

Challenge to the Clinical Definition of Late Lyme Disease and Post-Lyme Disease Syndrome

Christine Green, M.D.
Green Oaks Medical Center
5050 El Camino, Suite 110
Los Altos, California 94022

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This challenge is to the following portions of the IDSA Lyme disease guidelines:

Recommendation 1 (p. 1120), which states:

*“There is no well-accepted definition of post-Lyme disease syndrome. This has contributed to confusion and controversy and to a lack of firm data on its incidence, prevalence, and pathogenesis. In an attempt to provide a framework for future research on this subject and to reduce diagnostic ambiguity in study populations, a definition for post-Lyme disease syndrome is proposed in table 5. Whatever definition is eventually adopted, having once had objective evidence of *B. burgdorferi* infection must be a condition sine qua non. Furthermore, when laboratory testing is done to support the original diagnosis of Lyme disease, it is essential that it be performed by well-qualified and reputable laboratories that use recommended and appropriately validated testing methods and interpretive criteria [117, 118]. Invalidated test methods (such as urine antigen tests or blood microscopy for detection of *Borrelia* species) should not be used [337].” IDSA Guidelines (hereafter Guidelines)*

and

Recommendation 3 (p. 1113), which states:

*“Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with Ceftriaxone (2 g once per day intravenously for 2–4 weeks) (tables 2 and 3) (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-II). Response to treatment is usually slow and may be incomplete. **Re-treatment is not recommended unless relapse is shown by reliable objective measures.** Ceftriaxone is also recommended for children with late neurologic Lyme disease (tables 2 and 3) (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-III).”*

Key points:

1. Currently clinically available testing cannot prove that *Borrelia burgdorferi* infection has been eradicated; however testing has reliably demonstrated, that *Borrelia burgdorferi* can persist in animals and humans in a viable infectious state, after treatment with appropriate antibiotic therapy as delineated in these guidelines.^{1,2,3,4,5} [Phillips and Stricker, this document]
2. There is no evidence that a post-infectious syndrome occurs in Lyme disease nor is there any laboratory or diagnostic test or procedure that can identify post-Lyme disease syndrome.⁶ [Stricker, this document]
3. No symptom, whether considered objective or subjective, can allow a physician or researcher to distinguish between active infection by *Borrelia burgdorferi* or post infectious sequelae of *Borrelia burgdorferi*.^{7,8} Persistence or recurrence of symptoms indistinguishable from late Lyme disease, that cause significant reduction in quality of life, have been documented post treatment with appropriate antibiotic given according to these Guidelines.^{9,10,11} The Guidelines use CDC surveillance criteria for Lyme disease to diagnose late Lyme disease and by default use the same criteria to diagnose a post-Lyme disease syndrome. [Discussed in this chapter.]
4. Without the tools to establish active infection, these guidelines put patients at risk of being misdiagnosed, provided palliative medications for symptoms of unknown origin and subsequent progression of Late Lyme disease. [Discussed in this chapter.]
5. Response of Lyme patients to the same therapy is different patient to patient, confirming that Lyme patients exhibit Heterogeneity of Treatment Effects (HTE). As a result misinterpretation and generalization of clinical data leads to the guidelines discouraging clinicians to make decisions based on individual patient clinical and laboratory data. This leads to misapplication of Evidence based medicine and limitation of consideration of pathophysiology in individual patients. [Discussed in this chapter.]

Introduction

Since the discovery of the spirochete that causes Lyme disease, researchers have sought to understand the pathophysiology of Lyme disease. With the confirmation of a bacterial etiology, researchers have directed their efforts toward effecting a cure. Early studies observed heterogeneity in the patient course, and a wide clinical spectrum in the disease.^{12,13,14,15,16,17} Later studies required more rigid enrollment criteria, using CDC surveillance criteria for Lyme disease to select patients (Appendix 1)¹⁸. This reduced heterogeneity in the studies, but resulted in excluding groups of patients, with active Lyme disease from formal study.^{19,20,21,22,23,24,25,26} Seven of these later studies are cited by the IDSA as supportive of post-Lyme disease syndrome.

Early studies established subgroups of patients and observed that after 2-4 weeks of antibacterial therapy from the penicillin, tetracycline or cephalosporin class, partial response or relapse (PR/F) was 10-61%. Conclusions in early studies noted that subgroups with more dissemination or indolent

course resulted in higher persistence or failure rate after treatment for Lyme disease. During these studies some patients relapsed and were re-treated and improved.^{27,28,29} The response to therapy and confirmation of disease by methodology beyond serology confirmed active disease in these subgroups. Sometimes the disease was seronegative.^{30,31} Early authors, such as Halperin, concluded: "*We conclude that chronic Lyme borreliosis is often associated with a mild low grade, reversible inflammatory process in the CNS that typically presents as subtle difficulty with concentration and memory.*"³²

