede, H. J., Vos, F. J., van Middendorp, H., Vogelaar, M. L., Tromp, M.,…Kullberg, B. J., 2016, *The New England Journal of Medicine, 374*(13), 1209-1220. Copyright 2016 by the Massachusetts Medical Society.

Patients were appropriately randomized and blinded. Balance was established for age, sex, and duration of symptoms. Outcomes were assessed using the RAND-36 Health Status Inventory (RAND SF-36) which could be considered subjective. Berende et al. (2016) have again appropriately assessed and shown that longer-term antibiotic treatment does not lead to

better outcomes. Specific efforts were made during the study to ensure adherence to the study regimens by using Medication Event Monitoring System caps. The authors summarized findings from other smaller studies in comparison which had similar results. They also discussed that several non-comparative, open-label studies have shown beneficial effects of prolonged antimicrobial treatment, but randomized, control trials have not.

Striker (2007) does provide a counterpoint study that compares peer-reviewed literature pertaining to diagnostic Lyme disease testing, standard treatment results, and coinfection with other tickborne agents. The study looks at uncontrolled and controlled trials of prolonged antibiotic therapy in patients with persistent symptoms of Lyme disease. The author concludes that Borrelia burgdorferi can invade tissue, elude the immune system, and establish long-term infection in patients. He states that antibiotic therapy greater than four weeks may be beneficial for these patients.

Unfortunately, the studies cited by Striker (2007) that support better symptom outcomes using long term antibiotics were all uncontrolled trials and published from 1994 to 1999. These uncontrolled trials do not give accurate and valid results. The controlled studies cited had not been finished. There were not two independent reviewers of this study. Sufficient detail or statistics were not provided. The approach suggested for treatment did not follow current Infectious Diseases Society of America (IDSA) guidelines.

Marzec et. al (2017) discussed 5 illustrative cases that were reported to the CDC and evaluated regarding serious bacterial infections acquired during treatment of chronic Lyme disease. Septic shock, osteomyelitis, Clostridium difficile colitis, and paraspinal abscess being

among the outcomes with even one patient case outcome resulting in death. This article is limited by the small population reported and studied. The authors state that systematic investigations would be useful to better understand the scope and consequences of adverse effects that result from the treatment of chronic Lyme disease. These cases were identified retrospectively after being reported to the CDC. Relevant exposures and potential confounding factors were not addressed. Outcomes were discussed on a case to case basis.

Tseng, Cami, Goldmann, DeMaria, and Mandl (2015) performed a population-based retrospective cohort study that analyzed claims from a nationwide US health insurance plan in 14 high prevalence states over two periods: 2004-2006 and 2010-2012. The extended use of antibiotic definition for this study included greater than five weeks prescription. The incidence of extended antibiotic therapy for treatment of Lyme disease was higher in 2010-2012 (14.72 per 100,000 person-years; n=684) than in 2004-2006 (9.94 per 100,000 person-years; n=394) (p<.001) (Tseng, Cami, Goldmann, DeMaria, and Mandl, 2015).

Despite guidelines established by the Infectious Diseases Society of America (IDSA), the study conducted by Tseng et al. (2015) shows that considerable variation remains in the length of antibiotic use when treating Lyme disease. The study did list some factors that may have led to overestimation such as inaccurate coding and the fact that claims data reveal tests ordered but do not include test results. Therefore, negative test results may have been included. The study also stated some factors that may have led to underestimation including those patients diagnosed clinically with EM and never lab tested, therefore not meeting the post Lyme disease definition. Also, patients treated with antibiotics in an inpatient setting would not have been included. Some of the theories proposed about why there remains considerable variation in

courses of therapy despite consensus on the duration by the IDSA are reasons such as belief that longer courses of treatment are better at preventing long-term consequences, or that persistence of Lyme disease symptoms requires more extended therapy, or some may be related to patient fear of the possible long-term consequences of undertreated Lyme disease. Tseng et al. (2015) states that those still treating with extended antibiotic treatments may include a small group of providers.

Treatment of PTLDS Based on Symptoms

Myalgic encephalomyelitits/chronic fatigue syndrome.

One of the main syndromes often associated and compared to PTLDS is myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Both have several clinical features in common including fatigue, musculoskeletal pain, and cognitive difficulties. Patrick et. al (2015) conducted a case-control study enrolling 13 patients with alternatively diagnosed chronic Lyme syndrome (ADCLS), 25 patients with chronic fatigue syndrome (CFS), 25 matched healthy controls, and 11 patients with systemic lupus erythematosus (SLE). Patients completed a history, physical exam, screening laboratory tests, seven functional scales, reference serology using the Centers for Disease Control and Prevention criteria, reference serology for other tick-associated pathogens and cytokine expression studies. The baseline clinical data and functional scales showed significant disability among both ADCLS and CFS patients when compared to the control group but no differences between each other. Data was statistically significant at $p<0.05$ as shown in Table 4. The small sample size made it harder to detect small differences between the groups. This kind of study may suffer from recall bias as a function of strong

personal identification with a diagnosis and its associated risk factors and symptoms. Selection bias is also a risk but was minimized by using identical exclusion criteria across all study groups. This study identifies ADCLS and CLS as indistinguishable based on medical histories, physical exam functional scales and a range of laboratory tests.

