

Obstruction to Treatments Meeting International Standards for Lyme and Relapsing Fever Borreliosis Patients

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Abstract—We reviewed how certain institutional policies and practices, as well as questionable research, are creating obstacles to care and informed consent for Lyme and relapsing fever Borreliosis patients. The interference is denying access to treatments that meet the internationally accepted standards as set by the Institute of Medicine. This obstruction to care contributes to significant human suffering, disability and negative economic effect across many nations and in many regions of the world. We note how evidence based medicine emphasizes the importance of clinical experience and patient-centered care and how these patients benefit significantly when their rights to choose among treatment options are upheld.

Keywords—Conflicts of interest, obstacles to healthcare accessibility, patient-centered care, the right to informed consent.

NOMENCLATURE

AGREE	Appraisal of Guidelines, Research and Evaluation
AIDS	Acquired immune deficiency syndrome
CDC	Centers for Disease Control and Prevention
COI	conflict of interest
CPG	clinical practice guideline
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECDC	European Centre for Disease Prevention and Control
FDA	Food and Drug Administration
FY	fiscal year
G-I-N	Guidelines International Network
GRADE	Grades of Recommendation Assessment, Development and Evaluation
HHS	Department of Health and Human Service
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IDSA	Infectious Diseases Society of America
ILADS	International Lyme and Associated Diseases Society
IOM	Institute of Medicine
MCID	minimal clinically important difference
MUS	medically unexplained symptoms
NGC	National Guidelines Clearinghouse

NIH	National Institution of Health
OID	Office of Infectious Diseases
RCT	randomized controlled trials
SF-36	Short Form Survey-36 is a set of generic quality-of-life measures
USA	United States of America
US	United States (of America)
WHO	World Health Organization
WIPO	World Intellectual Property

I. INTRODUCTION

THE World Health Organization (WHO) has recognized Lyme borreliosis as a multi-region ‘disease of consequence’ for decades [1]-[4]. In August 2017, the European Centre for Disease Prevention and Control (ECDC) published a handbook and manual for the prioritization of infectious disease threats that includes Lyme borreliosis (LB) among the 30 most threatening diseases for public health [5].

LB was selected as one of 30 diseases deemed a “serious cross-border threat to life” according to Decision 1082/2013/European Union. This decision defines such diseases as “life-threatening or otherwise serious hazard to health of biological [...] origin which spreads or entails a significant risk of spreading across the national borders of Member States, and which may necessitate coordination at Union level in order to ensure a high level of human health protection”. A subsequent risk ranking exercise refined criteria to include the economic impact of the disease, the individual level of discomfort caused by a disease episode, the economic impact of the disease and the case fatality proportion at peak incidence levels.

The dynamic nature of scientific investigation makes controversy commonplace. Nevertheless, regardless of the grim ECDC criteria associated with LB, there remain entrenched views that promote LB as a rather insignificant and rare disease easily cured with a short dose of antimicrobials and is not considered a public health priority in developing countries. Furthermore, decades of research into the nature of the bacteria have shown widely different results for an infection

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that can cause a wide range of systemic complications and manifestations, many of which resemble other illnesses.

These and other factors have contributed to a situation wherein many LB patients are denied access to critical treatment protocols that have been validated by internationally accepted criteria and health authorities such as the United States (US) government's Agency for Healthcare Research and Quality. Within the framework of health human rights –the obstruction of patient access to obtain validated treatment options and informed consent is recognized as a human rights abuse.

A report that outlined this obstruction and resulting harm against persons living with borreliosis infections, such as relapsing fever and LB was submitted to WHO on March 30, 2017. This same report resulted in a meeting between a United Nations Human Rights Council Special Rapporteur and medical professionals, scientists, human rights experts and advocates on June 7, 2017 in Geneva, Switzerland [6], [7].

Special Rapporteur Dr. Dainius Pūras heard presentations on the range of these violations –including those prompted by the outdated science represented in the International Classification of Diseases (ICD) codes for borreliosis infections. The ICD codes are developed and managed by WHO. The report analyzed how, on a global scale, existing ICD codes are excluding presentations which prevent proper diagnosis, create significant obstacles to treatment options, and support the denial of coverage for medical services for borreliosis including Lyme and relapsing fever borreliosis.

The report and presentation were provided by the Ad Hoc Committee for Health Equity in ICD11. The Ad Hoc Committee is concerned with bacterial infections that lead to human illness caused by multiple species of spirochetes from the *Borrelia burgdorferi* sensu lato complex and relapsing fever borreliosis distributed worldwide.

The Ad Hoc Committee represents professionals from North America, Asia Pacific region, Africa, South America and Eastern, Western and Northern Europe. Many members are scientific and medical experts and have worked on borreliosis for two and three decades, and among them have many hundreds of peer-reviewed publications and studies and have treated many thousands of LB patients.

They serve as leaders, clinicians and professors across numerous well respected academic and research centers and have members who consult regularly to the WHO and governments on the development of health systems, surveillance practices, patient-centered care, ageing, zoonosis and other specialized areas. Other members are experts in governance, accountability, institutional reform, climate change, capacity building and human rights.

II. LACK OF CONSENSUS, DISCRIMINATION AND MARGINALIZATION RELATED TO RELAPSING FEVER AND LYME BORRELIOSIS

Patients sickened with emerging illnesses often fight for validation and access to care and those infected with borreliosis bacteria are no exception. Those diseases associated with marginalized groups and the negative impacts of human activity

on the planet –such as climate change and pollution– are particularly marginalized along with their patient groups. Such patients are often accused of faking their illness and are commonly diagnosed with 'medically unexplained symptoms' or MUS, which is a form of hypochondria and over-preoccupation with non-medical symptoms [7], [8]. MUS is a term for psychosomatic illness that has been repudiated by the American Psychiatric Association.

These forms of discrimination have played throughout medical history. For example, until recent decades, patients suffering from asthma, ulcers or multiple sclerosis were considered to have non-medical conditions caused by emotional issues [8]. There are so many such cases it has been theorized MUS and similar diagnoses are patient-blaming terms used when there are inadequate understandings of a disease [8, p. 649], [9].

In the USA and Europe, patients suffering from persistent LB and symptoms not associated with the acute form of the illness are often wrongly designated as MUS, required to take psychotropic medicine, deprived of medical care for infection and sometimes find themselves accused of criminal actions because they seek medical treatment for themselves or their children [6]. Additionally, patients who are misdiagnosed with autoimmune or neurological disorders are often treated with drugs that are counter indicated in bacterial illness, leading to further disability or death.

Furthermore, it is not uncommon for practitioners who treat persistent LB to be penalized and their medical licenses modified (limited) or taken [10]. It should be noted that research has not uncovered any other illness –known to be caused by bacterial infection– where physicians risk their medical licenses when treating with antimicrobial protocols from clinical practice guidelines that have met internationally accepted standards according to the (US) National Academies of Medicine –also referred to as the Institute of Medicine (IOM). [10]. Climate change and re-emerging reservoirs of vector borne diseases contribute to a rapidly expanding LB patient group—a group that is facing obstruction to treatment options [11], [12].

LB patients experience stigma generated by government institutions, not unlike that of acquired immune deficiency syndrome (AIDS) patients in the first 15 years of the AIDS crisis when the Centers for Disease Control and Prevention (CDC) policy stated human immunodeficiency virus (HIV) infection was linked to those with 'certain lifestyles' and dismissed the possibility that heterosexual females could contract HIV [13].