Steiner in 2003 noted that "*with Lyme disease studies in general the patient group studied may be heterogeneous, as it might be expected in the absence of accepted diagnostic criteria or biological markers. Positive therapeutic findings may therefore have been masked by biological noise.*"³³ Later studies, perhaps in an effort to reduce heterogeneity in the Lyme subjects, restricted entrance criteria to patients who had objective manifestations as delineated in the CDC surveillance criteria for Lyme disease (Appendix 1)³⁴. The CDC has cautioned against using this surveillance criteria for clinical diagnosis: "*Comment: This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis.*" Because almost all studies after the mid 1990s required objective manifestations contained in the CDC Lyme surveillance criteria, subjects enrolled in these later studies represented the early and the early-disseminated Lyme disease subgroups. In spite of confining subjects to the most easily treated subgroups, these later studies revealed a partial response or failure rate of about 10-20%.^{35,36,37,38,39,40,41}

In spite of persistence post treatment for Lyme disease in a significant percentage of patients in later studies as in earlier studies, authors in later studies came to different conclusions than those of earlier studies. Conclusions in later studies suggest: 1) results regarding early or early-disseminated subgroups could be generalized to all Lyme patients in all subgroups, and 2) that the symptoms that persisted post treatment for early or early-disseminated Lyme disease were no more severe or frequent than symptoms in the general population and represented a post-infectious syndrome (post-Lyme disease syndrome). Good epidemiological studies have established that symptoms which occur post treatment for Lyme disease are more frequent than in the general population and significantly reduce quality of life in a substantial percentage of post treatment Lyme patients.^{42,43} Patients in earlier studies, some seronegative but with other objective evidence of active infection, and some with only clinical subjective symptoms, achieved improvement after further treatment with antibiotics.

Partial failure or recurrence of symptoms post 2-4 weeks of single agent antibiotic treatment for Lyme has been well established. The percentage of persistence or recurrence can be predicted from the subgroup.

Early Studies:

Post 2-4 weeks of treatment for Lyme disease with a single antibiotic in the tetracycline, penicillin or cephalosporin class, 10-61% of patients will recur or relapse with debilitating symptoms (PR/failure=partial response/failure), that are indistinguishable from late Lyme disease (Tables 2 and 3).^{44,45,46,47,48,49,50} In the best case when patients are treated early for Early (ELD) or Early disseminated Lyme disease (EDLD), 10-20% of these patients will experience partial response or failure (PR/F) and continue to have symptoms. These persistent symptoms represent significant morbidity in the population and need to be addressed. The Center for Disease Control estimates that reported cases of Lyme are under-reported by 6-12 times of actual cases.⁵¹ In 2007, 27444 cases of Lyme were reported in the United States.⁵² By CDC estimates conservatively, 164664 (27444*6) cases occurred in 2007. If 10-20% of those cases experience debilitating persistent or recurrent symptoms, 16,466 - 32,932 people will experience continued symptoms, indistinguishable from late Lyme disease.

Early studies used broad inclusion criteria for patient selection, often selecting patients referred to a University program for probable Lyme disease^{14,30,47} (see Table 1). Lyme disease was confirmed by a variety of tests including culture and PCR, serology; cell-mediated immunity; CSF parameters protein levels, cell counts, immunoglobulin synthesis; EMG, nerve biopsy; Neurospect scanning, MRI and others. Subgroups of Lyme patients with more dissemination or with evidence of central nervous system symptoms, (Encephalopathy or Paresis) had partial failure or recurrence rate from 15-71%, with the median of the subgroups shown at 51% (See Table 1). Patients with peripheral nervous system symptoms had between 32 and 56% partial response or failure. In the patients with evidence of more localized infection with radiculopathy or cranial neuritis patients had between 7 and 25% partial response or failure. More generalized infectious disease symptoms of fatigue or arthralgia resulted in between 28 and 40 percent partial response or failure. Groups with arthritis overall respond favorably and seem to be an outlier with partial response failure of about 0-20%,^{47,50,53} Researchers in these studies concluded that patients were heterogeneous and response was associated with acuteness, dissemination and duration of illness. Most noted that individual patients responded to increased antibiotic dose or longer courses or re-treatment in the study that at times were prolonged to achieve improvement^{47,53,54}. Halperin states: *"We conclude that chronic Lyme borreliosis is often associated with a mild, low grade reversible process. ...The reversibility of these lesions (MRI) ... all point to this being a true pathologic process associated with B burgdorferi infection."*⁵⁵

Table 1. Early Studies with Subgroup Analysis

Study	PR/F*	Overall PR/F*
Halperin, Volkman (1991) ¹⁴	AMR 7% AEML 50% IEML 64%	61%
Logigian, Steere (1990) ⁸	Poly neuro 32% Encephalopathy 36%	37%
Halperin, Heyes (1992) ⁴⁶	Encephalopathy 51%	51%
Luft (1988) ¹⁵	Arthritis 0% Periph neuro 10% Fatigue 33%	33%
Halperin, Luft (1989) ⁴⁸	Enceph 15% Periph nervous 56% Cranial Neuritis 0	44%
Halperin, Krupp (1990) ⁴⁹	Encephalopathy 50%	50%
Dattwyler (1988) ⁵⁰	Arthralgia 40% Arthritis 20% Meningitis 0% Encephalopathy 21.6% Fatigue 20.2%	29%