Table 4. Demographic and Clinical Characteristics of the Study Cohort (N=74)

Table 2. Demographic and Clinical Characteristics of the Study Cohort (N = 74)

					P Value			
Group	Healthy (n = 25)	SLE (n = 11)	CFS (n = 25)	ADCLS (n = 13)	SLE vs Healthy	CFS vs Healthy	ADCLS vs Healthy	CFS vs ADCLS
Male sex	4 (16)	0 (0)	4 (16)	3 (23)	.3	1.0	.7	.7
Age, y, median (IQR)	53 (30–69)	51 (29–75)	54 (34–67)	45 (18–71)	.5	.9	**.02**	**.02**
Highest level of education					.4	.7	.9	1.0
High school	4 (16)	2 (18)	6 (24)	3 (23)				
Undergraduate	16 (64)	9 (82)	13 (52)	7 (54)				
Postgraduate	5 (20)	0 (0)	6 (24)	3 (23)				
Current annual income, median (IQR)	$35 000 ($15 000– $55 000)	$45 000 ($12 500–$55 000)	$35 000 ($17 500–$65 000)	$22 500 ($2,500–$45 000)	.7	.8	.4	.3
Ethnicity					.08	**.04**	.4	.4
Aboriginal	0 (0)	0 (0)	2 (8)	0 (0)				
White	20 (80)	5 (45)	23 (92)	13 (100)				
Chinese	3 (12)	3 (27)	0 (0)	0 (0)				
Other	2 (8)	3 (27)	0 (0)	0 (0)				
Symptom onset sudden	NA	4 (36)	13 (52)	3 (23)	NA	NA	NA	.2
Core symptoms								
Fatigue	4 (16)	9 (82)	25 (100)	12 (92)	**<.0001**	**<.0001**	**<.0001**	.3
Postexertional fatigue	2 (8)	5 (45)	25 (100)	11 (85)	**.02**	**<.0001**	**<.0001**	.1
Nonrefreshing sleep or sleep disturbance	8 (32)	8 (73)	25 (100)	12 (92)	**.03**	**<.0001**	**.001**	.3
Pain or headache	15 (60)	10 (91)	25 (100)	13 (100)	.1	**.001**	**.008**	1.0
Neurological/cognitive dysfunction	1 (4)	5 (45)	25 (100)	11 (85)	.006	**<.0001**	**<.0001**	.1
Swollen joints	1 (4)	5 (45)	8 (32)	7 (54)	**.006**	**.02**	**.001**	.3
Painful joints	7 (28)	8 (73)	17 (68)	12 (92)	**.03**	**.01**	**<.0001**	.1
Meeting Fukuda CFS definition	0 (0)	0 (0)	25 (100)	11 (85)	1.0	**<.0001**	**<.0001**	.1
Putative triggers associated with symptom onset								
Viral illness	NA	3 (27)	11 (44)	7 (54)	NA	NA	NA	.7
Bacterial infection	NA	1 (9)	4 (16)	3 (23)	NA	NA	NA	.7
Tick bite	NA	0 (0)	4 (16)	2 (15)	NA	NA	NA	1.0
Skin rash	NA	5 (45)	2 (8)	2 (15)	NA	NA	NA	.6

Values are presented as No. (%) for categorical variables and median (IQR) for continuous variables. *P* values were calculated with Fisher exact test for categorical variables or Wilcoxon rank-sum test for continuous variables.

Bold values denote statistically significant at $P < .05$.

Abbreviations: ADCLS, alternatively diagnosed chronic Lyme syndrome; CFS, chronic fatigue syndrome; IQR, interquartile range; NA, not applicable; SLE, systemic lupus erythematosus.

Note. Adapted from "Lyme disease diagnosed by alternative methods: A phenotype similar to that of chronic fatigue syndrome", by Patrick, D. M., Miller, R. R., Gardy, J. L., Parker, S. M., Morshed, M. G., Steiner, T. S.,…Tang, P. 2015, Clinical Infectious Diseases, 61(7), 1084-1091. Copyright 2015 by the Oxford University Press.

In contrast, Ajamian, Cooperstock, Wormser, Vernon, & Alaedini (2015) referenced a study done by Chandra et. al (2010) finding IgG anti-neural antibody reactivity was significantly increased patients with PTLDS (41 of 83; 49.4%) versus patients who had been treated for Lyme

disease and did not have residual symptoms (5 of 27; 18.5%) and healthy controls who had never had Lyme disease (3 of 20; 15%) (p<0.01 for both comparisons). They compared this study to their study which found no significant difference in the prevalence of anti-neural antibody reactivity between ME/CFS patients (4 of 51; 7.8%) and healthy controls (7 of 53; 13.2%) (p=0.5) (Ajamian, Cooperstock, Wormser, Vernon, & Alaedini, 2015). As a result, anti-neural antibody reactivity may be a distinguishing factor between the two syndromes. This study did list a potential limitation being the methodology of the initial study done by Chandra et al. (2010), which primarily detects the prominent expressed neural proteins and may miss reactivity of the minor proteins or non-protein antigens. It was suggested that further inquiry into B cell activation mechanisms and auto antibody response may also be useful in distinguishing between PTLDS and ME/CFS.

