UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
TEXARKANA DIVISION

LISA TORREY, et al.,	§	
	§	
Plaintiffs	§	Civil Action No. 5:17-cv-00190-RWS
	§	
v.	§	
	§	
INFECTIOUS DISEASES SOCIETY OF AMERICA, et al.,	§	JURY TRIAL DEMANDED
	§	
	§	
Defendants	§	

MOTION OF ANTHEM, INC., THE INFECTIOUS DISEASES SOCIETY OF AMERICA, AND THE DOCTOR DEFENDANTS FOR INDEPENDENT MEDICAL EXAMINATIONS OF THOSE PLAINTIFFS WHO CLAIM TO HAVE LYME DISEASE

Defendants Anthem, Inc., the Infectious Diseases Society of America, and the Doctor Defendants[1] (herein, "Moving Defendants") file this motion pursuant to Fed. R. Civ. P. 35 requesting that the Court order the Plaintiffs who allege that they have (or have had) Lyme disease—including so-called "chronic Lyme disease" (the "Lyme Claimants")[2]—to submit to an independent medical examination by infectious disease specialist Dr. Dina Torten.[3]

I. Background

The Lyme Claimants allege that they have suffered debilitating injuries because they have been denied appropriate medical treatments for so-called "chronic Lyme disease," allegedly due to an unlawful conspiracy among the Defendants to monopolize the treatment of Lyme disease. *See, e.g.*, Docket No. 1 at 36 ¶¶ 131-32.[4] Nearly all of the Lyme Claimants allege that they still suffer from the disease today and many claim that they are currently disabled or otherwise unable

[1] The individual doctors named in this suit are: Dr. Gary Wormser, Dr. Raymond J. Dattwyler, Dr. Eugene Shapiro, Dr. John J. Halperin, Dr. Leonard Sigal, and Dr. Allen Steere (collectively, the "Doctor Defendants"). One additional defendant doctor, Dr. Robert Nadelman, died during the pendency of this action and was dismissed.

[2] Lisa Torrey, Amy Hanneken, Jane Powell, Carol Fisch, Christopher Valerio, Steven Ward, Randy Sykes, Brienna Reed, Rosetta Fuller, Adriana Monteiro Moreira, Jessica Mckinnie, Kristine Woodard, Dr. Michael Fundenberger, Gayle Clarke, Allison Lynn Caruana, Chloe Lohmeyer, Max Shindler, Tawnya Dawn Smith, Monet Pitre, Ashleigh Peacher, Alarie Bowerman, Elisa Bowerman, Emory Bowerman, and Anais Bowerman. Those Plaintiffs who are suing solely on behalf of an estate, or the next friend, of another person are excluded from this motion.

[3] An abbreviated copy of Dr. Torten's CV is attached to this motion as Exhibit A and a list of times that are available for scheduling the IMEs is attached as Exhibit B. Moving Defendants have filed an abbreviated copy of Dr. Torten's CV to comply with the Court's standing order regarding attachments to discovery motions but a full version is available upon request.

[4] Plaintiffs pled RICO claims as well in their Complaint. On September 27, 2018, the Court dismissed Plaintiffs' RICO and fraudulent concealment claims and gave Plaintiffs 30 days to replead those claims. Plaintiffs have not attempted to replead those claims but instead filed a motion asking for more time and more discovery, thereby admitting that they lack the facts necessary to support their original RICO and fraudulent concealment claims.

to work due to their illness. Docket No. 1 at 36 ¶¶ 132-140. The Lyme Claimants allege that they have been injured – and hence have standing to bring their claims here – because

> they were forced to pay for their *treatments*, were forced to pay all expenses associated with *treating their Lyme disease*, were forced to travel long distances for *treatment*, were forced to try to find doctors who would *treat* them, and were unable to work or earn money because of their *debilitating illness*. Further, because Plaintiffs were not timely diagnosed or treated, they now *suffer long-term complications and are forced to continue to pay future medical costs for treatment* and out-of-pocket expenses to *receive this treatment*.

See, e.g., Docket No. 1 at 44 ¶147 (emphasis added).

On January 29, 2019, the Lyme Claimants designated dozens of "physicians, medical providers, nurses, aides, lab technicians, physician's assistants, radiologists, and other providers who participated in the care and treatment of Plaintiffs" to potentially testify as experts regarding the Lyme Claimants' medical conditions and ongoing treatment needs. *See* Declaration of Michael Tuteur at ¶3, attached as Exhibit C.

As their Complaint and Designation of Experts make manifest, the Lyme Claimants' medical conditions, and in particular whether they currently or have ever suffered from Lyme disease, the severity of their symptoms, and whether those symptoms are attributable to Lyme disease or some other cause, are at the heart of this case and were put into controversy by the Lyme Claimants themselves. Well-prepared, peer-reviewed studies have established that as many as 88% of patients who have been told they have "chronic Lyme disease" either do not have – or, in many cases, *never* have had – Lyme disease in any form**.** *See, e.g.,* P. Lantos, *Chronic Lyme Disease,* Infectious Disease Clinics of N. America, Vol. 29:2, 325-340 (2015), a copy of this article is attached in the Appendix of Non-Legal Authorities.[5] Thus, a fundamental issue in this case for

[5] As discussed in Lantos, *supra*, "[m]any patients referred for Lyme disease are ultimately found to have a rheumatologic or neurologic diagnosis. Rheumatologic diagnoses commonly misdiagnosed as Lyme disease include osteoarthritis, rheumatoid arthritis, degenerative diseases

each Lyme Claimant will be whether the Lyme Claimant actually contracted Lyme disease at any time or (at a minimum) presently has an active Lyme disease infection that could be treated effectively with antibiotics now. Because the Lyme Claimants have chosen to place their medical conditions squarely "in controversy," Defendants must be afforded an opportunity to test their claims. This is precisely the purpose of Rule 35. *See, e.g., Ellis v. Union Pacific Railroad Company,* No. 9:07-cv-231, 2008 WL 11344788, *2 (E.D. Tex. Feb. 20, 2008) ("good cause for an independent medical examination exists when the plaintiff has placed his medical condition at issue"); *Gonzalez v. Wal-Mart Stores Texas, LLC,* No. 1:14-cv-402, 2015 WL 11023494, *1 (E.D. Tex. June 5, 2015) ("Because Wal-Mart disputes the nature and origin of [Plaintiff's] injuries, good cause exists for compelling a medical exam").

Moving Defendants have identified a specialist in infectious diseases, Dr. Dina Torten, M.D., who has an office within the Eastern District of Texas, at 4461 Coit Road, Pavilion 2, Suite 409, Frisco, TX 75035.[6] Moving Defendants request that Dr. Torten be authorized to perform an independent medical examination (IME) to examine the Lyme Claimants and determine whether

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of the spine, and spondyloarthropathies. Some patients are found to have neurologic diseases, including multiple sclerosis, demyelinating diseases, amyotrophic lateral sclerosis, neuropathies, and dementia." *Id.* at App. 3 (footnotes omitted). The National Institutes of Health agree: "The term 'chronic Lyme disease' (CLD) has been used to describe people with different illnesses. While the term is sometimes used to describe illness in patients with Lyme disease, it has also been used to describe symptoms in people who have no clinical or diagnostic evidence of a current or past infection with B. burgdorferi [the bacteria that causes Lyme disease]." *Chronic Lyme Disease,* found at https://www.niaid.nih.gov/diseases-conditions/chronic-lyme-disease (last viewed February 12, 2019), a copy of this article is attached in the Appendix of Non-Legal Authorities.