*Partial Response/Failure

A corollary of subgroup analysis is the observation that Lyme patients, treated promptly after appearance of symptoms are more likely than patients treated later in the course of the disease, to respond to treatment. Researchers involved with both early and late studies have observed that earlier treatment is desirable to increase the percentage response to treatment. Cameron has published a prospective study regarding the cost of delayed treatment.⁵⁶ He had 2 groups, Lyme patients who had delay in treatment (cases) and a group who had no delay (controls). He admitted a consecutive 100 patients. Cases were *"less likely to report a tickbite, more likely to have been treated with steroids and had significantly more failure than controls post the first treatment."* Shadick observed *"Persons who had persistent symptoms of Lyme disease at evaluation reported a longer duration of infection before receiving treatment than did those without symptoms."*⁵⁷ Donta noted that *"a history of a longer duration of symptoms before antibiotic treatment was associated with longer treatment times to achieve improvement or cure."*⁵⁸ Halperin, in a 1991 Neurology paper, gave enough information in 3 groups of patients to assess response based on duration of symptoms, combining all subgroups, i.e., those with early and those with late disseminated borreliosis (Table 4).¹⁴

Table 2. Cairns⁴² Studies Used in Meta-Analysis

Studies	Date Enroll	Requirement for entry	% PR/F
Shadick (1994) ⁵⁷	1991	EM or LL Or both (1990 CDC)	34%
Shadick (1999) ⁵⁹	1993-1996	Chart Review Fit CDC 1990 criteria	36%
Vazquez (2003) ⁶⁰	1984-1998	CDC surveillance case definition 1997 facial palsy	21%
Seltzer Shapiro (2000) ⁶¹	1984-1991	Random selection of cases in Ct b/t 1984-91 blinded review of charts matchCDC1997	20%
Wang (1998) ⁶²	1993-1995	MD/ NP dx of LD metCDC surveil 1997 serology,elisa WB	34%
LL late Lyme manifestation from CDC 1990 criteria all used standardized exam and or standardized instruments			

Table 3. IDSA Studies Cited to Support p-LDS

Studies	Date Enroll	Requirement for entry	% PR/F
Gerber Shapiro (1996) ¹⁹	Not known	EM 65.7 % ME/ED 27.9% LL, arthritis 6.4%	3.9%
Smith (2002) ²⁰	Not known	EM ,CC 100% ED 7.6%	10%
Luger Wormser (1995) ²¹	1990	EM PC	11%
Dattwyler et al. (1997) ²²	1990-1994	EM PC ED +2nd syx ME,PC,EDLD 95% Face palsied 7.1%	21%
Wormser (2003) ²⁴	1992-1994	EM PC	18.6%
Nowakowski (2003) ²⁵	1991-1994	EM PC CC	20% p226
Salazar Gerber (1993) ²⁶	1985-1990	EM PC	11%

EM Erythema migrans; ME Multiple erythema; EDLD early disseminated Lyme disease; LL Late Lyme arthritis; PC physician confirmed; CC culture confirmed EM

Table 4. Response according to duration of illness in Halperin (1991)¹⁴

All subgroups	% PR/F	
	<1 yr duration of symptoms	<2 duration of symptoms
Meningitis/Meningoradiculitis/Acute encephalomyelitis/Indolent Encephalomyelitis	22/30 N (27%)	23/37 N (62%)

Late Studies:

These studies consider only a more responsive subgroup, that of early or early-disseminated Lyme disease, because CDC surveillance criteria has been required for entrance to most studies after the mid 1990s.

More recent studies have concluded that after 2-4 weeks of single antibiotic treatment for early or early-disseminated Lyme disease, almost all patients are cured because the patients have no objective signs that match CDC Lyme surveillance criteria¹⁹⁻²⁶ (see Table 3). As noted above, the CDC advises against use of this surveillance criteria in clinical diagnosis: "*Comment: This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis*" (Appendix 1)¹⁸. Because the clearest objective sign of Lyme Disease is EM rash, the result of requiring Lyme subjects in studies to meet objective manifestations from the CDC surveillance criteria is that almost all recent studies have enrolled a single subgroup of early and early-disseminated Lyme patients.

Of seven studies cited by the IDSA as supportive of the existence of a non- infectious post-Lyme disease syndrome, six require physician-confirmed Erythema migrans (EM) rash (Table 4). The seventh had physician-confirmed EM rash in 83.6% of patients; 10 patients (7.4%) in these seven studies did not have EM. Because EM rash appears within a month of the tick bite, all patients in these seven studies were treated promptly, soon after onset of symptoms. In the Dattwyler study that had 7.4% non-EM subjects, patients were treated within 10 days of the symptoms of Lyme appearing.¹⁹⁻²⁶

The percentage of persistence of Late Lyme disease symptoms after treatment in the 7 studies was calculated from the data in the studies, ignoring different treatment groups (i.e. total number of evaluable patients at the last contact were counted in order to obtain the number of complete responders). The number of patients with remaining symptoms or recurring symptoms post treatment were counted as partial responders and divided by the total number of evaluable patients at the last contact. In spite of prompt treatment of early and early disseminated disease in 6/7 of these studies, 10-20% of these patients have persistent or recurrent symptoms (PR/F), which represents significant morbidity in the population and needs to be addressed. Gerber's study was not used here as this study used no standardized measures and no school records to evaluate persistent symptoms in children. They simply called parents to ask if the children with previous Lyme were well. The data provided led to an estimate of 3.9% but not enough information was given to be comfortable with the accuracy of that number.