Surveillance criteria are the selected symptoms that can be used indicate an illness –they do not describe the clinical presentation of the disease and they are not to be used for clinical diagnosis. In the case of LB patients, the CDC, the NIH and health ministries in other nations erroneously claim those patients who fall outside of a strictly defined set of symptoms – associated with surveillance criteria and the early acute phase of the infection– have a number of issues or conditions other than LB infection.

These might include MUS, an inability to live with the typical aches and pains of daily life, a tendency to fabricate conditions that include ‘fake’ serious disability, undiagnosed issues that result in attention-seeking behaviors, or have other undiagnosed illnesses causing their health issues. Furthermore, the marginalization and stigmatizing of female patients living with chronic and complicated cases of LB is even greater than that of males because of the unfounded gender bias that indoctrinates the conceptualization of somatic symptoms [14]-[18].

Additionally, the health-related quality of life (HRQoL) indicators of disabled LB patients is worse than those suffering congestive heart failure, stroke, multiple sclerosis, asthma, and other chronic conditions [19].

Lyme and relapsing fever borreliosis are zoonotic diseases. Zoonotic diseases such as relapsing fever disproportionately affect poor and marginalized populations –many of whom practice animal husbandry for their livelihoods. Over 600 million people globally are livestock-dependent and are exposed to ‘spill over’ or vector-transmitted pathogens at the human-animal interface [20], [21].

Furthermore, geographic, political, economic and socio-cultural factors marginalize 70 percent of this population group from political representation, political processes, and access to health care and education [22]. In Africa, economic activities related to animal husbandry and agriculture expose humans to tick-borne pathogens, including tick-borne relapsing fever borreliosis.

While *Borrelia hermsii* is the most common cause of relapsing fever in the US, *B. duttonii* is responsible for the relapsing fever found in central, eastern, and southern Africa. *B. crocidurae* is found in West Africa and a common animal reservoir for the infection –the Guinea multimammate mouse and the African grass rat– expand the range of infection to Algeria, Burundi, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Egypt, Eritrea, Ethiopia, Kenya, Malawi, Mauritania, Morocco, the Republic of the Congo, Rwanda, Sudan, Tanzania, Uganda, Yemen and Zambia.

Furthermore, a 2015 study found 15 tick-borne relapsing borreliosis infected rodent and shrew species common to many areas of Africa [23]. Nevertheless, in malaria endemic countries, many feverish conditions –with or without neurological complications– are often misdiagnosed as ‘malaria’ and these patients subsequently receive the wrong and ineffective treatment [24], [25].

Lyme and relapsing fever borreliosis bacteria are spirochetes similar to syphilis. These are intracellular pathogens, and in opposition to syphilis, are difficult to cure. [26]. They are known to evade immune response and form biofilms that are difficult to eradicate. It has been demonstrated that borrelial spirochetes survive in many cell types even when treated with powerful antimicrobials, e.g. ceftriaxone [27].

LB patients experience symptoms that range from flu-like to life threatening and fatal conditions [28]. Autopsies have shown that patients on short course antimicrobial treatment are still riddled with bacteria [29].

The results of research into relapsing fever borreliosis have been less contested. However, patients with relapsing fever borreliosis often go undiagnosed and misdiagnosed as the research has not translated into medical awareness of the range and occurrence of the infection. Additionally, LB is a public health concern in many European nations, as well as the United States of America (USA) and Canada whereas relapsing fever is often mischaracterized as an illness found in developing nations and therefore not a priority of industrialized nations.

LB infection creates complex conditions and many are potentially fatal. Hundreds of peer reviewed studies and publications describe a range of physical conditions caused by the infection. As with syphilis, the LB infection can affect every bodily system, be congenitally transferred from mother to fetus and persist as latent as well as seronegative infection.

TABLE I
 CONDITIONS CAUSED BY LYME BORRELIOSIS, INCLUDING THOSE CAUSED BY PERSISTENT INFECTION

^a Conditions
Congenital Lyme disease*
Primary Infection, seronegative
Persistent infection
Borrelial lymphocytoma
Acrodermatitis atrophicans
Granuloma annulare, morphea
Localized scleroderma
Lichen sclerosis and atrophicus
Lyme disease of skin and mucous membranes
Lyme alopecia
Lyme oculopathy
Lyme iridocyclitis, iritis
Lyme uveitis
Lyme meningitis*
Lyme nephritis*
Lyme hepatitis*
Lyme myositis
Lyme aortic aneurysm*
Coronary artery aneurysm*
Late Lyme endocarditis*
Lyme carditis*
Symptomatic Late Lyme neuroborreliosis*
Late Lyme neuritis or neuropathy*
Meningovascular and neuroborreliosis – with cerebral infarcts*
Lyme Parkinsonism*
Late Lyme meningoencephalitis or meningomyeloencephalitis*
Atrophic form of Lyme meningoencephalitis with dementia and subacute presenile dementia*
Neuropsychiatric manifestations
Late Lyme borreliosis of other musculo-skeletal tissue
Late Lyme borreliosis of bone and joint
Late Lyme borreliosis of Bronchus* and lung
Late Lyme borreliosis of liver* and other viscera
Late Lyme borreliosis of kidney* and ureter
Latent Lyme borreliosis, unspecified

^a Those with asterisks (*) represent fatal conditions and all conditions presented are supported by no less than three peer-reviewed and published studies [6].

LB is considered a ‘clinical diagnosis’ rather than a laboratory confirmed diagnosis. Routinely recommended tests

for diagnosing both relapsing fever and Lyme borreliosis suffer from low accuracy because they lack sensitivity and do not detect multiple strains and emerging strains of the infection.

For example, the recommended two-tiered tests for LB average a 40 percent accuracy for females and 50 percent accuracy for males [30]. According to a 2016 meta-analysis of Food and Drug Administration (FDA) cleared LB tests, tests averaged from 30.6 to 86.2 percent in accuracy [31]. The two-tier methodology endorsed by the CDC show a 53.7 percent sensitivity [31].

Nevertheless, national health systems and insurance companies often dismiss clinical diagnosis of patients and require a 'positive' test result in order to cover medical treatment therapies. This is particularly true in cases where the patient is not in an acute early phase of the illness.

Differing research outcomes and low accuracy diagnostic tools have contributed to disputes about appropriate treatment that often leave LB patients with disabling symptoms and no access to treatment options that have met the evidence-based criteria as detailed by the IOM's Grades of Recommendation Assessment, Development and Evaluation (GRADE) working group [32]-[34].

Despite these challenges and controversies, there is a way forward that honors evidence-based medicine, patient-centered care and the human rights of borreliosis patients. Bioethicist Diane O'Leary, of the Kennedy Institute of Ethics at Georgetown University has studied the LB access to care situation.

Dr. Leary notes that global and national health organizations have clear ethical obligations and states,

"In the context of scientific debate about the biological origins of chronic Lyme, policy makers have a duty to proactively protect the right to health. Ethically speaking, it is not possible to justify the risk involved in continuing to obstruct access to medical care for chronic LB patients [10]."

III. OVERVIEW OF EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

Since 1999 to date, there have been several international collaborative initiatives to improve the quality of clinical practice guidelines (CPGs) development. These include the Appraisal of Guidelines, Research and Evaluation (AGREE or AGREE II) Consortium and the IOM's GRADE working group [35], [36]. The GRADE and AGREE guidance assist in the use of consistent evidence-based criteria when developing or selecting CPGs to treat or prevent illness.