[6] Under settled jurisprudence, IMEs under Rule 35 are to be performed in the forum chosen by plaintiffs to bring their lawsuit. *Ornelas v. S. Tire Mart, LLC,* 292 F.R.D. 388, 399–400 (S.D. Tex. 2013). As a result, Moving Defendants have identified an infectious disease specialist within the Eastern District of Texas to perform the IMEs. Counsel for Anthem has also informed counsel for the Lyme Claimants that, if the Lyme Claimants prefer (and this Court allows), Moving Defendants are willing to have the IMEs performed by a specialist physician who practices closer to each Lyme Claimant's residence rather than in this judicial district. Counsel for the Lyme Claimants have to date been unwilling to discuss either possibility.

they have, or have had, Lyme disease, identify their symptoms, recommend any further testing required in order to determine whether they are currently suffering from Lyme disease, and assess the treatment they have received to date. At a minimum, Moving Defendants expect—and ask this Court to allow—the examiner to take a complete history and physical examination of the individual plaintiff, including a full review of systems, if she believes they are necessary to assess whether the Lyme Claimant is currently suffering from Lyme disease or has had Lyme disease in the past. Dr. Torten will request that, before appearing for the IME, each Lyme Claimant must submit blood and urine samples for testing relevant to Lyme disease – specifically an ELISA and Western Blot test for Lyme disease – to a recognized national FDA-approved testing lab (such as LabCorp or Quest or another lab approved by Dr. Torten). Moving Defendants request that Dr. Torten be permitted to request other tests she deems appropriate following the exam if necessary to determine whether the Lyme Claimant is currently suffering from Lyme disease or had Lyme disease in the past.[7]

Moving Defendants conferred with Plaintiffs' counsel regarding the IMEs and Plaintiffs have refused to consent to this motion in any form. *See* Exhibit C ¶¶4 – 5 and Certificate of Conference. Accordingly, the Moving Defendants request that the Court enter an Order pursuant to Rule 35 requiring the Lyme Claimants to submit to a medical examination performed by Dr. Torten**,** involving the tests and examinations described above. Moving Defendants further request

[7] Counsel for Moving Defendants has communicated with Dr. Torten only to determine whether she would be willing and able to perform the IMEs discussed herein; and to learn from Dr. Torten the sort of examinations and tests she would need to perform this task. At Dr. Torten's request, she also has been given a copy of the Original Complaint and the Defendants' Answers thereto. Counsel for Moving Defendants has not suggested the nature or scope of the examinations that Dr. Torten would perform, instead leaving that to the professional judgment of Dr. Torten with respect to each Lyme Claimant.

that all IMEs be completed by April 30, 2019. Specifically, Dr. Torten is available to perform the IMEs on the dates and times listed on the attached Exhibit B.[8]

II. Rule 35 Standard

Rule 35(a) of the Federal Rules of Civil Procedure empowers a court to order an independent medical examination of a party when the party's physical or mental condition is "in controversy" and good cause is shown. *See Acosta v. Tenneco Oil, Co.*, 913 F.2d 205, 208 (5th Cir. 1990). "Rule 35(a) should be construed liberally in favor of granting discovery." *Avance v. Kerr-McGee Chem. LLC*, 5:04CV209, 2005 WL 5315651, at *2 (E.D. Tex. Dec. 9, 2005) (internal citations omitted). A party seeking an IME under Rule 35 can make its showing through the pleadings, affidavits or other evidence. *McCormick v. Payne*, 4:15-CV-809, 2016 WL 3124624, at *1 (E.D. Tex. June 3, 2016) (internal citations omitted).

When, as here, plaintiffs place their "mental or physical condition in controversy through representations made during the course of litigation" the pleadings alone can be sufficient to establish the "in controversy" requirement. *Ornelas v. S. Tire Mart, LLC*, 292 F.R.D. 388, 391 (S.D. Tex. 2013). "Good cause" requires a showing of specific facts that demonstrate the need for the information sought and lack of means for obtaining it elsewhere. *McCormick*, 2016 WL 3124624 at *2. However, when plaintiffs put their mental or physical condition in controversy and intend to rely on expert testimony to establish that condition and the injuries that allegedly resulted from it, the defendant shows good cause for a Rule 35 exam. *Graham v. Dyncorp Int'l LLC*, 4:13-CV-782-Y, 2014 WL 11485247, at *3 (N.D. Tex. Dec. 30, 2014).

[8] Exhibit B contains Dr. Torten's availability between March 1, 2019 and the close of discovery. To the extent the Court allows the IMEs to occur after March 19, 2019, Moving Defendants will supplement the dates and times that Dr. Torten is available.

"A plaintiff may not avoid a Rule 35 examination simply on the grounds that other sources of information, such as medical reports and depositions of plaintiff's treating physicians, are available." *Ornelas v. S. Tire Mart, LLC*, 292 F.R.D. 388, 391–92 (S.D. Tex. 2013)

III. The Court should order independent medical examinations by Dr. Torten.

The Lyme Claimants put their medical conditions directly in controversy by filing the Original Complaint and alleging that they have suffered injuries directly related to Lyme disease and their inability—as a result of the Defendants' alleged Sherman Act conspiracy—to find long-term antibiotic treatment for their disease. Clearly, if the Lyme Claimants do *not* have Lyme disease—and never did—they have not suffered actual injuries that flow from the alleged conspiracy. Rather, whatever it may be that is otherwise causing the Lyme Claimants' symptoms, the existence *vel non* of the alleged conspiracy to deny so-called chronic Lyme patients long-term antibiotic care would have made no difference to these plaintiffs at all. *Ornelas v. S. Tire Mart, LLC*, 292 F.R.D. 388, 399–400 (S.D. Tex. 2013). Indeed, if the Lyme Claimants never suffered from "chronic Lyme disease," then they have suffered no injury (never mind an antitrust injury) and have no standing to further prosecute this suit. **(***See, e.g.,* Docket No. 114 at 15 (*citing Brunswick Corp. v. Pueblo Bowl–O–Mat, Inc.*, 429 U.S. 477, 488–89 (1977) ("Antitrust injury exists when (1) the injury was of the type antitrust laws were intended to prevent and (2) t*he injury "flows" from or was caused by the defendant's unlawful conduct*") (Emphasis added).)

Moving Defendants propose to use an expert physician in the field of infectious diseases, Dr. Torten, to examine the Lyme Claimants and determine whether they currently have, or previously have had, Lyme disease. The IMEs will assist this Court – and, if necessary, the jury – to determine whether all (or any) of the Plaintiffs have suffered injuries that are relevant to the allegations made in the Complaint.

IV. Conclusion

For the reasons set forth above, Moving Defendants respectfully request that the Court grant this motion, and order any Plaintiff who alleges that he or she currently has, or has had, Lyme disease to submit to an independent medical examination with Dr. Dina Torten, and that she be allowed to perform the examination and order the relevant tests as she deems appropriate in her professional judgment.

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ATTORNEYS FOR DEFENDANT ANTHEM, INC.

CERTIFICATE OF CONFERENCE

Counsel have complied with the meet and confer requirement in Local Rule CV-7(h). On December 28, 2018, Anthem's counsel sent an email to Plaintiffs' counsel regarding this request for independent medical examination. Plaintiffs' counsel did not respond. Accordingly, Anthem's counsel sent a follow-up email on January 10, 2019. By email later that day, Plaintiffs' counsel rejected any IME on the grounds that, "[w]hile there are a number of reasons and problems with your request, first and foremost this is not a personal injury case. Therefore IME's are no [*sic*] appropriate." On January 16, 2019, Michael Tuteur (as lead counsel for Anthem) and Tom Hetherington (as local counsel for Anthem) conducted a telephone conference with Gene Egdorf, counsel for Plaintiffs. Counsel for Plaintiffs stated that the call was unnecessary because the parties were at an impasse regarding the IME, that Plaintiffs would not consider an IME conducted by any physician who was not a member of ILADS, and that arranging examinations closer to the individual Plaintiffs' homes would not change Plaintiffs' position on the requested IMEs. Accordingly, the parties are at an impasse regarding this request for an IME and it must be submitted to the Court for resolution.

/s/ Michael J. Tuteur
Michael J. Tuteur

/s/ Thomas F.A. Hetherington
Thomas F.A. Hetherington

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the above and forgoing document has been served on February 14, 2019, to all counsel of record who are deemed to have consented to electronic service via the Court's CM/ECF system per local rule CV-5(a)(3).