Dattwyler, in one of the seven IDSA cited studies, concludes "*Among the patients whose **infections were cured**, 18 of 67 patients in the Ceftriaxone group (27%) reported one or more residual symptoms*

at the last follow-up visit, as did 10 of 71 patients in the Doxycycline group (14%, $P 0.05$)."³⁸ Cure cannot be proven by a serological test (see Steven Phillips, MD, "Active Infection: Clinical Definitions and Evidence of Persistence" in this document). In spite of prompt treatment of early and early-disseminated disease in these seven studies, 10-20% of these patients have persistent or recurrent symptoms (PR/F). IDSA guidelines conclude that these 10-20% of patients with partial response/failure after treatment for LD simply have aches and pains that are no more severe or numerous than in the general population without a history of Lyme disease (The Guidelines, p 1115).

The studies that the IDSA Guidelines use to support the diagnosis of a post infectious post-Lyme disease syndrome, rely on objective manifestations as listed in the CDC surveillance criteria for Lyme disease. Objective and subjective symptoms do not distinguish active infection from a post infectious state.

The IDSA guidelines use the CDC Lyme surveillance criteria to diagnose late Lyme disease and define those who fall outside the criteria as having post-Lyme disease syndrome. In addition to Erythema migrans (EM), the CDC surveillance description delineates a small number of objective manifestations of Late Lyme in the musculoskeletal, neurologic and cardiologic systems (Appendix 1)¹⁸. It is unclear why these "objective symptoms" were chosen and other documented, measurable, objective symptoms were not; i.e., Neurospect scanning^{63,64} MRI changes^{7,14}; Small Fiber Neuropathy as confirmed by nerve biopsy and sural nerve biopsy^{14,65}, CSF protein >45 ¹⁴, non-specific EKG changes especially new onset with other systems suggesting Lyme, sinus bradycardia without block, atrial arrhythmias;^{66,67} IBS, colitis, GERD, lymphocytic colitis,⁶⁸ Intestinal Pseudoobstruction.^{69,70,71} In many cases, these symptoms have been shown to improve with antiborrelia antibiotics^{7,10,64}.

In addition, the IDSA guidelines differentiate between objective and subjective symptoms, implying subjective symptoms alone indicate a non-infectious condition, and qualify the patient for a post-Lyme disease syndrome diagnosis. Subjective symptoms by default are those that escape measurement. Some measurements mentioned above could confirm these subjective symptoms as objective if allowed by the guidelines. However even if these tests were considered confirmatory of Lyme disease, some patients might not have access to the measurement for financial, insurance, or distance reasons. Other symptoms are only measurable at a population level or by measuring an individual response to treatment. In 1989 Halperin concluded that there are three different ways to confirm association between *Borrelia burgdorferi* infection and disease: "1) good epidemiological studies, 2) Demonstrate a local immune response to the causative organism and 3)...another approach is to detect a quantifiable abnormality that would not be expected to remit spontaneously and to assess its severity before and after specific antimicrobial therapy in a population receiving no other form of treatment."⁷² The guidelines consider post treatment Lyme patients who are symptomatic, but do not show objective manifestations as noted in the CDC surveillance criteria, to be cured. The guidelines state "In many patients post treatment symptoms appear to be more related to the aches

and pains of daily living rather than to ether Lyme or a tickborne coinfection." (Guidelines, p.1115)
 The evidence contradicts this statement.

Symptoms that persist post treatment of Lyme disease cause significant morbidity and are more frequent than in the general population.

Cameron and Cairns have presented population studies confirming that symptoms post treatment of LD are significant, with marked reduction in quality-of-life standardized scores, and that the frequency of significant symptoms in these patients is significantly higher than in the general population^{42,43}. Cameron has reviewed double-blind placebo controlled trials of post-treatment Lyme disease patients and found that the degree of morbidity is significantly higher in Lyme patients than in patients with congestive heart failure, diabetes, rheumatoid arthritis and a number of other conditions (Table 5)⁴³.

Table 5. Standardized SF-36 Scores for Specific Disease, Cameron (2008)⁴³

Condition	SF-36 PCS
Heart disease	39
Diabetes	42
Sciatica	46
Cancer not skin related	41
Depression	45
Osteoarthritis	39
Rheumatoid arthritis	42
Lyme Fallon	37.1
Lyme Klemperer 1	33
Lyme Klemperer 2	35.8

Cairns, in a meta-analysis of five population studies of patients post treatment of Lyme disease, confirmed significant increases in fatigue, neurocognitive problems and pain⁴² (see Table 2). Cairns concludes that: *"This meta-analysis provides strong evidence that some patients with LB have fatigue, musculoskeletal pain, and neurocognitive difficulties that may last for years despite antibiotic treatment."* The authors of the IDSA guidelines dispute this meta-analysis, stating that the studies are too old and therefore do not have well characterized Lyme patients, and that the meta-analysis may suffer from recall bias⁴² (Table 3). The guidelines cite seven studies (see Table 3) as contradicting the Cairns meta-analysis and confirming that post treatment Lyme patients do not have more than *"aches and pains of daily living"* (The Guidelines, p. 1115).