According to DynaMed Plus, chronic fatigue syndrome (2018) there are not FDA approved medications for CFS. Recommended treatment options include a healthy, balanced diet, exercise therapy (level 1 [likely reliable] evidence), counseling or behavioral therapy (level 2 [mid-level] evidence), acupuncture, and/or the recommended off-label use of methylphenidate 10 mg twice daily for 4 weeks (level 1 evidence) but with the risk of habituating and tolerance developing.

A cochrane review was performed by Price, Mitchell, Tidy, & Hunot (2008) where 15 studies (1043 CFS participants) were included. In 6 of the studies mean fatigue scores were highly significant in favor of cognitive behavior therapy (CBT) compared to usual care. 40% of the CBT participants showing clinical response compared to only 26% receiving usual care (95% CI 0.29-0.76). In four other studies CBT was compared to other psychological therapies,

including relaxation, counseling, and education/support. Again, the mean fatigue scores favored CBT (95% CI -0.65 to -0.20). Limitations included inconsistent findings at follow up and a small group of studies.

Kaiser (2015) performed an open-label, proof-of-concept trial on 15 participants that were all given low-dose methylphenidate in combination with mitochondrial support nutrients. At 12 weeks it was found the 87% of the participants had a greater than or equal to 25% reduction in fatigue and concentration disturbances (p<0.0001). This study was limited in a small study group size and did not include a placebo group for comparison.

Lyme neuroborreliosis.

Neurological symptoms are also a common finding in PTLDS. Ramesh, Martinez, Martin, & Philipp (2017) conducted a study where dexamethasone, a steroid that inhibits the expression of several immune mediators and meloxicam, a non-steroidal anti-inflammatory drug that inhibits cyclooxygenase-2 (COX-2) were evaluated for effects on Borrelia burgdorferi-induced inflammation in glial and neuronal cells of the CNS. Freshly harvested frontal cortex tissues were collected from three rhesus macaques that were euthanized in accordance with the recommendation of the American Veterinary Medical Association's Panel on Euthanasia. Two-mm sections of the frontal cortexes were divided into 12-well plates. Tissue sections were exposed to medium containing Bb spirochetes in the presence or absence of dexamethasone or meloxicam. Controls with no spirochetes were also included. After 48 hours the tissues were evaluated. As shown in Figure 1, dexamethasone resulted in significantly reduced levels of pro-inflammatory cytokines or chemokines being evaluated whereas meloxicam treatment showed

no significant reduction in the same levels. This study tests the hypothesis that inflammatory mediators are the key factor in Lyme neuroborreliosis (LNB). Caution is expressed for use of steroids if facial palsy is associated with Lyme neuroborreliosis because studies have shown an opposite effect.