/s/ Kimberly A. Klinsport
Kimberly A. Klinsport

4840-9252-9798.13

EXHIBIT A

Exhibit A

DINA N .TORTEN, MD

DFW INFECTIOUS DISEASES
4461 Coit Road, Suite 409, Frisco, Texas 75035

LANGUAGES

English, Spanish, Hebrew, French

MILITARY SERVICE

First Lieutenant, General Clinic and Emergency Field Medicine | Medical Service for the IDF
1985 – 1987

EDUCATION

Ben-Gurion University School of Medicine, Be'er Sheva University
1984 | MD (Six year Program)

POST GRADUATE TRAINING

Fellowship in Infectious Diseases | New York University
New York, NY **|** 1992 – 1994

Internship and Residency in Internal Medicine | New York Downtown Hospital (Beekman)
(Affiliated with NY University & Medical Center)
New York, NY **|** 1988 – 1991

Rotating Internship (Med, Surg, Peds, Ortho, and Derm.) | Sheba Medical Center
Tel Hashomer, Israel | 1984 – 1985

LICENSURE AND CERTIFICATION

Medical License | State of Texas | September 2007

Board Certified | Infectious Diseases (ABIM) | November 1996, Recertification 2007 and 2017

Board Certified | Internal Medicine (ABIM) | September 1991

Certificate of Israel Specialty Boards in Internal Medicine and in Infectious Diseases | February 1995

Medical License | State of New York | 1991

Federal Licensing Examination (FLEX) | 1990

Educational Commission for Foreign Medical Graduates (ECFMG) Certificate | 1985

Medical License | Israel | 1985

POSITIONS HELD

Infectious Disease Attending, Consultant [Private Practice] | DFW Infectious Disease | 2016 – present
4461 Coit Road, Suite 409, Frisco, Texas 75035

Infectious Disease Attending, Consultant [Private Practice] | ID Doctors PA | 2010 – 2016
One Medical Parkway, Suite 210, Dallas, Texas 75234

Infectious Disease Attending, Consultant [Private Practice] | Medical Edge Healthcare Group | 2007 - 2010
9229 LBJ Freeway, Dallas, TX 75243

Attending Physician, Infectious Disease Consultant | Kaplan Medical Center | 1998 – 2000 & 2002 – 2007
(Affiliated with Hebrew University Medical School - Jerusalem)
"Neve-Or" National AIDS Center (Clinical Immunology Dept.), Emergency Dept
Rehovot, Israel

Attending Physician, Infectious Diseases (HIV and HCV care) | Sheba Medical Center | 2000 – 2002
National Hemophilia Center & Infectious Diseases Unit (Including duties in IDF patient care units)
Tel Hashomer, Israel

Attending Physician | New York City Health & Hospitals Corporation (HHC) | 1994 – 1997
Medical Walk-In/Urgent Care Clinic
HIV Gouverneur Hospital Diagnostic & Treatment Center
New York, NY

Attending Physician | Souraski Medical Center | 1995
(Affiliated with Tel Aviv University)
Infectious Diseases, Infectious Diseases Unit
Tel Aviv, Israel

Attending Physician | Manhattan Veterans Administration (VA) Medical Center | 1992 – 1997 (part-time)
(Affiliated with NYU University & Medical Center)
Emergency Department
New York, NY

Attending Physician | Bellevue Hospital Center [NYC Health & Hosp Corp (HHC)] | 1995 – 1996 (part-time)
(Affiliated with NYU Univ. & Medical Center)
Emergency Medical Services
New York, NY

Attending Physician | New York Downtown Hospital | 1991 – 1992
(Affiliated with NYU & Cornell Medical Centers)
Emergency Department
New York, NY

Physician (Temporary Duty) | Brookhaven National Laboratory (US Dept. of Energy) | 1992
Medical Mission to the Marshall Islands

CURRENT HOSPITAL COMMITTEE MEMBERSHIP

Medical Director - Infection Prevention | Texas Health Resources
Plano, Texas, 2017 – present

Co-Chair – Clinical Practice Committee/Committee on Evidence-Based Medicine | Texas Health Resources
Plano, Texas, 2017 – present

Pharmacy and Therapeutic Committee | Baylor Scott & White
Carrollton, Texas, 2015 – present

Infection Prevention Committee | Baylor Scott & White
Carrollton, Texas, 2017 – present

[THIS IS AN ABBREVIATED CV, PREPARED FOR COMPLIANCE WITH STANDING ORDER REGARDING ATTACHMENTS TO DISCOVERY MOTIONS. A FULL CV, WHICH INCLUES DR. TORTEN'S PUBLICATIONS AND OTHER EXPERIENCE, IS AVAILABLE UPON REQUEST]

EXHIBIT B

EXHIBIT B

Dr. Torten's Availability for Independent Medical Examinations

DATE	TIMES
MARCH 1, 2019 [FRIDAY]	8:30 am 9:15 am 10:00 am 10:45 am 11:15 am
MARCH 4, 2019 [MONDAY]	8:30 am 9:15 am 10:00 am 10:45 am 11:15 am
MARCH 5, 2019 [TUESDAY]	8:30 am 9:15 am 10:00 am
MARCH 7, 2019 [THURSDAY]	8:45 am 9:30 am
MARCH 8, 2019 [FRIDAY]	8:30 am 9:15 am 10:00 am 10:45 am
MARCH 15, 2019 [FRIDAY]	8:30 am 9:15 am 10:00 am 11:00 am
MARCH 18, 2019 [MONDAY]	9:30 am 10:45 am
MARCH 19, 2019 [TUESDAY]	8:30 am 9:30 am

EXHIBIT C

Exhibit C - Declaration

1. My name is Michael Tuteur. I am of sound mind, am over the age of twenty-one (21), have never been convicted of a felony or other crime involving moral turpitude, and am capable of making this declaration. Unless otherwise stated, I have personal knowledge of the matters set forth herein and could testify competently thereto if called upon to do so.
2. I am attorney of record for Anthem, Inc. in *Torrey v. IDSA, et. al.,* Cause No. 5:17-cv-00190-RWS, pending in the United States District Court for the Eastern District of Texas (the "Lawsuit"), and am submitting this declaration in support of the motion for independent medical examinations of those plaintiffs who claim presently to have Lyme disease (the "Motion").
3. On January 29, 2019, Plaintiffs served their designation of experts in the Lawsuit (the "Designations"). The Designations span 56 pages and designate more than 100 non-retained experts, including unidentified individuals who work at healthcare facilities that have treated the plaintiffs (making it impossible to provide an accurate tally of the designated experts).
4. On December 28, 2018, I sent an email to counsel of record for the Plaintiffs, copying the attorneys of record for all defendants. A screenshot of this email is below:

> **Dear Counsel:**
>
> **On behalf of defendant Anthem, Inc., and various other defendants in this action, we intend to request independent Physical and Mental Examinations ("IMEs") for some or all of the Plaintiffs, in accordance with Fed. R. Civ. P. 35. As such IMEs must be made on motion, we are hereby seeking your consent for these IMEs to go forward. If one or more of the Plaintiffs has objections to our request for an IME, please let me know as soon as possible so that we can promptly schedule a meet and confer.**
>
> **We anticipate that each IME will involve a complete history and physical examination of the individual plaintiff, including blood and urine testing relevant to Lyme disease, as well as testing related to any other tick-borne infections, as deemed appropriate by the examiner and consistent with the symptoms the individual has complained of. We also anticipate that, with respect to certain of the Plaintiffs, the IME will include psychiatric, neurologic or neuropsychological evaluations, as deemed appropriate by the examiner.**
>
> **As you know, the law provides that IMEs are generally to take place within the forum district or within the court's 100 mile "bubble". However, given the many locations in which Plaintiffs live, we are prepared to seek agreement with you on other locations where the IMEs could take place. We are also open to discussing mutually convenient dates for each of the individual Plaintiffs, so long as the IMEs can be completed before the close of discovery.**
>
> **Please let us know your position on our Rule 35 request as soon as possible.**

5. Plaintiffs' counsel did not respond to my December 28, 2018 email and on January 10, 2018, I sent a follow-up email (to the same recipients). Gene Egdorf, counsel for Plaintiffs responded a few hours later:

Dear Counsel –

I write in follow-up to my email of December 28, attached below. Despite the passage of nearly two weeks, I have heard nothing – not even an acknowledgement of my email – from Plaintiffs' counsel. And, as you know, discovery in this case is rapidly coming to a close, and we recognize that scheduling and performing IMEs on each of the Plaintiffs will take time and the cooperation of all parties.