These seven studies are considered more reliable by the IDSA guidelines because the guidelines state: *"Subjects in the prospective studies were well characterized. Most had localized or disseminated early Lyme disease associated with Erythema migrans (the most common presentation of definite B.*

burgdorferi infection and were promptly treated with appropriate antibiotic regimens" (The Guidelines, p. 1116). These are the aforementioned studies in Table 3. The implication is that these well-defined patients, who are promptly treated and selected according to CDC surveillance criteria, better characterize all Lyme patients than the five studies analyzed in the meta-analysis. These seven studies cited by the IDSA provide results that do not contradict the Cairns analysis and, in fact, confirm that 10-20% of patients have partial response/failure after treatment with 2-4 weeks of a single antibiotic for Lyme disease (see Table 3).

The evidence indicates that the meta-analysis uses data that is published at about the same time as the seven IDSA cited studies, with patient enrollment over almost the exact same years as the seven cited IDSA studies (see Tables 2 and 3)^{19-22,24-26,52,54-57}. In addition, the Cairns meta-analysis excluded studies that did not carefully confirm Lyme disease in the subjects; four out of five studies required CDC surveillance criteria to be met by chart review, the fifth, Seltzer's, did not, but research assistants confirmed independently that the subjects met criteria for a diagnosis of Lyme disease, and the subjects were taken from reported cases in Connecticut⁶¹.

Three out of five studies in the meta-analysis had physicians examine patients for objective signs of Lyme^{73,74,75}. Four out of five studies in the meta-analysis used standardized instruments to measure symptoms and symptom severity^{61,62,73-75}. Finally, IDSA guidelines suggest that Shadick's study suffers from recall bias as a possible confounder in the meta-analysis. In a letter, Shadick and Logigian presented the statistics from their study to confirm that recall bias is not in their data, as they allowed for it in the statistics.⁷⁶

When the meta-analysis statistics are applied to the reported incidence of Lyme disease by the CDC, Shapiro, Wormser and Dattwyler noted in a letter that: *"thus more than 30% of adults after treatment for Lyme disease could be regarded as having post-Lyme disease syndrome or post treatment Lyme disease."*⁷⁷ (p 1437, 2nd para). Shapiro et al. used this statistic to contest the meta-analysis, stating it was too high an incidence of post-treated Lyme symptoms. But as noted above, the incidence of symptoms post treatment for Lyme disease varies between 10 and 61%. The studies used in the meta-analysis and the Shapiro letter confirm that approximately 30% of patients treated with 2-4 weeks of single antibiotic for Lyme disease, will persist or recur with significant symptoms that greatly reduce quality of life scores on standardized instrument measures.^{57,59,60,61,62}

According to the Center for disease control, thirty-two percent of Lyme patients do not get an EM rash.⁷⁸

The later studies, or those with more restrictive entrance criteria, studied only one to two subgroups of Lyme patients, groups with physician confirmed Erythema migrans (EM) rash or early-disseminated Lyme disease, as evidenced by multiple Erythema migrans or facial palsy. EM rash usually develops within a month of a tick bite, resulting in prompt treatment after appearance of symptoms of the disease (no delay) and treatment of early, no dissemination or minimally

disseminated Lyme disease. i.e. the studies that require EM for admission are studying 68% of the patients who contract Lyme disease. What can be concluded from these seven studies cited in the guidelines is this: if the Lyme patient is identified early, is among the 68% of Lyme patients with EM rash, and is treated for a duration of 14 to 28 days with Doxycycline, Ceftriaxone, Cefuroxime or Amoxicillin, that patient will very rarely have recurrence of the rash as stated in the guidelines. *"On the basis of numerous studies of patients with Erythema migrans, it can be expected that few—if any—patients who are compliant with antibiotic therapy will have persistence or recurrence of the skin lesion. A rare patient, however, will develop an objective extracutaneous manifestation of Lyme disease, such as a new seventh nerve palsy or meningitis [138, 142]"* (p. 1114). The guidelines are somewhat misleading in this statement as the concern is not the skin lesion, which spontaneously remits; the concern is the 10-20% partial response or failure in cardiologic, neurologic, neurocognitive, or neuropsychiatric systems. As noted above this represents a large number of patients, as the CDC estimates that actual incidence of Lyme disease is 6-12 times that reported. Again the 2007 reportable cases would estimate 27,444 persistently symptomatic Lyme patients post treatment if 10% were to remain ill. Actual persistence / failure rate is higher than 10-20%, since these studies represent only 68% of patients at best. 32% of reported cases of Lyme disease to CDC do not have the Erythema migrans rash. In these guidelines this fact results in 2 groups of patients not being studied:

1. Those newly diagnosed and never treated months to years after symptoms started
2. Those diagnosed previously who were treated and responded partially or failed 2-4 weeks of antibiotics or those that relapsed later.

Later studies exclude some patient subgroups. These excluded subgroups improved with antibiotic treatment in early studies.