Figure 1

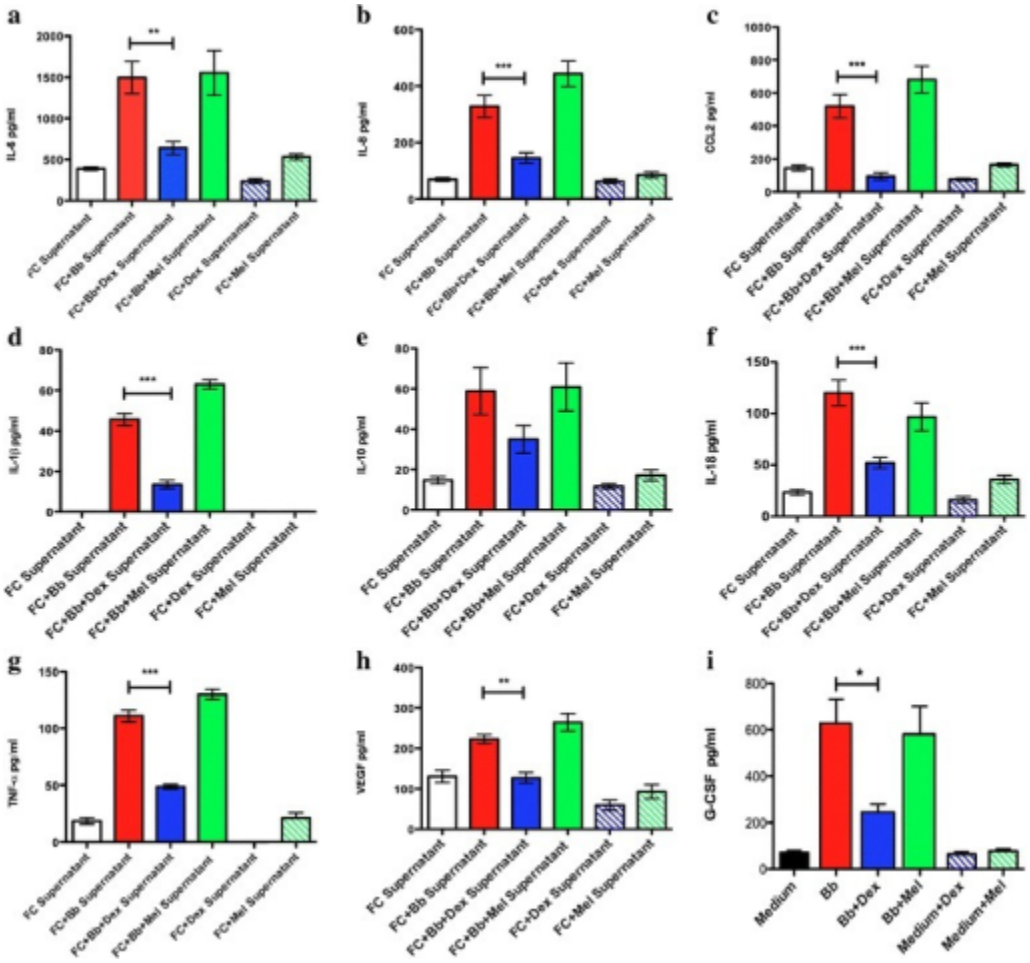

Fig. 1 Dexamethasone but not meloxicam reduces the levels of Bb-induced cytokines and chemokines in frontal cortex explants after 6 h of incubation. The graphs represent the effect of the anti-inflammatory drugs on the levels of a IL-6, b IL-8, c CCL2, d IL-1β, e IL-10, f IL-18, g TNF-α, h VEGF, and i G-CSF. The two-way ANOVA and Tukey's multiple comparison test were used to evaluate the statistical significance between means and SEM of triplicate data sets, *p < 0.05, **p < 0.01, ***p < 0.001

Note. Adapted from "Effects of dexamethasone and meloxicam on Borrelia burgdorferi-induced inflammation in glial and neuronal cells of the central nervous system", by Ramesh, G.,

Martinez, A. N., Martin, D. S., & Philipp, M. T., 2017, *Journal of Neuroinflammation, 14*(1), 28.

Lyme disease-associated facial palsy (LDFP) is an acute manifestation of neuroborreliosis which is a common finding when dealing with PTLDS. A retrospective cohort study included 51 patients who had a prior diagnosis of unilateral LDFP (Jowett, Gaudin, Banks, & Hadlock, 2017). These patients were followed to determine differences in outcomes between those that were treated with antibiotic monotherapy (MT); dual therapy (DT) with antibiotics and corticosteroids; and triple therapy (TT) with antibiotics, corticosteroids, and antivirals. These patients were followed for up to 84 months. Significantly worse facial outcomes were seen in patients receiving DT and TT compared to MT. This study demonstrates an association between corticosteroid use in acute LDFP and worse long-term facial function. Care still needs to be taken in initial diagnosis to distinguish between viral, idiopathic facial palsy or LDFP. Bias was found in that the sample population was principally representative of a smaller subset of LDFP patients who develop post paralysis facial palsy. Bias was also found in patient self-selection to the testing center. Confounding factors included the proportion of patients prescribed antibiotics alone versus with corticosteroids in the general population because it is currently unknown.

Lyme arthritis.

More than a third of the Lyme disease cases reported to the CDC involve arthritis as the manifestation of the presenting disease (Arvikar & Steere, 2015). The location is usually one or a few of the larger joints presenting with pain and swelling. Diagnosis is usually made by PCR testing of the synovial fluid positive for Bb before treatment. It however is not a reliable

marker for eradication of Bb after treatment. Arvikar & Steere (2015) discussed treatment recommended by the IDSA that used several small, double blinded or randomized studies to determine an algorithm presented below in Figure 2. Initial use of oral doxycycline with minimal or no improvement of symptoms has seen moderate improvement when treatment is switched to IV administration. Arvikar & Steere (2015) recommends combination therapy using NSAIDS (ibuprofen or naproxen) and DMARDs (hydroxychloroquine or methotrexate) to treat persistent arthritis after initial treatment. The last resort may be a synovectomy.