Please let me know if you consent to our request to perform IMEs on some or all of the named Plaintiffs pursuant to Fed. R. Civ. P. 35. If you do not consent, please provide me with times as soon as possible for a meet and confer to discuss our request. If I have not heard back from you by the close of business on Monday, January 14th, we will consider your silence as a refusal to meet and confer pursuant to Local Rule CV-7(h).

Thank you,
Michael Tuteur

Counsel : We do not agree to IME's. While there are a number of reasons and problems with your request, first and foremost this is not a personal injury case. Therefore IME's are no appropriate.

Gene Egdorf

6. The Designations and a copy of the email chain described above (with the complete email headers) is not attached to the Motion, in order to comply with the Court's standing order regarding the length of attachments to discovery motions. Should the Court require either document, I will be happy to provide them to the Court.

I declare under penalty of perjury of the laws of the United States of America that the foregoing is true and correct.

EXECUTED on February 13, 2019.

Michael J. Tuteur

4818-0968-8456.1

APPENDIX OF NON-LEGAL AUTHORITIES

Two non-legal authorities are cited in the motion for independent medical examinations. Moving Defendants submit this appendix with courtesy copies of those two authorities.

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Chronic Lyme Disease

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Keywords

Lyme disease; Chronic Lyme disease; *Borrelia burgdorferi*; Chronic fatigue; Chronic pain; Antibiotics

THE CHRONIC LYME DISEASE CONTROVERSY

Chronic Lyme disease (CLD) is a poorly defined term that describes the attribution of various atypical syndromes to protracted *Borrelia burgdorferi* infection. These syndromes are atypical for Lyme disease in their lack of the objective clinical abnormalities that are well-recognized in Lyme disease and, in many cases, the absence of serologic evidence of Lyme disease as well as the absence of plausible exposure to the infection. The syndromes usually diagnosed as CLD include chronic pain, fatigue, neurocognitive, and behavioral symptoms, as well as various alternative medical diagnoses—most commonly neurologic and rheumatologic diseases. Perhaps the most recognized and contentious facet of this debate is whether it is effective, appropriate, or even acceptable to treat patients with protracted antibiotic courses based on a clinical diagnosis of CLD.

The dialogue over CLD provokes strong feelings, and has been more acrimonious than any other aspect of Lyme disease. Many patients who have been diagnosed with CLD have experienced great personal suffering; this is true regardless of whether *B burgdorferi* infection is responsible for their experience. On top of this, many patients with a CLD diagnosis share the perception that the medical community has failed to effectively explain or treat their illnesses. In support of this patient base is a community of physicians and alternative treatment providers as well as a politically active advocacy community. This community promotes legislation that has attempted to shield CLD specialists from medical board discipline and medicolegal liability for unorthodox practices, to mandate insurance coverage of extended parenteral antibiotics, and most visibly to challenge legally a Lyme disease practice guideline. The advocacy community commonly argues that Lyme disease is grossly underdiagnosed and is responsible for an enormous breadth of illness; they also argue that the general scientific and public health establishments ignore or even cover up

Financial Disclosures/Conflicts of Interest: None.

The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

evidence to this effect. A large body of information about CLD has emerged on the Internet and other media, mostly in the forms of patient testimonials and promotional materials by CLD providers. For a medical consumer and for the physician unfamiliar with this subject, this volume of information can be confusing and difficult to navigate.

The CLD controversy does not, however, straddle a simple divide between 2 opposed scientific factions. Within the scientific community, the concept of CLD has for the most part been rejected. Clinical practice guidelines from numerous North American and European medical societies discourage the diagnosis of CLD and recommend against treating patients with prolonged or repeated antibiotic courses.[1–21] Neither national nor state public health bodies depart from these recommendations. Within the medical community, only a small minority of physicians have accepted this diagnosis: 1 study found that only 6 of 285 (2.1%) randomly surveyed primary care physicians in Connecticut, among the most highly endemic regions for Lyme disease, diagnosed patients with CLD and still fewer were willing to prescribe long courses of antibiotics.[22,23]

THE CONFUSING TERMINOLOGY OF CHRONIC LYME DISEASE

The mere name “chronic Lyme disease” is in itself a source of confusion. Lyme disease, in conventional use, specifically describes infection with the tick-borne spirochete *B burgdorferi* sensu lato. The diagnosis “chronic Lyme disease,” by incorporating that terminology, connotes a similar degree of microbiologic specificity; the addition of the word “chronic” further implies that there is some distinction between “chronic” Lyme disease and other manifestations of the infection. This distinction in itself is problematic because several manifestations of Lyme disease may indeed present subacutely or chronically, including Lyme arthritis, acrodermatitis chronicum atrophicans, borrelial lymphocytoma, and late Lyme encephalopathy.

“Chronic Lyme disease,” however, has no clinical definition and is not characterized by any objective clinical findings. The only published attempt to define CLD provisionally produced a description too broad to distinguish CLD from myriad other medical conditions, and the case definition did not mention evidence of *B burgdorferi* infection (Box 1).[24] The absence of a definition makes it impossible to investigate whether a patient population with putative CLD has evidence of infection with *B burgdorferi*; this would seem to be a basic requirement to include a syndrome within the term “Lyme disease.” It stands to reason that it is impossible to even posit a well-designed antibiotic trial when the study population is undefined.

Box 1

Working definition of chronic Lyme disease proposed by ILDAS

For the purpose of the ILADS guidelines, ‘chronic Lyme disease’ is inclusive of persistent symptomatologies including fatigue, cognitive dysfunction, headaches, sleep disturbance and other neurologic features, such as demyelinating disease, peripheral neuropathy and sometimes motor neuron disease, neuropsychiatric presentations, cardiac

presentations (including electrical conduction delays and dilated cardiomyopathy), and musculoskeletal problems.

Abbreviation: ILADS, International Lyme and Associated Diseases Society.

From Cameron D, Gaito A, Harris N, et al. Evidence-based guidelines for the management of Lyme disease. Expert Rev Anti Infect Ther 2004;2(Suppl 1):S4.

In the absence of a definition, it is instructive to examine the circumstances under which patients receive a diagnosis of CLD. These circumstances can be inferred from the breakdown of patients referred for suspected Lyme disease. In 7 studies conducted in endemic areas, comprising a total of 1902 patients referred for suspected Lyme disease, 7% to 31% had active Lyme disease and 5% to 20% had previous Lyme disease, based on concordance of their clinical presentations with recognized manifestations of Lyme disease.[25–31] The remaining 50% to 88%, however, had no evidence of ever having had Lyme disease. Most of these patients had either alternative medical diagnoses or had medically unexplained symptoms, such as chronic fatigue syndrome or fibromyalgia. Lyme disease was in many cases diagnosed simply for lack of an alternative diagnosis—referred to in 1 paper as a "diagnosis of Lyme disease by exclusion."[30] Two studies documented that many of the referred patients had psychiatric diagnoses and/or mal-adaptive psychological traits, such as catastrophization and negative affect.[26,28] Many patients had symptoms of long duration and had received multiple courses of antibiotics.

A common reason for referral was a positive Lyme disease serologic test. On clinical review, however, the patients lacked clinical findings concordant with a Lyme disease diagnosis. This is certainly a side effect of a great volume of Lyme disease testing conducted in the United States—more than 3 million tests are thought to be ordered annually.[32] Most such tests are ordered with a very low pretest probability in settings such as chronic nonspecific fatigue, based on patient request, after a tick bite (when even an infected patient would be most likely seronegative), or as part as a general neurologic or rheumatologic evaluation. In the absence of specific clinical findings, however, Lyme disease testing has a very low positive predictive value.[33] Patients may have positive Lyme serology for a variety of reasons, including asymptomatic seroconversion, cross-reactive antibodies generated by other infectious or inflammatory diseases, or a previous treated episode of Lyme disease; asymptomatic seropositivity is well-described in endemic areas.[25,29,30,33–40] Thus, the misattribution of chronic symptoms to Lyme disease is an inevitable consequence of high-volume, low-probability testing.