These instruments have been adopted by many medical institutions, intergovernmental bodies such as WHO and national health ministries throughout the world [37]. Furthermore, the Guidelines International Network (G-I-N) was formed to enhance collaboration in guideline development, implementation and adaptation. G-I-N has 103 organizations and additional individual membership representing 47 countries and supports a strong focus on evidence-based decision-making for the African context.

In addition, there has been increasing effort to separate decisions regarding the 'quality of evidence' from assessing the 'strength of recommendations.' However, there is little consensus in this area. For example, there is on-going debate regarding the quality of evidence from large, rigorous randomized controlled trials (RCTs) and that of expert opinion [38], [39]. The term 'expert opinion' remains vaguely defined.

David Sackett was an American-Canadian medical doctor and considered one of the fathers of evidence-based medicine. Sackett proposed that expert opinion was based upon individual clinical expertise and should reflect the judgement and proficiency physicians acquire through clinical practice. He considered expert opinion to further "integrate individual clinical expertise with the best available external clinical evidence from systematic research" [40]. Furthermore, he emphasized the importance of a patient-centered approach that included patient preferences, concerns and expectations in deciding treatment options and approaches.

However, is it not uncommon for the 'expert opinions' supporting CPGs to originate from professional researchers with little time spent in clinical practice and therefore removed from the patient-centered care experience and orientation.

Additionally, RCTs also have their limitations given the complexity of sociocultural and economic factors that contribute to creating health conditions. Even RCT outcomes that show consistent benefits with few side effects often have questionable parameters and identifiable weaknesses.

As of 2017, the art of medicine is still often based on expert opinion; this is due in part to the lack of quality research for many health conditions, including significant health conditions. Furthermore, key funding trends for medical research indicate increasing public-private partnerships and private sector funding that tends to focus medical research on health conditions that can be monetized by the funders [41], [42]. In such cases, the professional researcher, as opposed to the clinical practitioner, may be viewed as having the expert opinion.

IV. CONFLICTS OF INTEREST IN CLINICAL PRACTICE GUIDELINES FOR TREATING LYME AND RELAPSING FEVER BORRELIOSIS

To date, there have been no specific treatment guidelines developed for relapsing fever borreliosis. However, LB has competing CPGs that show widely differing orientations and two standards of care. Additionally, as LB was first recognized as a distinct disease in the USA, the CDC has played a role in the global defining of the disease and its treatment. Most national health systems that recognize LB have LB policies similar to that of the CDC.

There are CDC officials responsible for LB policies who are members of the Infectious Diseases Society of America (IDSA), a private medical society responsible for the 2006 LB guidelines promoted by the CDC. The CDC's IDSA members hold key CDC posts responsible for the Lyme policy, including the CDC's Office of Infectious Diseases; the National Center for Emerging and Zoonotic Infectious Diseases, the Division of

Vector-Borne Diseases, and the Bacterial Diseases Branch of Division of Vector-Borne Diseases [43].

The World Intellectual Property Organization (WIPO) is the global forum for intellectual property services, policy, information and cooperation. According to a senior WIPO official who asked to remain anonymous, the US government has unique laws that create many conflicts of interests (COIs) – for example, government officials may personally benefit from patents they have developed with taxpayers' monies while holding their government post. For example, in accordance with the Bayh-Dole Act,

“the National Institute of Health (NIH) distributes the royalty income in accordance with federal law and NIH policy. By law, federal inventors must receive the first \$2,000 of income received by the agency and at least 15 percent thereafter, up to a maximum of \$150,000 per year in royalties from all licensed technologies in which they are inventors... In fiscal year (FY) 2000 the inventors of NIH intramural technologies received, as a group, 13.5 percent of total NIH royalty revenue, and 28 NIH inventors currently receive the maximum \$150,000 annual royalty” [44].

Under this law, CDC officials can personally benefit from patents while in official post. For example, a CDC official who holds an LB-related patent may be responsible for assessing new technologies that are in direct competition with their own patent. With regards to LB, the CDC permits government officials to write official papers and make public statements dismissing the validity of tests, devices and inventions that compete with their patents [45].

Additionally, the CDC has never had performance measurements for LB that focus on reducing the disease burden experienced by patients. The current CDC global performance measurements for vector borne disease ignores the Lyme and relapsing fever borreliosis disease burden and only counts the ‘numbers of CDC reagents used’ as a measure of success. For disease surveillance, reagents are substances used to analyze the presence or indication of disease or infection. In this case, the sole recognition of CDC reagents may undermine scientific innovation from competitors in the reagents market as well as free market competition.

Since the 1990s, there have been numerous US congressional testimonials regarding COIs in LB policies, practices and technology –complaints have been made against the CDC, the NIH, state Departments of Health, medical boards, the insurance sector and the IDSA. However, in the US context, factors such as managed care [46], and the political power of the insurance sector and certain academic research centers that have benefited from many millions in LB grants, have held sway in promoting the denial of persistent LB and many of the potentially fatal conditions caused by this infection.

There is growing public awareness that the IDSA Lyme guidelines do not meet internationally accepted standards for CPGs and many USA states have adopted laws to protect Lyme patients' human rights to access treatments that are not found in the IDSA guidelines and do meet these international standards.

It should be noted, that in addition to the criticisms of the IDSA Lyme guidelines by Lyme advocacy groups and outspoken medical and scientific professionals, there are 17 US government authorities that have adopted policies that differ significantly from the CDC and IDSA opinions regarding Lyme borreliosis. These authorities recognize Lyme disease as a serious illness, easily incurred through common outdoor activity and livelihood occupations that, that may have systemic and chronic disabling complications. These authorities acknowledge that delayed treatment may be ineffective once the disease is systemic, that a delay in diagnosis may result in severe and chronic complications and prolonged antimicrobial treatments may be required. They acknowledge the illness may result in loss of livelihood and severe financial hardship [47].

These 17 authorities include the Health and Human Service (HHS), Office on Women's Health, Agency for Healthcare Research and Quality, National Guidelines Clearinghouse (NGC), Office of Personnel Management, Executive Office of the President, US Department of Veterans Affairs Center for Innovation, US Department of Agriculture, US Department of Commerce, National Institute of Standards and Technology, US Department of Labor, Occupational Safety and Health Administration, Office of Disability Employment Policy, Job Accommodation Network, US Department of State, US Department of Transportation and Federal Aviation Administration [48].

In 2006, the IDSA developed CPGs for Lyme borreliosis. The IDSA routinely denies the evidence of persistent LB infections and many of potentially fatal conditions that persistent infection may cause.

As of August 10, 2017, the IDSA continues to promote strictly limited antimicrobial treatment for LB – regardless of patient response– and states that antibiotic stewardship to minimize drug resistance bacteria to be a reason for the strict antimicrobial limits for LB patients. In contrast, open ended antimicrobial intravenous therapies are recommended by the IDSA for other patient groups, such as those with urinary tract infections [49].

Some IDSA members publish opinion pieces that theorize undiagnosed mental illness, rather than persistent infection, might explain why IDSA recommended protocols fail thousands of clinically diagnosed LB patients [50]. It should be noted that none of these IDSA authors are psychiatrists. They often indicate that those LB patients suffer from MUS. The 2013 Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) cautions it is ‘not appropriate to diagnose individuals with a mental disorder solely because a medical cause cannot be demonstrated and encourages clinicians to make a comprehensive assessment and use clinical judgment rather than [...] arbitrarily disqualify many people who are suffering with [...] another medical diagnosis from getting the help they need [51]’.