Figure 2

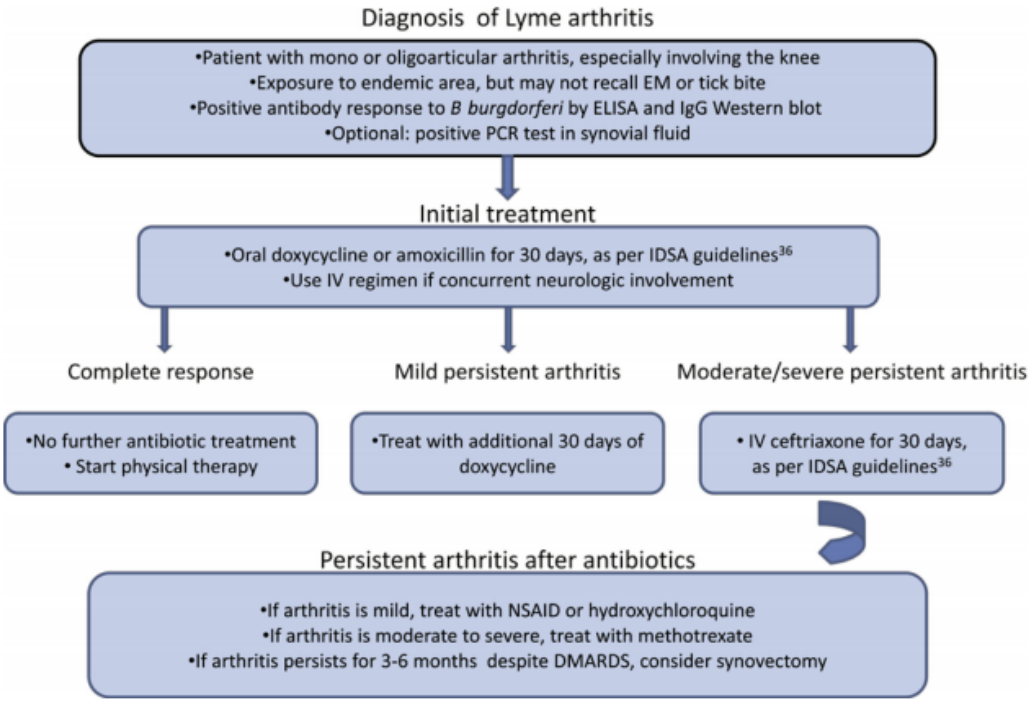

Fig. 2. Algorithm for the diagnosis and treatment of Lyme arthritis. DMARDs, disease modifying antirheumatic drugs; ELISA, enzyme-linked immunosorbent assay; EM, erythema migrans; IDSA, Infectious Disease Society of America; IV, intravenous; NSAID, nonsteroidal antiinflammatory drug; PCR, polymerase chain reaction.

Note. Adapted from "Diagnosis and treatment of Lyme disease", by Arvikar, S. L. & Steere, A. C., *Infectious Disease Clinics of North America, 29*(2), 269-280. Copyright 2015 by the Elsevier Inc.

Alternative Treatment Options for PTLDS

Lantos et al. (2015) performed internet searches using Google to identify what websites were marketing nonantimicrobial therapies for Lyme disease. Then PubMed was used to identify any scientific evidence to support these treatments. The authors categorized more than 30 alternative treatments found through the internet search into five broad categories. The categories included oxygen therapy, energy and radiation treatments, metal chelation, nutritional supplements, and biological/pharmacologic therapies. Review of the medical literature did not substantiate any efficacy for the advertised treatments found on the internet through Google.

Lantos et al. (2015) references the study done by Klempner et al. (2001) with 38% of placebo-treated patients having improved symptoms. This proportion was not significantly different than the patients who received antibiotics. The authors also found that the studies showing extended antimicrobial therapy ineffective with convincing evidence of possible harm justifies the website's promotion of alternative therapies is the only other option. This study admits to not presenting a comprehensive catalogue of the unorthodox therapies offered as this list continues to change. The study cannot measure how popular these nonconventional therapies are among patients.

Essential oils.

Feng et al. (2017) performed a study where 34 different essential oils were evaluated. Aliquots of these oils were added to a 96-well plate containing 110 uL of the seven-day-old stationary phase Borrelia burgdorferi culture. Each essential oil was assayed in four

concentration levels. An antibiotic combination of daptomycin, doxycycline, and cefuroxime was used as the control drug since it had been shown to completely eradicate Bb persisters in previous studies. A drug-free control was also included. All tests were run in triplicate. Results were obtained after 7 days of incubation. Oregano and cinnamon bark showed remarkable activity even at 0.05% concentration for complete eradication of the stationary phase of Bb. It was also noted that oregano oil dramatically reduced the size of aggregated biofim-like microcolonies compared to the antibiotic controls.

Though the Feng et al. (2017) study shows promise for alternative treatment options for Lyme disease, they caution that many factors still need to be considered. Future studies need to identify the active ingredients in the specific oils and determine effective dosage in vivo. Though carvacrol, the active ingredient in oregano, has not shown toxicity in mice, there is limited safety information regarding essential oil use in humans. Adequate animal studies need to confirm safety and efficacy of active essential oils before human studies can proceed. This study also indicates that further studies are needed to find an antimicrobial agent that penetrates the blood-brain barrier as well as the persistent Borrelia organisms do.

Supplements.

Nicolson, Settineri, & Ellithorpe (2012) conducted an open label study to determine if using a combination oral supplement containing a mixture of phosphoglycolipids, Coenzyme Q10, and microencapsulated NADH (marketed as ATP Fuel) could affect fatigue levels. Participants included 58 patients with chronic fatigue syndrome/myalgic encephalomyelitis, chronic Lyme disease, or other fatiguing illnesses. These patients took the recommended daily

dose for 8 weeks. The level of fatigue was measured by using the validated Piper Fatigue Scale. The study showed a 30.7% reduction in overall fatigue within 60 days (p<0.001) (Nicolson, Settineri, & Ellithorpe, 2012). The combination supplement was found to be both safe and effective.