THE MISDIAGNOSIS OF CHRONIC LYME DISEASE

Many patients referred for Lyme disease are ultimately found to have a rheumatologic or neurologic diagnosis. Rheumatologic diagnoses commonly misdiagnosed as Lyme disease include osteoarthritis, rheumatoid arthritis, degenerative diseases of the spine, and spondyloarthropathies.[26,27,41] Some patients are found to have neurologic diseases, including multiple sclerosis, demyelinating diseases, amyotrophic lateral sclerosis, neuropathies, and dementia.[27] Some CLD advocates have argued that these various conditions are simply manifestations of Lyme disease,[24,42–44] but these hypotheses are

untenable. Lyme disease is transmitted quite focally,[45] and there is no epidemiologic evidence that these alternative diagnoses cluster in regions with high Lyme disease transmission. There has been no association between diagnoses such as multiple sclerosis, amyotrophic lateral sclerosis, or rheumatoid arthritis and antecedent Lyme disease, these diagnoses do not arise concurrently with other recognized manifestations of disseminated Lyme disease (such as Lyme arthritis), and there is no quality evidence associating any of these diagnoses with seroconversion to *B burgdorferi*. Although there can certainly be clinical overlap between Lyme disease and other conditions, objective findings and studies will generally allow them to be differentiated.

Medically unexplained symptoms, whether resulting in entities such as fibromyalgia and chronic fatigue syndrome or syndromes with a less distinct pattern, account for most of the remaining patients who are diagnosed with CLD. Unlike Lyme disease, these frustrating conditions generally lack objective clinical or other objective abnormalities, and they are dominated by subjective complaints and functional impairment.[46–48] No evidence suggests that these clinical entities geographically cluster in regions with *B burgdorferi* transmission. Fibromyalgia has been found to follow Lyme disease temporally in some cases: in a prospective study of 287 patients treated for confirmed Lyme disease, 22 (8%) went on to develop fibromyalgia within 5 months of treatment.[49] Additional antibiotics were not beneficial. This finding, however, is contradicted by a prospective cohort study in which only 1 of 100 patients treated for culture-confirmed Lyme disease developed fibromyalgia during the subsequent 11 to 20 years.[50] Severe fatigue was found in 9 of these patients, but it was attributable in all cases to other causes.[51] Many patients experience prolonged symptoms during convalescence from systemic infections, including symptoms of fibromyalgia and chronic fatigue.[49,52] Such symptoms, however, do not seem to be associated particularly with antecedent Lyme disease; in fact, the prevalence of fatigue and fibromyalgia among patients with past Lyme disease is similar to their prevalence in the general population.

BIOLOGICAL EXPLANATIONS FOR CHRONIC LYME DISEASE

Several arguments have been made to support the biological plausibility of CLD and to justify its treatment with lengthy courses of antibiotics. One is that *B burgdorferi* localizes intracellularly in the infected host, and that the antibiotics typically chosen to treat it do not penetrate cells effectively. Aside from the fact that *B burgdorferi* predominantly occupies the extracellular matrix,[53] the antibiotics currently recommended to treat Lyme disease are well-established to treat a variety of intracellular infections. For example, doxycycline and azithromycin are first-line drugs for the treatment of *Mycoplasma*, *Chlamydia*, and *Legionella*, and doxycycline is the drug of choice for *Rickettsia* and related species. Ceftriaxone is effective against *Salmonella* and *Neisseria*, both of which are predominantly intracellular; amoxicillin is effective against *Listeria*.

Another commonly voiced argument is that *B burgdorferi* assumes a round morphology, variously described as “cyst forms,” “spheroplasts,” “L-forms,” and “round bodies.” These variants are said to be resistant to antibiotic treatment and require alternative antibiotics and dosing strategies. On close review of the literature there is little evidence that these variants

arise in vivo in humans, let alone that they are associated with CLD-like symptom complexes or that they require treatment.[54]

MICROBIOLOGIC INVESTIGATIONS INTO CHRONIC LYME DISEASE

There is very little microbiologic evidence that supports persistent *B burgdorferi* infection in patients who lack objective manifestations of Lyme disease, such as erythema migrans, arthritis, meningitis, and neuropathies. Advocates for CLD contend that our ability to detect *B burgdorferi* is hampered by current technology and an incomplete scientific understanding of *B burgdorferi*, and that conventional diagnostic testing misses patients with CLD.[55,56] Naturally, this raises the question of why we should assume that chronic *B burgdorferi* infection exists at all if we are so ill-equipped to detect it. Even when chronically symptomatic patients have a well-documented history of treated Lyme disease, investigators have been unable to document persistent infection.[57–59] A recent study in which ticks were allowed to feed on persistently symptomatic posttreatment patients yielded molecular evidence of *B burgdorferi* in 1 of 16 patients and no patient had cultivatable organisms.[60]

Studies reporting the retrieval of *B burgdorferi* from antibiotic-treated animals are indirect and have limited generalizability to human disease. First, it is impossible to create an animal model of CLD when this diagnosis is usually based on symptoms described by a patient. Second, rodents serve as reservoir species for *B burgdorferi* in nature and may tolerate persistent asymptomatic infection. Third, some experimental studies use large inocula of *B burgdorferi* that have been grown to stationary phase; the organism assumes a more drug-resistant phenotype under these growth conditions and this may not reflect natural infection.

Because validated testing methods fail to support the connection between *B burgdorferi* and clinically diagnosed CLD, physicians who specialize in CLD often turn to alternative tests. This has included the use of novel culture techniques, detection of *B burgdorferi* DNA in urine specimens, and enumeration of CD57-positive lymphocytes.[61–65] Independent investigations, however, have repudiated the validity of these tests.[66–70]

COINFECTIONS

Some CLD advocates emphasize that CLD is a polymicrobial infection in which patients suffer from multiple tick-borne coinfections.[71,72] In practice, patients with a diagnosis of CLD are often diagnosed with and treated for numerous superimposed infections, including *Babesia* spp and *Anaplasma phagocytophilum* (well-described tick-borne pathogens), *Bartonella henselae* (which is not known to be transmitted by ticks), pathogens of unclear clinical relevance such as the xenotropic murine leukemia virus-related virus, and even completely fictitious pathogens such as "*Protomyxozoa rheumatica*." There is no evidence to support chronic anaplasmosis; chronic symptomatic babesiosis when present invariably is associated with fever and molecular or microscopic evidence of parasitemia. *Bartonella* species are readily identified in ticks, but there is virtually no quality evidence of tick-borne transmission to humans or of simultaneous Lyme disease and bartonellosis.[73] It is important to recognize that, in the context of CLD, a diagnosis of coinfection may be just as spurious.

PERSISTENT SYMPTOMS AFTER TREATMENT FOR LYME DISEASE

It is well-recognized that some patients experience prolonged symptoms during convalescence from Lyme disease, and a subset suffer significant functional impairment.[57–59,74–78] The most common complaints among such patients are arthralgias, myalgias, headache, neck and backache, fatigue, irritability, and cognitive dysfunction (particularly perceived difficulty with memory and concentration).[57–59]

A working definition was developed to categorize patients with 'post-Lyme disease symptoms' (PLDS), those patients with persistent clinical symptoms after treatment for Lyme disease, but who lack objective evidence of treatment failure, reinfection, or relapse (Box 2).[20] PLDS is not strictly speaking a coherent clinical diagnosis; its primary value has been to define a patient cohort for further study. Nonetheless, it is worth considering how it conceptually differs from CLD. To meet criteria for PLDS, patients must have unequivocal documentation of appropriately treated Lyme disease, lack objective manifestations of Lyme disease, and have persistent symptoms that cannot be explained by other medical illnesses. Thus, of patients with chronic symptoms that have been *attributed* to Lyme disease, those meeting criteria for PLDS are those for whom infection with *B burgdorferi* is most plausible. This makes the studies of PLDS paradigmatic for the understanding of CLD.

Box 2

Proposed definition of post-Lyme disease syndromes from the Infectious Disease Society of America

Inclusion criteria

- 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. If based on erythema migrans, the diagnosis must be made and documented by an experienced health care practitioner.
- After treatment of the episode of Lyme disease with a generally accepted treatment regimen, there is 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.