LB patients given the MUS diagnosis are often shunted into a form of palliative care that routinely demands the ingestion of psychotropic medications, counselling and pain medications to manage medical symptoms. There are many documented cases where such patients, including children suffering from

borreliosis infection, have been forced into psychiatric wards for unwanted and ineffective intensive psychotropic therapies.

Some of the 2006 IDSA guideline authors hold prominent professional positions, have accumulated millions in US government grants, produced many publications and provide expert testimony on behalf of insurance companies against coverage for LB patients. They act as a gatekeeper to some of the world's most prominent medical journals thereby preventing "other scientific conclusions", have authored publications supported by millions in NIH grants that dismiss chronic LB infection and promote MUS as the cause of persistent symptoms [52]-[54]. In the US, between 2007- 2016, approximately 950 government grants for "Borrelia" were awarded. The authors of the 2006 IDSA Lyme Guideline's institutions received approximately two thirds more of these grants than other institutions.

In the last decade, over 32 million dollars of National Institute of Health research grants have supported unverifiable opinions and screeds that attack those concerned and affected by complicated and persistent cases of Lyme disease. These articles fail to meet their stated grant objectives, misapply MUS to those suffering from persistent infection and biological illness, ignore substantial body of peer reviewed studies showing evidence of persistent LB infection and defame and libel patients with complicated and persistent forms of LB and their human rights defenders.

Some of the IDSA Lyme Guidelines authors have published articles that claim –without substantiating proof– that LB patients and practitioners are dangerous, use outlandish dangerous treatments, are funded by 'unknown sources' and are 'nefarious threats' to science [55]-[57]. Still other NIH grants have supported publications dismissing evidence related to persistent LB infection and opine that elected representatives and the media have no legitimate role in representing patient concerns [58], [59].

Instead of advancing scientific and medical understanding, these publications trivialize serious and debilitating LB complications and marginalize LB patients and the medical professionals who serve them.

In 2011, the IOM formed a Committee on Standards for Developing Trustworthy Clinical Practice Guidelines and developed and published Clinical Practice Guidelines We Can Trust [33]. These 2011 IOM guidelines detailed the many reasons why CPGs need to be trustworthy and evidence-based [60]. In Chapter 3 of the publication, the committee noted that many CPGs lack transparency regarding their development methodologies and that such methods varied significantly among the CPG developers, e.g. the roles of independent review and consensus were unclear and the links between CPGs and evidence was often inconsistent or lacking.

As a case study to illustrate some of these shortcomings, the committee chose the IDSA's 2006 CPG for Lyme borreliosis. The IDSA case study –found on page 56, BOX 3-1– details the lack of transparency regarding development methodologies and how the lack of recognition of and treatments for chronic LB prompted concern over the quality of evidence supporting the CPG development.

The case study touches upon COIs and the selection of guideline review committee members, e.g. some CPG authors were expert witnesses in legal proceedings related to LB or expert witness in LB malpractice cases initiated by health insurance companies against doctors who treat chronic LB and LB with coinfections. Lack of patient consultation was noted by the committee, as was the lack of an independent review of the draft CPGs –an independent review was eventually undertaken following an antitrust suit by the Attorney General of Connecticut. On November 10, 2017, a group of LB patients filed a federal antitrust lawsuit in the U.S. District Court for the Eastern District of Texas, Texarkana Division - Case 5:17-cv-00190-RWS. The patients allege that major health insurers are denying coverage for LB treatments based on factitious guidelines that were established by their paid IDSA consultants.

The 2006 IDSA LB guidelines remained posted on the NGC until 2016, despite their failure to meet the IOM's 2011 criteria. To date, the CDC exclusively promotes the outdated 2006 guidelines. In response to public inquiries regarding the CDC's preferential treatment for the outdated CPGs, the CDC broadly states the 2006 guidelines represent the "best science" and "the best synthesis of the available evidence" –the CDC does not provide the references or criteria to substantiate this claim.

The classified nature of biowarfare research on borreliosis pathogens and other tick-borne infections may be driving the CDC's highly irregular practices regarding transparency and accountability surrounding LB 'evidence' and 'best science'. The US government recognizes the LB pathogen as a biowarfare threat pathogen [61]. Furthermore, the IDSA states that "Many of our members are researchers who study infectious microbes, including agents of bioterrorism ... Many of our members ... will be integrally involved should a bioterrorism event occur [62]." The IDSA's deep involvement in biowarfare could also explain why core federal laws regarding preferential treatment are suspended for the IDSA and why IDSA appears to enjoy a very powerful role in dictating CDC Lyme policy and a pivotal role in setting LB policy in sovereign nations outside of the USA.

International Lyme and Associated Diseases Society (ILADS) is the first medical society to issue CPGs on LB developed in accordance with the IOM 2011 standards. To date, the ILADS Guidelines for LB are the only CPGs that included an LB patient as an author and as a member of the CPG development panel. ILADS accepts that Lyme can be a persistent infection further complicated by coinfections.

ILADS has assembled over 600 peer-reviewed articles that support the evidence of persistence of Lyme and other tick-borne diseases. Members of the IDSA have contributed to a number of these peer-reviewed articles regarding persistent infection, yet the 2006 IDSA Lyme CPGs ignores this research [63]. ILADS recognizes this complicated disease requires patients to engage in informed consent for treatment decisions that weigh the risks and benefits of treatment options. The updated ILADS guidelines for LB have been posted on the NGC since 2015.

Following the lead of the CDC, many national health ministries have adopted the COI-riddled CPGs developed by

the IDSA, dismiss persistent infection and misapply MUS to LB patients. Additionally, medical boards in these countries also sanction or strip physicians –who treat this patient group according to the ILADS CPGs that have met GRADE– of their medical licenses.

Altogether, these policies and practices have generated much suffering and led to the human rights violations of LB patients as defined in the Right to Health [64]. This fundamental right is enshrined within the international human rights framework reminding us of the imperative of healthcare under the Availability, Accessibility, Acceptability, Quality (AAAQ) framework [65].

V. THE ROLE OF THE WORLD HEALTH ORGANIZATION IN THE HUMAN RIGHTS VIOLATIONS OF LYME AND RELAPSING FEVER BORRELIOSIS PATIENTS

“ACCESSIBILITY: Health facilities, goods, and services have to be accessible (physically accessible, affordable, and accessible information) to everyone within the jurisdiction of the State party without discrimination.”—WHO principles

The WHO ICD codes for LB parallel the views held by the IDSA and CDC. Caused by the bite of ticks, in the United States (US) alone there are an estimated 380,000 new annual Lyme borreliosis cases - more cases than breast cancer and more than six times the number of new HIV/AIDS cases [66]. Nevertheless, the ICD diagnostic codes for LB cover a fraction of the conditions LB may cause; these codes need to be updated to include chronic or persistent borreliosis and their complications.

Several highly unusual and rare conditions currently have their own diagnostic codes including: W61.62XD Struck by duck; W55.1 Bitten by a cow; V91.07 Burn due to water skis on fire; V95.40 Unspecified spacecraft accident injuring occupant; and R46.1 Bizarre personal appearance. Code elaboration for these unusual conditions stand in contrast to the code omission of serious complications spawned by the borreliosis pandemic.

Without accurate diagnostic codes, physicians are obstructed in their ability to properly care for their LB patients. Centralized electronic medical information systems use the ICD codes to inform the response made by physicians, governments and insurers for various health conditions. When a symptom or condition found in a certain illness does not match a code, the medical systems that utilize these codes default to the ‘unspecified illness’ category.