An open label study is not as reliable and unbiased as a randomized control study. There is not a placebo group so there is a chance that these patients could have felt better after eight weeks even without treatment. According to Nicolson, Settineri, & Ellithorpe (2012) statistical analysis was performed using ANOVA and Turkey test and linear regression analysis, with significance defined as p<0.05. The regression analysis suggests that the data was consistent with a high degree of confidence, but the trial may have ended too soon and the peak benefits on fatigue were yet to be realized. Only two participants experienced minor symptoms, but this could not be directly linked to the supplement since their problems preceded entry into the trial.

DISCUSSION

Chronic Lyme disease and post treatment Lyme disease syndrome are still being used interchangeably. No matter what the problem is called, the fact that Feng et al. (2017) states that 10-20% of patients diagnosed and treated for Lyme disease continue to be symptomatic is too much to be ignored. A case definition has been established by the IDSA. Rebman et al. (2017) found that 59% of the participants with PTLDS were either misdiagnosed or diagnosis was delayed. This stresses the importance of keeping Lyme disease in the differential diagnosis for typical symptoms occurring in endemic areas or those who have travelled to endemic areas.

This subset of patients with PTLDS present with a spectrum of symptoms that have a big impact on the quality of life. Patient's jobs, schooling, and personal relationships are negatively affected. Those providers practicing in these endemic areas need to know how to appropriately manage and treat these patients.

Further research needs to be done to develop more specific and sensitive lab tests so that concrete diagnoses can be made when clinical symptoms are not as straight forward as EM. Rebman, Crowder, Kirkpatrick, & Aucott (2015) established that Lyme seroreactivity should not be retested after the initial positive test because it does not correlate with ongoing symptoms. It would also be beneficial if the lab test could be used to identify if PTLDS is truly caused by residual Lyme disease or other inflammatory/infectious conditions. Studies that describe precisely the risk factors and mechanisms of illness to guide improvement of diagnostic specifics and treatment options would be beneficial.

One of the questions that remains and needs to be researched further is if these symptoms are a direct or indirect consequence of Lyme disease. The study by Middelveen et al. (2018) does indicate the possibility of Borrelia spirochetes surviving initial treatment, but with a study group of only 12 patients and other problems stated with the study, further research is needed. This study does however provide evidence that persistent infection is at least partly responsible for ongoing symptoms in Lyme disease. If this question is answered, we may be able to establish guidelines for treatment. As of now the literature is showing that we have no concrete answers.

In patients who were treated appropriately for Lyme disease but develop PTLDS, does extended course antibiotic therapy versus symptomatic treatment versus alternative treatments help relieve PTLDS symptoms most effectively?

Family practice providers must be aware of Lyme disease symptoms and appropriately treat these patients to the best of our abilities as soon as possible to try to prevent PTLDS. As for treatment of PTLDS, the one area of study that shows the most research is the use of extended antibiotics. These studies show that extended use of antibiotics in treatment of PTLDS is not beneficial and increases the risk of adverse effects. The study done by Klempner et al. (2001) proving this, still holds true after all these years and was again justified by another large study done by Berende et al. (2016). Numerous smaller studies have been done in between. All studies showing that there are no significant differences in outcomes between those patients treated with long term antibiotics versus the placebo groups. Striker (2007) was unable to support the counterpoint of benefit of long-term antibiotics in his article only using uncontrolled studies without accurate or valid results. What Striker (2007) does provide is evidence that the theory of extended use of antibiotic treatment for chronic Lyme disease was challenged and not just assumed. Marzec et al. (2017) established that even though the risk of adverse reactions to extended use of antibiotics is small, it is still a factor that needs to be considered. The adverse effects of these cases represent the need for patients and health care providers to be informed of the risk of inappropriate antibiotic use.

What is interesting is that even though the studies prove that extended antibiotic use is not effective in treating PTLDS and the risk of adverse reactions remains, it is still being done.

As established by Tseng, Cami, Goldmann, DeMaria, and Mandl (2015), the fact that extended antibiotic use is still being prescribed is most likely a consequence of not having established guidelines for treatment of PTLDS. Providers are at a loss of what to do for their patients that are suffering from persistence of symptoms.

In contrast to the concrete evidence showing that extended use of antibiotics is not beneficial, there have been potential studies showing that alternative therapies may be something of use in the future. With studies being done by Feng et al. (2017) on animals using oregano or cinnamon bark to eradicate the borrelia spirochetes, human studies for dosing and safety concerns still need to be done. Nicolson, Settineri, & Ellithorpe (2012) have established that supplements can safely help improve the fatigue portion of the symptoms of PTLDS but does not address the other symptoms associated with PTLDS.

One of the controversies that remains over PTLDS is that without concrete diagnostic measures there is overlap when just diagnosing using symptoms. That leaves the only option for treating patients with PTLDS as assessing every individual patient separately and treating the symptoms appropriately. The fatigue, musculoskeletal pain, and cognitive difficulties of PTLDS are clinically similar to ME/CFS as established by Patrick et al. (2015) and one may want to try treatment options that have been studied and used for ME/CFS such as diet, exercise, counseling or behavioral therapy, acupuncture, and/or recommended off-label use of methylphenidate (DynaMed Plus, chronic fatigue syndrome, 2018).