Exclusion criteria

- An active, untreated, well-documented coinfection, such as babesiosis.
- The presence of objective abnormalities on physical examination or on neuropsychologic testing that may explain the patient's complaints. For example, a patient with antibiotic-refractory Lyme arthritis would be excluded. A patient with late neuroborreliosis associated with encephalopathy, who has recurrent or refractory objective cognitive dysfunction, would be excluded.
- A diagnosis of fibromyalgia or chronic fatigue syndrome before the onset of Lyme disease.
- A prolonged history of undiagnosed or unexplained somatic complaints, such as musculoskeletal pains or fatigue, before the onset of Lyme disease.
- A diagnosis of an underlying disease or condition that might explain the patient's symptoms (eg, morbid obesity, with a body mass index [calculated as weight in kilograms divided by the square of height in meters] of 45 kg/m^2 or greater; sleep apnea and narcolepsy; side effects of medications; autoimmune diseases; uncontrolled cardiopulmonary or endocrine disorders; malignant conditions within 2 years, except for uncomplicated skin cancer; known current liver disease; any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa or bulimia nervosa; and active drug abuse or alcoholism at present or within 2 years).
- Laboratory or imaging abnormalities that might suggest an undiagnosed process distinct from post-Lyme disease syndrome, such as a highly elevated erythrocyte sedimentation rate (150 mm/h); abnormal thyroid function; a hematologic abnormality; abnormal levels of serum albumin, total protein, globulin, calcium, phosphorus, glucose, urea nitrogen, electrolytes or creatinine; significant abnormalities on urine analysis; elevated liver enzyme levels; or a test result suggestive of the presence of a collagen vascular disease.
- Although testing by either culture or polymerase chain reaction for evidence of *Borrelia burgdorferi* infection is not required, should such testing be done by reliable methods, a positive result would be an exclusion.

From Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43(9):1121; with permission.

The frequency of PLDS is difficult to estimate, but as a function of patients with a known history of Lyme disease, it seems to be rare. This is exemplified by the great difficulty 3 investigative teams had in recruiting subjects for clinical trials investigating this condition.[57–59] Of 5846 patients screened over several years, only 222 (3.8%) could be randomized ultimately, which is striking considering that between 30,000 and 300,000 Americans are thought to contract Lyme disease annually. PLDS also seems to be

uncommon among subjects in clinical trials. In 10 prospective studies of erythema migrans and early disseminated Lyme disease, fewer than 10% of subjects described persistent symptoms such as myalgias and fatigue after 9 or more months (range, 0%–23%), and the prevalence of severe symptoms was 0% to 2.8%.[79–88] One trial found that, after 12 months, patients treated for erythema migrans were no more likely to have subjective symptoms than an uninfected control group.[80]

If PLDS is rare among patients with a history of Lyme disease, in the general population it becomes impossible to discern from the high background rate of similar symptoms among adults. Up to 20% of surveyed adults report chronic fatigue.[89,90] In 1 report, 3.75% to 12.1% of the general population suffered severe pain and 36.4% to 45.1% moderate pain, whereas only 42.5% to 59.1% of the general population was pain free.[91] In a separate study, 11.2% of respondents suffered chronic, widespread pain.[92] One-quarter to one-third of the general population describe chronic cognitive dysfunction.[91] These symptoms often coincide with anxiety or depression, which in their own right are common in the general population. Interestingly, many who complain of cognitive dysfunction are found to be normal when formally tested.[59,75,79,93–96] In all likelihood, subjective post-Lyme symptoms are not unique to Lyme disease but rather are common to the recovery from many systemic illnesses. Bacterial pneumonia, for example, can be followed by months of nonspecific symptoms that impair quality of life.[97]

RISK FACTORS FOR PERSISTENT SYMPTOMS AFTER TREATMENT FOR LYME DISEASE

Patients with the most severe symptoms on clinical presentation are the most likely to have persistent symptoms during convalescence.[98–100] Severe headache, arthritis, arthralgias, and fatigue at presentation predicted persistent symptoms in a retrospectively examined cohort of 215 patients.[101] In a prospective treatment trial for early Lyme disease, persistent symptoms at several late follow-up visits (6 months through 5 years) were more common in patients who had more symptoms, higher symptom scores and multiple (vs solitary) erythema migrans lesions.[85] Patients with a longer duration of symptoms may also be at greater risk of persistent symptoms: a review of 38 subjects who had been previously treated for Lyme disease found that persistent somatic and neuropsychological sequelae were strongly associated with prolonged illness before treatment.[77]

On the other hand, the duration of antibiotic therapy does not influence the persistence of subjective symptoms after treatment. In a prospective trial of therapy for 180 patients with early Lyme disease, neuropsychologic deficits were equally common among patients treated for 10 versus 20 days at follow-up 30 months later.[87] In a retrospective study of 607 patients treated for early Lyme disease, 99 ± 0.2% of patients were well after 2 years of follow-up, regardless of whether they had received fewer than 10, 11 to 14, or more than 14 days of therapy.[88] In a randomized, open-label trial of therapy for late Lyme disease, patients treated for 14 days were no more likely to have severe symptoms than those treated for 28 days, even though objective treatment failures were significantly more likely in the 14-day arm.[102] After 3 weeks of parenteral ceftriaxione, an additional 100 days of oral amoxicillin was no better than placebo at improving cognitive and somatic outcomes.[103]

We have an incomplete picture as to why some patients are left with chronic symptoms after Lyme disease whereas the majority does well. Genetic variability among *B burgdorferi* isolates and its significance for clinical disease is an important emerging area of research. This is difficult to link with clinical outcomes, however, because different strains of the organism cannot be discriminated by standard clinical testing. Anti-*Borrelia* antibody titers are higher among patients with PLDS compared with those with an uncomplicated post-Lyme disease course; antibody profiles are different between these 2 groups as well.[104] Patients with neurologic Lyme disease have elevated cerebrospinal fluid biomarkers, including CXCL13 and neopterin.[105] These return to normal after antibiotic therapy, and are not increased in patients with PLDS. Further research is needed to better characterize the biology of PLDS.

EXTENDED ANTIBIOTICS FOR THE TREATMENT OF POST-LYME DISEASE SYNDROMES

Three research groups have examined prospectively the effectiveness of prolonged antibiotic courses for post-Lyme disease syndromes.[57–59,75] All trials had strict entrance criteria similar to the aforementioned definition of PLDS. The Klempner and colleagues[58] study reported 2 parallel trials in which their cohort of 129 subjects was divided into seropositive (n = 78) and seronegative (n = 51) arms. Subjects randomized to treatment groups received 30 days of intravenous (IV) ceftriaxone followed by 60 days of oral doxycycline. Those randomized to the placebo arm received IV placebo for 30 days, followed by an oral placebo for 60 days. The primary outcome was health-related quality of life as assessed by standardized instruments (the Medical Outcomes Study 36-item Short-Form General Health Survey [SF-36] and the Fibromyalgia Impact Questionnaire). These instruments were administered at baseline, and then 30, 90, and 180 days. There was no difference in any outcome measure between placebo and treatment groups in either the seropositive or seronegative arm, or in a detailed battery of neuropsychological tests that was published subsequently.[75] Although all patients had complained of cognitive dysfunction at baseline (and this was the primary complaint in >70%), objective measures of cognitive function, such as memory and attention, were normal compared with age-referenced normative data. Depression, anxiety, and somatic complaints improved in both the antibiotic and placebo arms groups between baseline and day 180.