Clinical decision support software is based on the same ICD codes and the software is programmed to recommend ‘experimental treatment’ for ‘unspecified illness’. Experimental treatment is rarely covered by national health systems or insurers. However, in the case of LB, there are validated treatment protocols that have not been imbedded in the codes because the codes ignore the evidence of persistent infection and many complications. This creates a clear obstruction to validated treatment options and the practice of informed consent for this patient group. This patient group is then forced to pay out-of-pocket for care, if they are able to

afford these costs. This obstruction to care and choice among validated treatment options is in opposition to the AAAQ of the Right to Health.

A 2008 US government report, *Analyses of the Effects of Global Change on Human Health and Welfare and Human Systems*, [67] states that children are considered particularly vulnerable to LB infection –children join other vulnerable groups challenged by the financial costs of LB treatments resulting from the outdated codes. Other vulnerable groups include low income and poor women, men and the elderly. The lack of codes –for the persistent infection, serious complications, congenital transmission and other debilitations– result in great personal hardship, pain, disability and expense for those without much disposable income or less power to decide how family resources are allocated.

The ICD codes are also used for national surveillance purposes. The missing codes make many patients invisible and marginalized within the medical system and to those guiding public policy. The codes are also a standard statistical instrument used to track cause-specific mortality data, morbidity and mortality reporting, epidemiological surveillance, health management efforts, and the development of sound, rational, cost-effective and humane public health policy. However, the soundness of these statistics and policies are impaired by the failure to recognize many clinical manifestations of the infections and results in public health policies divorced from the realities of those individuals, families and communities struggling with the impacts of the illness –particularly the economic impact of these health burdens [68] and the true number of related fatalities.

WHO, like all UN institutions, has a robust stakeholder engagement policy and strong commitment to human rights. WHO held numerous events to engage stakeholders –including patient stakeholders– while developing the ICD 11 version of the codes. For example, stakeholders representing more than 450 individuals and institutions from around the world attended the ICD11 Revision Conference in Tokyo, Japan. The countries represented included: Albania; Algeria; Argentina; Australia; Brazil; Cambodia; Canada; China; Denmark; Egypt; Ethiopia; Finland; India; Indonesia; Iran; Japan; Kenya; Korea; Kuwait; Malaysia; Mexico; Mozambique; Myanmar; Namibia; Nepal; Netherlands; Philippines; Republic of Korea; Russian Federation; Rwanda; Slovakia; Sri Lanka; Sweden; Tanzania; Thailand; Turkmenistan; Uganda; United Kingdom; and the United States of America [69].”

Patients representing all ‘diseases of consequence’ have been engaged by WHO –except for those living with LB. As a stakeholder group representing patient concerns from multiple nations, the Ad Hoc Committee for Health Equity in ICD11 requested a meeting with WHO to discuss their research findings and better ensure their recommendations were incorporated into the ICD 11 version that is currently under formulation. In violation of the WHO stakeholder engagement policy, all the meeting requests were denied with no reasons provided, even when the request for this meeting came from the Global Health Ambassador from the UN Foundation.

On June 2, 2017, the Ad Hoc committee received a response to their report recommendations from Dr. Ian Smith, the Executive Director of the Director-General's Office of the WHO. He stated, "Lyme disease is a condition that is well represented in the international classification of diseases."

Dr. Smith's response ignored the Ad Hoc Committee's report detailing reasons for adapting Lyme borreliosis to be analogous to syphilis ICD codes. The WHO coding system is supposed to be 'logical' and the coding rules are supposed to be applied with uniform logic. However, this is clearly not the case for Lyme borreliosis.

Like the spirochetal infection syphilis, the LB spirochetal infection can be systemic and fatal. LB is also known as the 'cousin' to syphilis. However, the ICD codes do not treat LB with the same 'uniform' logic applied to syphilis. Medical professionals who treat LB patients must search throughout the code system and investigate broad and generic terms of 'bacterial infection' in the hopes of finding appropriate proxies for the systematic manifestations caused by LB infection – many of which are not found in the ICD system. In contrast, the syphilis codes are linear and connected, making it easy to link all the systemic manifestations of the disease back to the main infection and then to appropriate treatment.

The reasons for WHO's lack of action regarding the LB codes remain unclear – particularly when the analysis and guidance has been provided in detail and included recommendations by those who routinely advise WHO. However, it is clear the current status of the ICD codes will continue to perpetuate the human rights violations experienced by LB patients. Therefore, the Ad Hoc Committee will continue to work with the Special Rapporteur and other parties to ensure the ICD codes for Lyme borreliosis are updated.

VI. THE BENEFITS OF ACCESS TO TREATMENT FOR LYME BORRELIOSIS PATIENTS

Many LB patients' medical conditions improve following the short-term antibiotic treatment recommended by the IDSA or the CDC. The IDSA recommends antibiotic treatment for cases of LB proven by serology. However, when other diagnoses have been eliminated and an LB diagnosis is highly probable, many physicians successfully treat seronegative cases of LB.

Some institutions agree with this common empiric and clinical practice. For example, in 2011 the CDC included the diagnosis of "probable LB" in the list of diagnosis which should be reported by physicians. The diagnosis is confirmed by the response to an empiric antibiotic treatment. Currently, the French High Council for Public Health (Haut Conseil de la Santé Publique) has acknowledged the lack of sensitivity of Lyme serologies and has recommended that, in the absence of reliable diagnostic tests, an empiric antibiotic treatment is to be given to patients with a probable LB [70].

The IDSA and CDC opine that LB is cured after three or four weeks of an antibiotic treatment with amoxicillin, ceftriaxone iv or doxycycline. The official explanation for the persistent of LB symptoms following short term antibiotic treatment is that the symptoms are sequelae from long undetected infection or are psychosomatic in nature (an 'over preoccupation' with

distressing symptoms such as debilitating pain) rather than the result of ongoing infection.

However, most LB patients suffering from a chronic form of the disease have a progressive illness or experience a relapse after the end of antibiotic treatment. Furthermore, the low level of evidence of the IDSA guidelines for LB is now well established [71]. For example, several studies demonstrate that patients with chronic LB are not cured after a few weeks of antibiotic treatment [72]-[77].

A 1994 study showed that 34% of patients who had received short-term treatment had persistent signs and symptoms after a mean post-treatment period of 6.2 years and 62% of 215 treated patients were still sick after a mean post-treatment period of 3.2 years [72]. In the 2012 pediatric study by Skogman et al, following short-term treatment, 43% of the children had symptoms that negatively impacted their school performance [74]. In a 2011 study on neuroborreliosis, 16% of patients had persistent cognitive disorders 30 months after the end of treatment [75]. Five hundred and four short-term treated patients complained of more fatigue, more musculoskeletal pain and more neuro-cognitive disorders than 530 control persons in a 2005 meta-analysis [76]. Additional research has shown that objective anomalies could be seen in these patients [77].

Many Lyme literate medical doctors throughout the world follow the ILADS CPGs for LB; they prescribe long-term anti-infectious treatments for LB patients with persistent symptoms [33], [34]. Antibiotics are often combined with antiparasitic drugs to be effective against coinfections and anti-infectious courses can be intermittent in the maintenance phase of the treatment. A 1996 study showed many American doctors are open-minded and follow ILADS recommendations to manage LB [78]. These practitioners have accumulated many tens of thousands of documented cases showing how these protocols have helped severely compromised and debilitated patients regain functional independence, and resume their economic, family and social responsibilities. Nevertheless, despite the high frequency of patient recovery and the strong support of the associations of patients, these patient-centered options of therapy are contested by the IDSA, CDC and other institutions that promote strict antimicrobial limitations for LB therapies [79], [80].