Logigian enrolled a group of late Neuroborreliosis patients in studies in 1990 and again in 1999. The earlier study admitted patients with clinical Neuroborreliosis (encephalopathy, increased CSF protein levels, polyneuropathy with radicular pain, some positive on MRI and EMG)^{8,64}. The later study excluded patients who did not meet CDC Lyme surveillance criteria: seven patients who met the clinical and laboratory criteria for Lyme disease were excluded because the particular neuropsych testing applied did not show objective evidence of cognitive problems, or because of lack of laboratory evidence of Bb infection. Five patients were not enrolled because they previously had one month of Ceftriaxone. In 1999 Logigian noted: *"The most common symptom of Lyme encephalopathy was memory difficulty, usually requiring patients to compensate with new behaviors such as list making, relying on spouses, or making greater efforts to concentrate. Obvious memory loss on bedside testing was present in only 1."* In both studies patients improved. Some patients without CDC objective criteria improved in the 1990 study.

Logigian did not admit patients in the 1999 study, who previously had received one month of Ceftriaxone. Oksi in 2007 undertook a trial with patients with disseminated Neuroborreliosis.⁷⁹

Some of these patients had recurrence post previous treatment, and some had new onset of Neuroborreliosis. Oksi noted that all Neuroborreliosis patients were treated with three weeks of Ceftriaxone, because [regardless of first treatment or recurrence]: "... *earlier evidence of the efficacy of CRO [Ceftriaxone] treatment is so favorable that PBO [placebo] control of the initial treatment would have been unethical.*" In all groups improvement after Ceftriaxone was 79% (i.e. 21% PR/F). Duration of illness was variable as, Oksi noted, sometimes development was so indolent it was difficult to tell duration. Oksi 2007 went on to treat with amoxicillin vs. placebo (see below section).

Placebo controlled double blind re-treatment trials in symptomatic patients post-initial treatment of Lyme disease suggest evidence for improvement with re-treatment and evidence against. All of the trials are small, with limited power and should be considered pilot studies.

Double blind, placebo-controlled re-treatment studies undertaken in post-treated Lyme disease patients also clarify that some patients post treated for Lyme disease, who have fatigue and neurocognitive compromise, improve upon re-treatment with 3-10 weeks of Ceftriaxone. Krupp and Fallon found that patients re-treated for partial response/failure improved in parameters of fatigue, pain and functionality.^{10,11} Both researchers found that neurocognitive compromise did not improve, although Fallon found that patients improved at the three-month measurement, but did not sustain improvement at the six-month measurement.

Oksi did a partial re-treatment trial and partial new patients. As noted above all patients received Ceftriaxone for 3 weeks and improvement was 79% for both new onset borreliosis and recurrence or persistence (PR/F 21%). The 2007 Oksi study was designed to test if longer treatment after 3 weeks of IV Ceftriaxone resulted in improvement of outcome. In this study, 10 weeks of further treatment treatment with oral Amoxicillin (1500mg a day) did not further improve outcome.

The IDSA guidelines favor Klempner's trial, which found no improvement with re-treatment. This trial has statistical limitations, making it difficult to generalize the outcome to all post treatment Lyme patients.^{9,80,81} These three trials represent a heterogeneous group of post-treatment Lyme patients. Two showed improvement with treatment¹⁰⁻¹¹; one did not⁹. Although not all parameters in Krupp and Fallon sustained improvement, improvement in fatigue is a highly significant outcome, often allowing disabled patients to return to work and family life. Due to the power of these three studies and the number of subjects, the studies should be considered pilot studies. Further investigations are needed to clarify how to identify this disease or its recurrence early, and how to treat it adequately, both when an infection is present and when it is past.

The significant morbidity in the post-treated Lyme patient will result in risk of polypharmacy to improve quality of life. Until studies confirm active versus post infectious etiologies, the clinician should be encouraged to individualize treatment.

Because of the significant morbidity in Lyme patients who have partial response/failure to treatment as noted above, palliative treatments to relieve pain and fatigue, insomnia, mood disorders resulting from disease or persistent illness will be offered to these patients. Analgesics, neuropsychiatric modulators, hypnotics, antiepileptic medications and others are now used for post-treatment Lyme patients. These medications have potential side effects, and if these drugs are provided palliatively, in the context of an active bacterial infection, there is potential harm to the patient and an unacceptable risk. Chronic ingestion of NSAIDs, aspirin and Tylenol over 10 years increases risk of kidney failure.⁸² Ulcers and gastrointestinal bleeding incidence increases with NSAIDs and aspirin, and newer data implicates these drugs in cardiovascular events.⁸³ Opiates change reaction time and driving safety, as do hypnotics. Antidepressants have been associated with allergy, serotonin syndrome and chemical hepatitis.

Patients with inflammatory neurological or rheumatologic symptoms with unknown etiology will often receive steroids. This is contraindicated in active bacterial infection and in Borreliosis. Again researchers note *"...considerable support to the hypothesis that the cognitive difficulties described in our patients reflect active CSF disease. ...Since we found NO evidence of other immune abnormalities in the spinal fluid, and the patients symptoms generally improved with antibiotic treatment this finding is more likely due to the presence of active CNS infection"*.⁸⁴ Several authors have observed that response to antibiotic treatment is poor in patients treated with antibiotics^{83,85,86}. Animal studies in primates and dogs also lend evidence to a contraindication of steroid in borreliosis.^{87,88}

Lyme patients represent a case of Heterogeneity of Treatment Effect (HTE). In conditions in which response to the same treatment is different in different patients, guidelines need to emphasize the importance of clinical judgment in individual cases.