In a separate trial, Krupp and colleagues[59] investigated the effect of antibiotics for persistent severe fatigue after treatment for Lyme disease. Twenty-eight patients were randomized to receive 28 days of IV ceftriaxone and 24 received IV placebo. The primary outcome measure was score on the Fatigue Severity Scale (FSS-11). Additional outcomes were visual analog scales (VAS) of fatigue and pain, the SF-36, the Center for Epidemiologic Studies Depression Scale, and a comprehensive battery of cognitive function. Outcomes were measured at baseline and at 6 months. At follow-up, there was a significant but partial improvement on the FSS-11 in the ceftriaxone arm compared with placebo, with 18 of 26 (69%) versus 5 of 22 (23%) patients showing improvement from baseline (P = .001). The fatigue VAS, although not significant, corroborated a benefit for the treatment arm (P = .08). No measure of mood or cognitive function differed at the 6-month follow-up. It was noted

that a much higher proportion of patients on ceftriaxone correctly guessed their treatment assignment. Whether this was a failure of masking, and whether this would have affected the outcome of a subjective measure like fatigue, is difficult to discern. The commonality and nonspecificity of fatigue, and the observation that antibiotics may improve chronic fatigue in noninfectious or other postinfectious illnesses, raise doubts as to whether it was the elimination of *B burgdorferi* that resulted in this outcome.[106–108]

Fallon and colleagues[57] investigated a more prolonged IV treatment course. In this cohort, 23 patients were randomized to receive IV ceftriaxone and 14 patients to receive IV placebo for 10 weeks, followed by 14 weeks of observation off of therapy. Six domains of cognitive function were tested and compiled to produce a composite 'cognitive index' score. The primary outcome of interest was cognitive index compared with baseline and between groups at week 24. An interim evaluation at week 12 demonstrated significant improvement over baseline in the ceftriaxone group ($P<.01$), whereas this was not the case for the placebo group. A between-group comparison at week 12 approached statistical significance ($P = .053$) as well. At week 24, however, these differences had disappeared: both groups had improved over their within-group baseline, but there was no difference between groups ($P = .76$). Five of the randomized patients withdrew from the study owing to adverse events, leaving only 20 drug and 12 placebo patients available for statistical analysis. An additional 4 ceftriaxone patients remained in the study despite adverse events that truncated their therapy. The patients who dropped out were not analyzed by intention to treat, which, given the small sample size in this trial, might have affected the published statistics.

Adverse events were common in these studies, particularly catheter-associated venous thromboembolism, catheter-associated bacteremia, allergic reactions, and ceftriaxone-induced gallbladder toxicity. In the Klempner and colleagues[58] trial, 1 patient on ceftriaxone suffered a pulmonary embolism and 1 experienced a syndrome of fever, anemia, and gastrointestinal bleeding that was felt to be an allergic phenomenon. In the Krupp and colleagues[59] trial, 3 patients on IV placebo developed line sepsis and 1 patient on ceftriaxone had an anaphylactic reaction. In the Fallon and colleagues[57] trial, 6 patients on ceftriaxone had adverse events: 2 venous thromboembolic events, 3 allergic reactions, and 1 case of ceftriaxone-induced cholecystitis (requiring cholecystectomy), in addition to a placebo patient who developed line sepsis. Other studies reiterate the frequency of adverse events in persons with prolonged exposure to IV catheters and antibiotics. In an observational study by Stricker and colleagues,[109] there were 19 potentially life-threatening adverse events among 200 patients on long-term IV antibiotics for the treatment of CLD. These included 4 cases of venous thromboembolic disease, 6 cases of suspected line sepsis, 7 patients with allergic reactions, and 2 who developed ceftriaxone-induced gallbladder disease (both necessitating cholecystectomy). The mean duration of antibiotic therapy in this cohort was 118 days, and the adverse events reported occurred after a mean of 81 days from initiation of therapy. Although no deaths occurred in these studies, there have indeed been documented fatalities and near fatalities owing to prolonged IV antibiotic therapy for the treatment of Lyme disease.[110–112]

CLINICAL APPROACH TO PATIENTS WITH A CHRONIC LYME DISEASE DIAGNOSIS

Even if CLD lacks biological legitimacy, its importance as a phenomenon can be monumental to the individual patient. This is because many if not most patients who believe they have this condition are suffering, in many cases for years. Many have undergone frustrating, expensive, and ultimately fruitless medical evaluations, and many have become quite disaffected with a medical system that has failed to provide answers, let alone relief.

Beyond this generalization, patients referred for CLD have heterogeneous medical, social, and educational backgrounds. Furthermore, there is great variation in their "commitment" to a CLD diagnosis. Some patients are entirely convinced they have CLD, they request specific types of therapy, and they are not interested in adjudicating the CLD diagnosis. By contrast, others are not particularly interested in CLD per se, and are content to move on to a broader evaluation. In the author's experience most patients fall somewhere in between—a certain amount of time must be spent reviewing past experiences and past laboratory tests, then explaining why Lyme disease may not account for their illnesses.

Several strategies are generally helpful in approaching CLD in the clinic. First, the physician needs to suppress preconceptions or biases about such patients. Some encounters are long, some are short, some are tense, and some are congenial—but this is hardly unique to Lyme disease. Second, the process of clinical information gathering in medicine, that is, complaint, history, physical examination, and diagnostic testing, is no different in the context of CLD. Even if much discussion is centered on CLD, the goal of the encounter should still be to evaluate the patient and make the soundest assessment and plan.

Finally, it is of utmost importance to not seem to be impatient, dismissive, or rushed. Many patients who seek care for CLD already have accumulated frustration if not outright disaffection with the medical community. Subtle cues like body language, tone of voice, and affect can be critical to gaining or losing a patient's trust. Furthermore, each patient's clinical story and personal history is unique and valid, even if one concludes that they do not have Lyme disease.

SUMMARY

A limitation of modern medicine is our ability to explain and treat chronic pain, fatigue, and other disabling symptoms. It should come as no surprise that patients suffering from these symptoms have placed their hope in treatable conditions. Over time, a number of infectious diseases have been hypothesized as responsible, including *Candida*, *Brucella*, Epstein–Barr virus, xenotropic murine leukemia virus-related virus, and *B burgdorferi*. The scientific community has largely rejected chronic, treatment-refractory *B burgdorferi* infection, usually termed CLD, based on the absence of a defined patient population, the failure to detect cultivatable, clinically relevant organisms after standard treatment. Because the label CLD is applied to a highly heterogeneous spectrum of patients, the term CLD is better thought of as describing a phenomenon of attribution rather than a single disease. Even the subset of chronically symptomatic patients with a well-documented history of Lyme disease,

usually termed PLDS, have little evidence of active infection, and their symptoms do not respond to antibiotics any better than to placebo. Controversies such as that over CLD are likely to persist for as long as patients suffer from poorly explained, disabling symptoms. We must hope that future research will provide better explanations and safe, effective treatments.

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KEY POINTS

- There is no accepted clinical definition for chronic Lyme disease.
- Most patients with a diagnosis of chronic Lyme disease have no evidence of Lyme disease.
- Persistent subjective symptoms during recovery from Lyme disease are not active infection.
- Prolonged antibiotic courses are ineffective and unsafe patients for patients with prolonged symptoms after Lyme disease.

Skip to main content

National Institute of Allergy and Infectious Diseases

Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases

Chronic Lyme Disease

What is "chronic Lyme disease?"

Lyme disease is an infection caused by the bacterium *Borrelia burgdorferi*. In the majority of cases, it is successfully treated with oral antibiotics. In some patients, symptoms, such as fatigue, pain and joint and muscle aches, persist even after treatment, a condition termed “Post Treatment Lyme Disease Syndrome (PTLDS)”.

The term “chronic Lyme disease” (CLD) has been used to describe people with different illnesses. While the term is sometimes used to describe illness in patients with Lyme disease, it has also been used to describe symptoms in people who have no clinical or diagnostic evidence of a current or past infection with *B. burgdorferi* . Because of the confusion in how the term CLD is employed, and the lack of a clearly defined clinical definition, many experts in this field do not support its use.

How is Lyme disease treated?

For early Lyme disease, a short course of oral antibiotics such as doxycycline or amoxicillin is curative in the majority of the cases. In more complicated cases, Lyme disease can usually be successfully treated with three to four weeks of antibiotic therapy.

In patients who have non-specific symptoms after being treated for Lyme disease and who have no evidence of active infection (patients with PTLDS), studies have shown that more antibiotic therapy is not helpful and can be dangerous.

Has NIAID looked at the potential benefits of long-term antibiotic therapy on PTLDS?

Yes. NIAID has funded three placebo-controlled clinical trials on the efficacy of prolonged antibiotic therapy for treating PTLDS. The published results were subjected to rigorous statistical, editorial, and scientific peer review.