With Lyme neuroborreliosis, Ramesh, Martinez, Martin, & Philipp (2017) established that the use of dexamethasone was more effective than meloxicam for treatment of all

neurological symptoms except for facial palsy. The exception to this rule was presented by Jowett, Gaudin, Banks, & Hadlock (2017) establishing that corticosteroids and antivirals lead to worse long-term facial function compared to the monotherapy of antibiotics which is the recommended treatment for LDFP. Implications of dexamethasone regarding the treatment of human disease still are not clear. Further evaluation is required to ascertain which inhibitors of inflammation may be safely used to mitigate signs and symptoms of LNB.

Arvikar & Steere (2015) lists a treatment algorithm established by the IDSA as the guideline for treating Lyme arthritis which is similar to chronic inflammatory arthritis by using NSAIDS and DMARDS if antibiotics are unsuccessful. Synovectomy would be the last resort.

It is not surprising that with the controversy regarding chronic Lyme disease, patients would seek answers from the internet. The easy accessibility to testimonials from patients in the form of online blogs, discussion boards, and promotional materials by alternative therapy can be persuasive to vulnerable populations of patients suffering prolonged symptoms. Calling attention to these unconventional treatment options may serve to discourage their use. It is important for healthcare providers treating these patients that attribute their symptoms to chronic Lyme disease, to provide counseling and education about the risks and costs of unconventional therapies.

APPLICATION TO CLINICAL PRACTICE

Even though the controversy continues, PTLDS does have a case definition and studies showing that symptoms can persist after appropriate treatment of Lyme disease. If the patient

falls under the case definition, symptoms should be taken seriously and treated appropriately so that these patient's quality of life is improved to the best of our abilities.

What is known and proven by numerous studies shows that extended use of antibiotic therapy is not appropriate or beneficial in most cases of PTLDS. The studies also show that patients are at increased risk of adverse effects with use of extended antibiotic treatment. The exception to this rule appears to be with Lyme arthritis which recommends an additional 30-day treatment with doxycycline or ceftriaxone if still symptomatic.

The use of alternative treatment options has not been studied thoroughly enough on the human population to be safely recommended by the medical community. Patients must be warned that the efficacy of treatments listed on the internet, such as oxygen therapy, energy and radiation treatments, metal chelation, nutritional supplements/essential oils, and biological/pharmacologic therapies, are not evidence based and therefore, should be avoided. Again, there is one exception, as the supplement ATP Fuel has been proven to help decrease the symptom of fatigue.

Therefore, the most appropriate treatment option left for providers to follow is to treat each patient individually according to their specific symptoms. Fatigue, musculoskeletal pain, and cognitive difficulties, with similarities to ME/CFS, may include treatment such as diet, exercise, cognitive behavioral therapy, acupuncture, or off-label methylphenidate. The best treatment outcomes for Lyme neuroborreliosis seem to be with dexamethasone, except in the case of facial palsy where monotherapy of antibiotics is recommended. Lyme arthritis, if not

resolved with antibiotic therapy, should be treated with NSAIDS or methotrexate. Synovectomy would be last resort.

REFERENCES

Ajamian, M., Cooperstock, M., Wormser, G. P., Vernon, S. D., & Alaedini, A. (2015). Anti-neural antibody response in patients with post-treatment Lyme disease symptoms versus those with myalgic encephalomyelitis/chronic fatigue syndrome. *Brain, Behavior, and Immunity, 48*,354-355. https://dx.doi.10.1016/j.bbi.2015.04.006

Arvikar, S. L. & Steere, A. C. (2015). Diagnosis and treatment of Lyme disease. *Infectious Disease Clinics of North America, 29*(2), 269-280. https://dx.doi:10.1016/j.idc.2015.02.004

Berende, A., ter Hofstede, H. J., Vos, F. J., van Middendorp, H., Vogelaar, M. L., Tromp, M.,…Kullberg, B. J. (2016). Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. *The New England Journal of Medicine, 374*(13), 1209-1220. https://dx.doi:10.1056/NEJMoa1505425

Chandra, A., Wormser, G. P., Klempner, M. S., Trevino, R. P., Crow, M. K., Latov, M., & Alaedini, A. (2010). Brain, Behavior, and Immunity. *Anti-neural antibody reactivity in patients with a history of Lyme borreliosis and persistent symptoms. 24*(6), 1018-1024. http://dx.doi.10.1016/j.bbi.2010.03.002

DynaMed Plus (Internet). Ipswich (MA): EBSCO Information Services. 1995-. Record No. 114365, Lyme disease; (updated 2018 Jul 26, cited 2018 Nov 03); [about 27 screens]. Available from http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=114365. Registration and log in required.

DynaMed Plus (Internet). Ipswich (MA): EBSCO Information Services. 1995-. Record No. 115094,

Chronic fatigue syndrome; (updated 2018 Sep 10, cited 2018 Dec 01); [about 30 screens]. Available from http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=115094. Registration and log in required.