Kravitz notes that the need for individual therapy is related to the heterogeneity of treatment effects (HTE). HTE is present when the same treatment produces different results in different patients.⁸⁹ Early and late studies presented in this paper confirm that in controlled studies different Lyme patients have different responses to a standardized treatment^{53,77} (see Tables 1,2,3). In the presence of HTE clinical trials often result in underestimating treatment effects²³. Clinical trials, by convenience narrow inclusion criteria⁸⁹. This is what has occurred in Lyme disease. Kravitz notes that in the presence of HTE, in clinical trials "treatment effects can be dramatically underestimated and even assiduous investigators can be misled into thinking that their results are more generalizable than they actually are"^{9,80-81,89}. The heterogeneity of response to the same therapy in Lyme patients is apparent in the literature. The current understanding of Evidence Based Medicine applies average response in clinical trials to all patients with a given condition. Application of the average in the case of Lyme disease and other diseases with HTE, will not apply to part of the population and: "misapplying averages can cause harm by giving patients treatment they don't need or denying patients treatment that would help." Kravitz notes that this misapplying averages can: "take an especially perilous turn if practice guidelines inadvertently encourage physicians to

discount difference between their patients (and settings) and those studied in the primary trials⁸⁹. Until clinical trials can clarify subgroups of Lyme patients and the subgroup response to treatment, guidelines need to help clinicians make individual decisions, based on available data.

A model of differential diagnosis may be found in some literature, that may help the clinician individualize patient therapy.

Table 6. Characteristics of patients with culture/ PCR proven relapse of Lyme disease⁷

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13
History previous EM	+	+	-	+	+	-	-	-	-	-	-	-	+
Arthritis	-	-	-	-	-	-	+	-	-	-	-	-	-
Arthralgia	-	+	-	+	+	+	+	-	+	-	+	-	+
Myalgia or Fibromyalgia	+	+	-	-	+	+	+	-	+	-	+	-	+
Headache	-	-	-	-	+	+	+	-	+	-	-	-	-
Dizziness	-	-	-	-	-	+	+	+	+	+	-	+	-
Meningitis	-	-	-	-	+	-	-	-	+	+	-	-	-
Radiculitis or neuritis	-	+	+	-	-	-	-	-	-	-	-	-	-
Neuropathy	+	+	+	-	-	-	-	-	+	-	+	-	-
Carpal tunnel syn	+	+	-	-	-	-	-	-	-	-	-	-	-
Diplopia	-	-	-	-	-	-	-	-	+	-	-	-	-
Epilepsy	-	-	-	-	-	-	-	-	+	-	-	-	-
Encephalitis	-	-	-	-	-	-	-	+	-	-	-	-	-
Transient hemiparasis	-	-	+	-	-	-	-	-	-	-	-	-	-
Febris	+	+	+	-	+	-	-	-	-	+	-	-	-
Hepatopathy	+	-	-	-	-	-	-	-	-	-	-	+	-
Chorioretinitis uveitis	-	-	-	-	-	-	-	-	-	-	-	+	-
Pleuritis/ pericarditis	-	-	-	-	-	+	-	+	-	-	-	-	-
Vasculitis (by biopsy)	+	-	-	-	-	-	-	+	-	+	-	-	-
Abnormal MRI	+	0	+	0	0	+	-	+	-	+	-	0	-

Oksi et al *Annals of Med* 1999. 31:225-232

In 1999, Oksi studied 13/32 patients who had clinical relapse, drawn from a previously treated cohort of 165 well-defined Lyme patients with serologically positive Borreliosis (32/165, 19.4%). 13 were chosen because they all had positive PCR or culture positive Borreliosis. 5/13 were seronegative; 9/13 of these patients improved with re-treatment. Table 4 lists Oksi's characteristics of patients⁷. Patient 4, 7, 8, and 13 all had only subjective symptoms. Some of these patients improved with antibiotic treatment. Some of the patients with objective symptoms improve with antibiotic treatment.

The Oksi methodology of displaying individual patients characteristics points out that subjective and objective symptoms overlap (see Table 6). He also charts the results of testing from MRI to culture. Oksi notes "*Randomized studies with long follow-ups are warranted to find out the most successful regimens and adequate durations of antibiotic treatments for disseminated LD*"⁷. Halperin also noted that subjective symptoms improved with treatment: "*we have shown that the frequent occurrence of mild sensory symptoms, such as intermittent limb paresthesias, reflects the presence of low-grade distal axonal damage in the peripheral nerves. Similarly using sensitive neuropsychological methods, we have shown that the mild confusional state described by many of these patients does represent a mild encephalopathy. Our preliminary MRI and CSF studies suggest that this encephalopathy is due to a low grade encephalitis. Most important, we have been able to demonstrate that the abnormalities of both the peripheral and central nervous systems appear to be reversible with appropriate antimicrobial therapy*"⁸⁴.