As previously noted, evidence-based medicine is a decision-making tripod combining published data in the medical literature, the clinical experience of the physician and the patient's choice [81]. The GRADE evaluation system emphasizes the experience of the physician is crucial in absence of good convincing published data, or when data have a low or very low level of evidence and the informed consent of the patient should evaluate the risk-benefit balance of the different options for disease management and have access to published data [33], [82].

Persistence of *Borrelia burgdorferi* after antibiotic treatment is now evident in the literature. Numerous scientific publications demonstrate that *Borrelia* sp. may change their form from mobile spiral-shaped bacteria to round forms. Persist bacterial cells may change their metabolism, hide in

biofilms and escape from antibiotics without becoming resistant [83]-[90].

Research spanning multiple decades have shown persistence of *Borrelia* sp. following antimicrobial treatment. This has been demonstrated in several animal species [91]-[96]. Furthermore, the persistence of *Borrelia* sp. has been demonstrated in humans after the end of an antibiotic treatment given for an erythema migrans, a primary form of the disease [97]-[99]. Moreover, persistence of *Borrelia* sp. has been demonstrated in humans after an antibiotic treatment of late persistent phases of LB [100]-[111].

However, there have been no significant research dollars devoted to showing the efficacy of prolonged antibiotic treatment, leaving these protocols open to controversy [78], [112], [113]. Several controlled, randomized versus placebo, studies failed, due to methodological flaws, to evaluate the efficacy of anti-infectious treatments for a duration longer than the three-week course usually recommended. But no study has evaluated a sufficiently prolonged antibiotic or anti-infectious treatment versus placebo.

Furthermore, there has been no investment in good clinical trials to evaluate prolonged anti-infectious treatments for chronic LB. Several open-labeled studies have shown that prolonged antibiotic treatment could cure or improve the medical condition of a high proportion of patients [114]-[117]. It has been observed that in many cases, long undiagnosed LB infections require prolonged treatment to obtain medical benefits.

In four published randomized studies, the duration of treatment evaluated versus placebo was short, from four weeks to three months maximum. In two randomized studies, patients had received a three-week antibiotic treatment, according to IDSA recommendations [118], [119]. In these two studies, patients who had persistent signs and symptoms after the end of treatment, such as debilitating fatigue or memory disorder, were given either a second line of treatment or a placebo (with a four-week duration in one study and a 10-week duration in the other).

A very significant effect of antibiotic treatment versus placebo was demonstrated on fatigue for patients retreated during the four-week duration and on memory disorders for patients treated during 10-week duration. In both studies, the highly significant beneficial effect was transient, however these second line treatments used inappropriately low doses of antibiotic and were rather short compared to most prolonged treatment practices.

Two other randomized studies have evaluated patients who had all received a two-week course of ceftriaxone, an antibiotic given intravenously. Randomization was made for an immediate continuation of a second line anti-infectious treatment after week two or for a placebo. This second line treatment had a three-month duration. In the 2001 study, patients in the antibiotic group received doxycycline [120]. In the nearly identical 2016 randomized study, there were three arms and the two treated arms received either doxycycline or a combination of clarithromycin and hydroxychloroquine [121].

The findings of both the 2001 and the 2016 studies are questionable given the quality of their methodological practices

and parameters. For example, signs and symptoms are only evaluated at baseline and their evolution is never analyzed at later time-points. Thus, it is impossible to evaluate the worsening, the stability or the improvement of the different categories of symptoms - e.g. neurologic, cardiac, muscular, articular, cutaneous, etc. A 2012 biostatistical study noted that the minimal clinically important difference (MCID) for the Short Form Survey-36 (SF-36) quality of life score has never been established for LB and therefore the chosen threshold for the 2001 study appears baseless and inappropriate [122]. The consequence of applying this inappropriate threshold was that the patients could not be correctly classified as 'improved'. The only judgment criterion is the SF-36 score, an unprecise score of quality of life which gives a mean general impression, without considering the evolution of objective signs analyzed at different time-points.

These two studies do not allow to differentiate between oscillations of signs and symptoms, exacerbations, and possible side effects of treatments. For example, every antimicrobial active against *Borrelia* sp. is often responsible for an exacerbation of signs and symptoms (Jarisch-Herxheimer reaction). These exacerbations may be quite strong, prolonged and have often a cyclic evolution with phases of improvement alternating with phases of worsening. Thus, in the study, the normal evolution of a treated LB with transient phases of worsening are systematically registered as "failure" or "side-effect".

The 2001 study was stopped prematurely after three months of treatment claiming that a significant difference between both groups was not seen yet. The 2016 study copied the same design 15 years later, despite the fact that the researchers knew that this design could not show a significant difference between groups.

It should be noted that the lead researchers of both the 2001 and 2016 studies assert the standard two-tiered Lyme diagnostic tests to be very accurate. Therefore, it is remarkable that both studies included high numbers of seronegative patients -40% of the patients included in the 2001 study and 20% of the patients included in the 2016 study [119], [120]. Both of these were 'retreatment' studies, in which a previously administered but failed treatment was again administered.

In conclusion, there have been no well-designed randomized study to evaluate the efficacy of prolonged anti-infectious treatment of chronic LB. Previous studies evaluated truncated treatment durations and the methodology did not consider the experience of Lyme literate medical doctors nor the advice of patients who have benefited prolonged treatment.

The financial burden of LB and coinfections is high for the societies, with huge costs for the management of never ending chronic conditions that are often combined with incapacity to work. These conditions create emotional burdens that erode family bonds and can destroy the future of children who are at high risk for this illness.

There is great need to fund well-designed randomized study -with objective criteria which could be evaluated at different time-points- to evaluate the efficacy of prolonged anti-infectious treatment of chronic LB. The recognition of this disease threat should make it an international priority to confirm

the benefit of these treatments and to remove all obstruction to care for the millions of patients abandoned throughout the world. Beyond the clear need for well-designed patient-centered studies, this pandemic requires responses and coordination among many key public and private institutions. Such actions would include:

1. Provide public funding to improve borreliosis diagnostic tests, which are currently unreliable. There should be a portion of this funding set aside for new innovators.
2. Until such tests are available, honor, support and accept the clinical diagnosis of Lyme and relapsing fever borreliosis and begin antimicrobial treatment.
3. Create enabling environments for multiple innovative diagnostic tests to compete with those patents and reagents held by the CDC and other institutions using outdated and/or low accuracy technologies and products.
4. Change the laws so that government institutions and officials responsible for promoting scientific and medical innovations cannot be patent holders in the same arenas of competition.
5. Modernize the WHO's ICD codes for Lyme borreliosis to reflect the complexity and seriousness of the disease.
6. Modernize the WHO's ICD codes for relapsing fever borreliosis.
7. Utilize the improved ICD codes to enhance the quality of borreliosis surveillance to: inform public health policy; strengthen the 'One Health' synergy - to obtain optimal health of people, animals, and the environment; and understand and prepare for the impact of climate change.
8. Official recognition of complicated and persistent Lyme and relapsing fever borreliosis is required.
9. Official recognition of physical disability caused by Lyme and relapsing fever borreliosis is required [123].
10. Require national health systems and private insurers to recognize and provide treatment coverage for complicated and persistent forms of Lyme and relapsing fever borreliosis. Qualifying treatments would include those that meet IOM's 2011 internationally accepted CPG standards.
11. Stop the persecution of doctors who utilize clinical diagnosis and treatments that meet IOM 2011 standards for clinical practice guidelines.
12. Penalize the slandering, libeling, stigmatizing and bullying of Lyme and relapsing fever borreliosis patients.
13. Make the differential diagnosis of Lyme and relapsing fever borreliosis part of standard medical assessments in countries where the diseases have been identified. The lack of differential diagnosis is particularly problematic for certain groups – such as the elderly. For example, untreated Lyme borreliosis symptoms can mimic conditions associated with aging, e.g. arthritis, dementia and vision and hearing loss.
14. Honor patients' rights to choose among treatment options and require medical professionals to inform patients of these choices.
15. Increase public funding for patient-centered research to improve diagnosis and treatments for borreliosis, other tick-borne diseases and co-infections.