These trials were designed to ensure that several key parameters were addressed:

- The susceptibility of *B.burgdorferi* to the antibiotics used

- The ability of the antibiotics to both cross the blood-brain barrier and access the central nervous system and to persist at effective levels throughout the course of therapy
- The ability of the antibiotics to kill bacteria living both outside and inside mammalian cells
- The safety and welfare of patients enrolled in the trials

The first clinical trial, which included two multicenter studies, provided no evidence that extended antibiotic treatment is beneficial. In those studies, physicians examined long-term antibiotic therapy in patients with a well-documented history of previous Lyme disease but who reported persistent pain, fatigue, impaired cognitive function, or unexplained numbness. Those symptoms are common among people reporting PTLDS. Patients were treated with 30 days of an intravenous (IV) antibiotic followed by 60 days of an oral antibiotic.

These studies reinforced the evidence that patients reporting PTLDS symptoms have a severe impairment in overall physical health and quality of life. However, results showed no benefit from prolonged antibiotic therapy when compared with placebo in treating those symptoms.

In another study, published in 2003, researchers examined the effect of 28 days of IV antibiotic compared with placebo in 55 patients reporting persistent, severe fatigue at least six months following treatment for laboratory-diagnosed Lyme disease. Patients were assessed for improvements in self-reported fatigue and cognitive function.

In that study, people receiving antibiotics did report a greater improvement in fatigue than those on placebo. However, no benefit to cognitive function was observed. In addition, six of the study participants had serious adverse events associated with IV antibiotic use, four requiring hospitalization. Overall, the study authors concluded that additional antibiotic therapy for PTLDS was not supported by the evidence.

Another study supported by the National Institute of Neurological Disorders and Stroke again showed that long-term antibiotic use for Lyme disease is not an effective strategy for cognitive improvement. Researchers compared clinical improvement following 10 weeks of IV ceftriaxone versus IV placebo. The patients were treated for Lyme disease and presented with objective memory impairment tests. In a complicated statistical model, the ceftriaxone group showed a slightly greater improvement at 12 weeks, but at 24 weeks both the ceftriaxone and the placebo groups had improved similarly from baseline. In addition, adverse effects attributed to IV ceftriaxone occurred in 26 percent of patients. The authors conclude that because of the limited duration of the cognitive improvement and the risks involved, 10 weeks of IV ceftriaxone was not an effective strategy for cognitive improvement in these patients, and more durable and safer treatment strategies are still needed.

The results and interpretations of these studies have been reexamined since their publication, including by their own authors. While one team questioned the statistical interpretation of parts of these clinical trials, other researchers continue to support the studies' initial conclusions.

In 2016, a clinical trial conducted in the Netherlands also concluded that in patients with persistent symptoms attributed to Lyme disease, longer term treatment with antibiotics did not provide additional benefits compared with shorter term regimens.

If long-term antibiotic therapy is not effective why do some people report improved symptoms following such treatment?

Carefully designed, placebo-controlled studies have failed to demonstrate that prolonged antibiotic therapy is beneficial. Although isolated success stories are always good to hear, such reports alone are not sufficient grounds to support a therapeutic approach.

A positive response to prolonged antibiotic therapy may be due to the placebo effect, which was reported as high as 40 percent in the studies described above.

Has NIAID looked at whether infection persists after antibiotic therapy?

Several recent studies suggest that *B. burgdorferi* may persist in animals after antibiotic therapy. In one study, NIAID-supported scientists found that remnants of *B. burgdorferi* remained in mice after antibiotic treatment. Another team of NIAID-supported investigators found that intact *B. burgdorferi* persist in nonhuman primates after antibiotic treatment. It was not possible to culture these bacteria and it is not clear whether they are infectious. More recent work by Hodzic *et al.* replicated the earlier finding of persisting DNA but non-cultivatable *B. burgdorferi* after antibiotic treatment using a mouse model. In 2017, scientists at the Tulane National Primate Research Centers, funded in part by an NIH research resources grant, reported evidence of persistent and metabolically active *B. burgdorferi* after antibiotic treatment in rhesus macaques.

In a first-of-its-kind study for Lyme disease, NIAID-supported researchers have used live, disease-free ticks to see if Lyme disease bacteria can be detected in people who continue to experience symptoms such as fatigue or arthritis after completing antibiotic therapy). This study remains underway.

NIAID has not limited its efforts to animal studies, and researchers have proposed the existence of drug-tolerant, persistor cells of *B. burgdorferi* in cell cultures. Additional research is needed and continues to be supported by NIAID to learn more about persistent infection in cell culture and animal models and its potential implication for human disease.

Content last reviewed on November 21, 2018

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
TEXARKANA DIVISION

LISA TORREY, et al.,	§	
	§	
Plaintiffs	§	Civil Action No. 5:17-cv-00190-RWS
	§	
v.	§	
	§	
INFECTIOUS DISEASES SOCIETY OF AMERICA, et al.,	§	JURY TRIAL DEMANDED
	§	
	§	
Defendants	§	

ORDER GRANTING INDEPENDENT MEDICAL EXAMINATIONS

Before the Court is the motion of Defendants Anthem, Inc., the Infectious Diseases Society of America, and the Doctor Defendants[1] (herein, "Moving Defendants"), pursuant to Fed. R. Civ. P. 35, requesting that the Court order those Plaintiffs who allege that they currently have, or previously have had, Lyme disease—including so-called "chronic Lyme disease" (the "Lyme Claimants")[2]—to submit to an independent medical examination by infectious disease specialist Dr. Dina Torten (the "Motion"). Having considered the Motion and the Lyme Claimants' response, the Court finds good cause for the independent medical examinations, that the Motion should be granted, and the following orders should be entered:

It is therefore ORDERED that the Motion be, and it is hereby, GRANTED.

[1] The individual doctors remaining in this suit are: Dr. Gary Wormser, Dr. Raymond J. Dattwyler, Dr. Eugene Shapiro, Dr. John J. Halperin, Dr. Leonard Sigal, and Dr. Allen Steere (collectively, the "Doctor Defendants")

[2] Lisa Torrey, Amy Hanneken, Jane Powell, Carol Fisch, Christopher Valerio, Steven Ward, Randy Sykes, Brienna Reed, Rosetta Fuller, Adriana Monteiro Moreira, Jessica Mckinnie, Kristine Woodard, Dr. Michael Fundenberger, Gayle Clarke, Allison Lynn Caruana, Chloe Lohmeyer, Max Shindler, Tawnya Dawn Smith, Monet Pitre, Mike Peacher, Ashleigh Peacher, Alarie Bowerman, Elisa Bowerman, Emory Bowerman, and Anais Bowerman.

It is further ORDERED that each Lyme Claimant appear for an independent medical examination at the offices of Dr. Torten, 4461 Coit Road, Pavilion 2, Suite 409, Frisco, TX 75035.

It is further ORDERED that each Lyme Claimant select a date and time for their independent medical examination from the list of available times attached to the Motion as Exhibit B, no later than [March 19, 2019].

It is further ORDERED that Dr. Torten shall be permitted to perform an independent medical examination on the Lyme Claimants to determine whether they have, or previously have had Lyme disease, identify their symptoms, recommend any further testing required in order to determine whether they are currently suffering from Lyme disease, and assess the treatment they have received to date.

It is further ORDERED that Dr. Torten is authorized to obtain a complete history and physical examination of the Lyme Claimants, including a full review of systems if she believes they are necessary to assess whether the Lyme Claimant is currently suffering from Lyme disease or has had Lyme disease in the past.

It is further ORDERED that Dr. Torten is authorized to request that each Lyme Claimant, before appearing for the exam, submit blood and urine samples for testing relevant to Lyme disease – specifically an ELISA and Western Blot test for Lyme disease – to a recognized national FDA-approved testing lab (such as LabCorp or Quest or another lab approved by Dr. Torten).

It is further ORDERED that Dr. Torten is authorized to request and obtain other tests she deems appropriate following the exam if necessary to determine whether the Lyme Claimant is currently suffering from Lyme disease or had Lyme disease in the past.