Conclusions

Putting post-treatment Lyme patients, whose symptoms fail to match CDC surveillance criteria into a post-infectious Lyme disease syndrome category, puts them at risk. Because we have no marker for a post-Lyme disease syndrome, and because we have no measure to exclude active infection, the patients in this group that have active infection, may not be given antibiotics to reduce pathogen load. They will likely be given palliative therapy with its inherent risks. This bacterial infection can be hard to find: "*Particularly puzzling has been the observations that organisms are extremely difficult to find in infected tissue. However, in many instances continued infection appears to be essential for symptoms to persist, no matter how small the number of organisms, as antimicrobial therapy is generally followed by clinical improvement.*"⁴⁶

The morbidity of the population that persists or recurs with symptoms of post-Lyme disease is significant and is a public health problem. Guidelines need to provide state-of-the-art information and clarify the known and the unknown data to the clinician, in this case the primary care doctor, who is likely to see the Lyme patient first.

- 1) A clear clinical picture of the multi-systemic presentation of this disease would allow the primary care doctor to put Lyme disease in a differential diagnosis during assessment of a chief complaint

and would aid in early treatment of early Lyme disease. This is particularly needed in the 32% of patients who do not see an EM rash, and who will often assume they have a "flu syndrome," as will the busy primary care doctor, if guidelines lead him or her to believe Lyme disease is not a problem in his or her vicinity.

2) Since currently available testing cannot prove existence of a post-Lyme disease syndrome, basing treatment recommendations on this abstract concept will result in patients receiving palliative care, with the subsequent risks of polypharmacy. In some cases these patients will have active infection and will not be provided with the antimicrobials needed to cure or improve the clinical picture.

3) Research should continue posing hypotheses that can lead to an answer to:

- a) Given the subgroup of Lyme patient, what is the best antibiotic protocol. Though not in this chapter, these subgroups include Lyme and coinfection patients, as well as the patient missed and not treated for months or years, the relapsed patient, the patient with severe neurological disease, the patient with diffuse indolent multi-systemic disease and so on.
- b) Can one measure permanent neurological damage?
- c) Is there an autoimmune *Borrelia burgdorferi* triggered disease in some patients? Can we identify a specific process if it exists?

Appendix 1: CDC Surveillance Description for Lyme Disease

Clinical description

A systemic, tickborne disease with protean manifestations, including dermatologic, rheumatologic, neurologic, and cardiac abnormalities. The best clinical marker for the disease is the initial skin lesion (i.e., Erythema migrans {EM}) that occurs in 60%-80% of patients.

Laboratory criteria for diagnosis

Isolation of *Borrelia burgdorferi* from a clinical specimen or

- **Demonstration of diagnostic immunoglobulin M or immunoglobulin G antibodies to *B. burgdorferi* in serum or cerebrospinal fluid (CSF). A two-test approach using a sensitive enzyme immunoassay or immunofluorescence antibody followed by Western blot is recommended (7).**

Case classification

Confirmed: a) a case with EM or b) a case with at least one late manifestation (as defined below) that is laboratory confirmed.

Comment:

This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis.

Definition of terms used in the clinical description and case definition:

Erythema migrans. For purposes of surveillance, EM is defined as a skin lesion that typically begins as a red macule or papule and expands over a period of days to weeks to form a large round lesion, often with partial central clearing. A single primary lesion must reach greater than or equal to 5 cm in size. Secondary lesions also may occur. Annular Erythematous lesions occurring within several hours of a tick bite represent hypersensitivity reactions and do not qualify as EM. For most patients, the expanding EM lesion is accompanied by other acute symptoms, particularly fatigue, fever, headache, mildly stiff neck, arthralgia, or myalgia. These symptoms are typically intermittent. The diagnosis of EM must be made by a physician.

Laboratory confirmation is recommended for persons with no known exposure.

Late manifestations. *Late manifestations include any of the following when an alternate explanation is not found:*

Musculoskeletal system. Recurrent, brief attacks (weeks or months) of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints. Manifestations not considered as criteria for diagnosis include chronic progressive arthritis not preceded by brief attacks and chronic symmetrical polyarthritis. Additionally, arthralgia, myalgia, or fibromyalgia syndromes alone are not criteria for musculoskeletal involvement.

Nervous system. Any of the following, alone or in combination: lymphocytic meningitis; cranial neuritis, particularly facial palsy (may be bilateral); radiculoneuropathy; or, rarely, encephalomyelitis. Encephalomyelitis must be confirmed by demonstration of antibody production against *B. burgdorferi* in the CSF, evidenced by a higher titer of antibody in CSF than in serum. Headache, fatigue, paresthesia, or mildly stiff neck alone are not criteria for neurologic involvement.














Cardiovascular system. Acute onset of high-grade (2nd-degree or 3rd-degree) atrioventricular conduction defects that resolve in days to weeks and are sometimes associated with myocarditis.

Palpitations, bradycardia, bundle branch block, or myocarditis alone are not criteria for cardiovascular involvement.














Exposure. Exposure is defined as having been (less than or equal to 30 days before onset of EM) in wooded, brushy, or grassy areas (i.e., potential tick habitats) in a county in which Lyme disease is endemic. A history of tick bite is not required.

Disease endemic to county. A county in which Lyme disease is endemic is one in which at least two confirmed cases have been previously acquired or in which established populations of a known tick vector are infected with *B. burgdorferi*.

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