16. In many countries, children are among in the highest risk groups for Lyme borreliosis. Help these children reach their potential and fulfill their dreams by organizing collaboration among key institutions to protect the health and advancement of these children.
17. Require public schools and universities to develop plans to accommodate students living with complicated and persistent forms of Lyme borreliosis and relapsing fever borreliosis.
18. Require that services provided by public institutions are accessible to those living with Lyme and relapsing fever borreliosis.
19. Assist private businesses and corporations in developing employer strategies that retain employees who have debilitation or other limitations due to Lyme and relapsing fever borreliosis.
20. Require that all standing governmental committees for borreliosis research and policy have patient and caretaker stakeholder representation.

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REFERENCES

- [1] Vector control-Public health importance CHAPTER 4 • BEDBUGS, FLEAS, LICE, TICKS AND MITES Page 268 - Tick-borne relapsing fever, Page 269 - Lyme disease. World Health Organization 1995.
- [2] Patz JA, Githeko AK, McCarty JP, Hussein S, Confalonieri U, de Wet N. Climate change and human health risks and responses. CHAPTER 6 - Climate change and infectious diseases Page 125 - BOX 6.2 Ecological influences and Lyme disease. WHO 2003 (IPCC contribution).
- [3] Lindgren E, Jaenson TGT. Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures. World Health Organization 2004.
- [4] Vector Biology and Control unit in WHO/EMRO Eastern Global report for Research Infectious diseases of Poverty. WHO publication 2012.
- [5] European Centre for Disease Prevention and Control. ECDC tool for the prioritisation of infectious disease threats – Handbook and manual. Stockholm: ECDC; 2017.
- [6] Luché-Thayer J, Ahern H, DellaSala D, Franklin S, Gilbert L, Horowitz R, Liegner K, McManus M, Meseko C, Miklossy J, Rudenko N, Stuckelberger A, contributing researchers: Beaton J, Blakely J, Freeman P, Garg K, Kraaijeveld H, Lloyd V, Meriläinen L. Updating ICD11 Borreliosis Diagnostic Codes: Edition One, March 29, 2017. ISBN-10: 1978091796 ISBN-13: 978-1978091795 CreateSpace Independent Publishing Platform October 7, 2017.
- [7] Web source: <https://botaborrelia.wordpress.com/> Accessed 08.20.2017.
- [8] Schein LA, Harold S, Bernard HS, Henry I, Spitz HI, Philip R, Muskin PR (Editors). Psychosocial Treatment for Medical Conditions: Principles and Techniques 1st Edition. Published by Brunner-Routledge 2003.