Feng, J., Zhang, S., Wanliang, S., Zubcevik, N., Miklossy, J., & Zhang, Y. (2017). Selective essential oils from spice or culinary herbs have high activity against stationary phase and biofilm Borrelia burgdorferi. *Frontiers in Medicine, 4*:169. https://dx.doi:10.3389/fmed.2017.00169

Halperin, J. J. (2015). Chronic Lyme disease: Misconceptions and challenges for patient management. *Infection and Drug Resistance*. 8: 119-128. doi:10.2147/IDR.S66739

Jowett, N., Gaudin, R. A., Banks, C. A., & Hadlock, T. A. (2017). Steroid use in Lyme disease-associated facial palsy is associated with worse long-term outcomes. *The Laryngoscope, 127*(6), 1451-1458. https://dx.doi:10.1002/lary.26273

Kaiser, J. D. (2015). A prospective, proof-of-concept investigation of KPAX002 in chronic fatigue syndrome. International Journal of Clinical and Investigational Medicine, 8(7), 11064-11074. Retrieved from http://www-ncbi-nlm-nih-gov.ezproxy.library.und.edu/pubmed/26379906

Klempner, M. S., Linden, T. H., Evans, J., Schmid, C. H., Johnson, G. M., Trevino, R. P.,…Weinstein, A. W. (2001). Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *New England Journal of Medicine, 345*(2), 85-92.

Lantos, P. M., Shapiro, E. D., Auwaerter, P. G., Baker, P. J., Halperin, J. J., McSweegan, E., & Wormser, G. P. (2015). Unorthodox alternative therapies marketed to treat Lyme Disease. *Clinical Infectious Diseases, 60*(12), 1776-1782. https://dx.doi:10.1093/cid/civ186

Marzec, N. S., Nelson, C., Waldron, P. R., Blackburn, B. G., Hosain, S., Greenhow, T.,…Mead, P. S. (2017). Serious bacterial infections acquired during treatment of patients given a diagnosis of chronic Lyme disease-United States. *Morbidity and Mortality Weekly Report, 66*(23), 607-609. https://dx.doi:10.15585/mmwr.mm6623a3

Middelveen, M., Sapi, E., Burke, J., Filush, K. R., Franco, A., Fesler, M. C., & Stricker, R. B. (2018). Persistent Borrelia infection in patients with ongoing symptoms of Lyme disease. *Healthcare, 6*(2), pii:E33. https://dx.doi:10.3390/healthcare6020033

Nemeth, J., Bernasconi, E., Heininger, U., Abbas, M., Nadal, D., Strahm, C., & Weber, R. (2016). Update of the Swiss guidelines on post-treatment Lyme disease syndrome. *Swiss Medical Weekly*. 146:14353. doi:10.4414.smw.2016.14353

Nicolson, G. L., Settineri, R., & Ellithorpe, R. (2012). Lipid replacement therapy with a glycophospholipid formulation with NADH and CoQ10 significantly reduces fatigue in intractable chronic fatiguing illnesses and chronic Lyme disease patients. *International Journal of Clinical Medicine, 3*:163-170. https://dx.doi:10.4236/ijcm.2012.33034

Patrick, D. M., Miller, R. R., Gardy, J. L., Parker, S. M., Morshed, M. G., Steiner, T. S.,…Tang, P. (2015). Lyme disease diagnosed by alternative methods: A phenotype similar to that of

chronic fatigue syndrome. *Clinical Infectious Diseases, 61*(7), 1084-1091. https://dx.doi.10.1093.cdi/civ470

Price, J. R., Mitchell, E., Tidy, E., & Hunot, V. (2008). Cognitive behavior therapy for chronic fatigue syndrome in adults. *The Cochrane Database of Systematic Reviews, 16*(3). https://dx.doi.10.1002/14651858.CD001027.pub2

Ramesh, G., Martinez, A. N., Martin, D. S., & Philipp, M. T. (2017). Effects of dexamethasone and meloxicam on Borrelia burgdorferi-induced inflammation in glial and neuronal cells of the central nervous system. *Journal of Neuroinflammation, 14*(1), 28. https://dx.doi:10.1186/s12974-017-0806-9

Rebman, A. W., Bechtold, K. T., Yang, T., Mihm, E., Soloski, M. J., Novak, C. B., & Aucott, J. N. (2017). The clinical, symptom, and quality-of-life characterization of a well-defined group of patients with posttreatment Lyme disease syndrome. *Frontiers in Medicine, 4*:224. https://dx.doi.10.3389/fmed.2017.00224

Rebman, A. W., Crowder, L. A., Kirkpatrick, A., & Aucott, J. N. (2015). Characteristics of seroconversion and implications for diagnosis of post-treatment Lyme disease syndrome: Acute and convalescent serology among a prospective cohort of early Lyme disease patients. *Clinical Rheumatology, 34*:585-589. https://dx.doi.10.1007/s10067-014-2706-z

Stricker, R. B. (2007). Counterpoint: Long-term antibiotic therapy improves persistent symptoms associated with Lyme disease. *Clinical Infectious Diseases, 45*(2), 149-157.

Tseng, Y. J., Cami, A., Goldmann, D. A., DeMaria, A. Jr., & Mandi, K. D. (2015). Incidence and patterns of extended-course antibiotic therapy in patients evaluated for Lyme disease. *Clinical Infectious Diseases, 61*(10), 1536-1542. https://dx.doi:10.1093/cid/civ636