- [9] Koch, LC, Rumrill PD. Rehabilitation Counseling and Emerging Disabilities: Medical, Psychosocial, and Vocational Aspects 1st Edition. Published by Springer Publishing LLC, 2017.
- [10] Human rights violations presented on June 7, 2017 to the Special Rapporteur Dr. Dainius Pūras, in addition to those documented in the report to WHO - Luché-Thayer J, Ahern H, DellaSala D, Franklin S, Gilbert L, Horowitz R, Liegner K, McManus M, Meseko C, Miklossy J, Rudenko N, Stuckelberger A, contributing researchers: Beaton J, Blakely J, Freeman P, Garg K, Kraaijeveld H, Lloyd V, Meriläinen L. Updating ICD11 Borrelia Diagnostic Codes. Technical Report accepted by WHO March 2017.
- [11] Walker AR, Bouattour A, Camicas J, Estrada-Pena A, Horak IG, Latif AA, et al. Ticks of Domestic Animals in Africa: A Guide to Identification of Species. Published by Bioscience Reports, Edinburgh, United Kingdom. 2003.
- [12] DA DellaSala, M Middelveen, KB Liegner, J Luché-Thayer. Lyme Disease Epidemic Increasing Globally Due to Climate Change and Human Activities. Elsevier Inc. 2017.
- [13] Web Source: https://www.publicartfund.org/view/exhibitions/5735_women_don't_get_aids_they_just_die_from_it Accessed 08.20.2017
- [14] Wormser GP, Shapiro ED. Implications of Gender in Chronic Lyme Disease. *J Womens Health (Larchmt)*. 2009 Jun; 18(6): 831–834. doi: 10.1089/jwh.2008.1193.
- [15] Presentation by Diane O'Leary. The Gender Principle as a Barrier to Healthcare Access for Women. Visiting Researcher, Kennedy Institute of Ethics, Georgetown University 2017.
- [16] Tasca C, Rapetti M, Carta MG, Fadda B. Women And Hysteria In The History Of Mental Health. *Clin Pract Epidemiol Ment Health*. 2012; 8: 110–119. Published online 2012 Oct 19. doi: 10.2174/1745017901208010110.
- [17] Barsky AJ, Peekna HM, Borus JF. Somatic Symptom Reporting in Women and Men. *J Gen Intern Med*. 2001 Apr; 16(4): 266–275. doi: 10.1046/j.1525-1497.2001.00229.x.
- [18] Oxford Textbook of Women and Mental Health, Edited by Dora Kohen. Oxford University Press Print ISBN-13: 9780199214365 Published online: Jul 2011 DOI: 10.1093/med/9780199214365.001.0001.
- [19] Johnson L, Wilcox S, Jennifer Mankoff J, Raphael B, Stricker RB. Severity of chronic Lyme disease compared to other chronic conditions: a quality of life survey. March 27, 2014. PubMed 24749006. <https://peerj.com/articles/322/>.
- [20] Daszak P, Cunningham AA, Hyatt, AD, Emerging infectious diseases of wildlife—threats to biodiversity and human health. *Science*; 287.5452:443-9. Jan 21, 2000.
- [21] Food and Agriculture Organization. The pro-Poor Livestock Policy Initiatives: A living from Livestock. Rome; 2004.
- [22] Molyneux D, Hallaj Z, Keusch GT, McManus DP, Ngowi H, Cleveland S, Ramos-Jimenez P, Gotuzzo E, Kar K, Ana Sanchez A, Garba A, Carabin H, Bassili A, Chaignat CL, Meslin FX, Hind M, Abushama HM, Arve L, Willingham AL, Kioy D. Zoonoses and marginalised infectious diseases of poverty: Where do we stand? *Parasit Vectors*. 2011; 4: 106.
- [23] Diatta G, Duplantier J-M, Granjon L, et al. Borrelia infection in small mammals in west Africa and its relationship with tick occurrence inside burrows. *Acta Tropica*. 2015;152:131–140.
- [24] Nordstrand A, Bunikis I, Larsson C, Tsogbe K, Schwan TG, Nilsson M, et al. Tickborne relapsing fever diagnosis obscured by malaria, Togo. *Emerg Infect Dis*. 2007;13:117–23.
- [25] Goutier S, Ferquel E, Pinel C, Bosserey A, Hoen B, Couetdic G, Bourahoui A, Lapostolle C, Pelloux H, Garnier M, Sertour N, Pelloux I, Pavese P, Cornet M. Borrelia crocidurae Meningoencephalitis, West Africa. *Emerging Infectious Diseases* • www.cdc.gov/eid • Vol. 19, No. 2, February 2013.
- [26] Mahmoud AAF. The challenge of intracellular pathogens. *New England Journal of Medicine* 326(11): 761. 1992.
- [27] Georgilis K, Peacocke M, and Klemmner MS. Fibroblasts protect the Lyme Disease spirochete, Borrelia burgdorferi, from Ceftriaxone In Vitro. *Journal of Infectious Diseases* 166: 440–444. 1992.
- [28] Fox M. Three die suddenly from rare Lyme disease complication. NBC News December 12, 2013.
- [29] Liegner KB. In the Crucible of Chronic Lyme Disease – Collected Writings & Associated Materials. Xlibris 2015. Library of Congress Control Number 2015911615.
- [30] Schwarzwald A, Schneider MF, Lydecker A, Aucott JN. Brief Report Sex Differences in the Clinical and Serologic Presentation of Early Lyme Disease: Results from a Retrospective Review. *Gender Medicine Vol. 7, No. 4*, 2010.
- [31] Cook MJ, Puri BK. Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. *International Journal of General Medicine* 2016;9:427–440.
- [32] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008; 336:924–6.
- [33] Editors: Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E. Clinical Practice Guidelines We Can Trust. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Washington (DC): National Academies Press (US); 2011.
- [34] Kavanagh B. The GRADE System for Rating Clinical Guidelines. *PLoS Med*. 2009 Sep; 6(9): E1000094.
- [35] AGREE, The Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice. guidelines: the AGREE project. *Qual Saf Health Care*. 2003;12:18–23.
- [36] Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010;182(18):E839–42.
- [37] Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P. Guidelines International Network: toward International Standards for Clinical Practice Guidelines. *Ann Intern Med*. 2012;156(7):525–31.
- [38] Rosen L, Manor O, Engelhard D, Zucker D. In Defense of the Randomized Controlled Trial for Health Promotion Research. *Am J Public Health*. 2006 July; 96(7): 1181–1186.
- [39] Victora CG, Habicht JP, Bryce J, Ed. Evidence-Based Public Health: Moving Beyond Randomized Trials. *Am J Public Health*. 2004 March; 94(3): 400–405.
- [40] Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996 Jan 13; 312(7023): 71–72.
- [41] Moses H, Matheson DHM, Cairns-Smith S, George BP, Palisch C, Dorsey ER. The Anatomy of Medical Research US and International Comparisons. *JAMA*. 2015;313(2):174-189.
- [42] UNESCO Science Report: towards 2030.
- [43] CDC officials who are IDSA members include Rima Khabbaz, Deputy Director for Infectious Diseases and Acting Director of Office of Infectious Diseases; recently retired Beth Bell was Director of the National Center for Emerging and Zoonotic Infectious Diseases, Lyle R. Petersen, Director, Division of Vector-Borne Diseases under National Center for Emerging and Zoonotic Infectious Diseases and CDC Spokesperson; C. Ben Beard, Branch Chief, Bacterial Diseases Branch of Division of Vector-Borne Diseases; and Christina Nelson, Medical Epidemiologist with the Bacterial Diseases Branch.
- [44] Department of Health and Human Services National Institutes of Health - NIH Response to the Conference Report Request for a Plan to Ensure Taxpayers' Interests are Protected. Page 7. July 2001. Web source: <https://www.ott.nih.gov/sites/default/files/documents/policy/wydenrpt.Pdf> Accessed 08.20.2017.
- [45] CDC official Barbara Johnson submitted a patent for Lyme diagnostics that would have been in competition to one she publicly dismissed as low quality after the competitor –working closely with the CDC– met all benchmarks for approval. The competitor is Dr. Sin Hang Lee, Sin Hang's areas of expertise include General pathology, surgical pathology, clinical microbiology, and molecular diagnostics by PCR/direct DNA sequencing. He has over 70 publications from a career that has spanned nearly six decades. He is currently suing the CDC for their anti-competitive practice against using Sanger sequencing for the diagnosis of Lyme borreliosis. According to Sin Hang, all laboratories can use this well-established generic method to diagnose Lyme borreliosis. According to US law, government entities and officials are privileged with a significant degree of immunity –one can only sue for personal damage via an SF-95 form with a specific amount of damage claimed to be listed on the initial Complaint. His filing for a court case is pending and his documents are now on public record.
- [46] Lightfoot RW, Luft BJ, Rahn DW, Steere AC, Sigal LH, Zoschke DC, Gardner P, MD; Britton MC, Kaufman RL. Empirical Parenteral Antibiotic Treatment of Patients with Fibromyalgia and Fatigue and a Positive Serologic Result for Lyme Disease: A Cost-Effectiveness Analysis. *Ann Intern Med*. 1993;119(6):503-509.
- [47] Web Source: <https://on-lyme.org/en/sufferers/lyme-stories/item/253-explaining-human-right-violations-around-lyme-disease> Accessed 08.20.2017.

- [48] Luché-Thayer J. CDC's Profile Plummets While 15 Government Authorities Act on Persistent and Disabling Lyme Disease. Technical paper submitted to Senate Budget Committee's Chief Investigator. July 4, 2017.
- [49] Web Source IDSA Statement on Reintroduction of Home Infusion Legislation, 06/20/2011 http://www.idsociety.org/IDSA_Statement_on_Reintroduction_of_Home_Infusion_Legislation/ Accessed 08.20.2017.
- [50] Web source <https://botaborrelia.wordpress.com/> Accessed 08.20.2017.
- [51] American Psychiatric Association (APA) Fact Sheet on Somatic Symptom Disorder. 2013 American Psychiatric Association.
- [52] Lantos PM. Chronic Lyme Disease. *Infect Dis Clin North Am*. 2015 Jun; 29(2): 325–340.
- [53] Lantos PM, Wormser GP. Chronic coinfections in patients diagnosed with chronic Lyme disease: a systematic literature review. *Am J Med*. 2014 Nov; 127(11): 1105–1110.
- [54] Luché-Thayer J. Lyme Patients Stigmatized and Scapegoated with Federal Support. July 25, 2016. Technical paper for US Congressional record.
- [55] Lantos PM, Shapiro ED, Auwaerter PG, Baker PJ, Halperin JJ, McSweeney E, Wormser GP. Unorthodox Alternative Therapies Marketed to Treat Lyme Disease. *Clin Infect Dis*. 2015 June 15; 60(12): 1776–1782.
- [56] Auwaerter PG, Bakken JS, Dattwyler RJ, Dumler JS, MD, Halperin JJ, McSweeney E, Nadelman RB, O'Connell S, Shapiro ED, Sood SK, Steere AC, Weinstein A, Wormser GP. Antiscience and Ethical Concerns Associated with Advocacy of Lyme Disease. Volume 11, No. 9, p713–719, September 2011.
- [57] Luché-Thayer J. NIH Grants Used to Claim Lyme Patients are Looney. June 30, 2016. Technical paper for US Congressional record.
- [58] Shapiro ED, Baker PJ, Wormser GP. False and Misleading Information about Lyme Disease. *Am J Med.*, Vol 130, No 7, July 2017.
- [59] Luché-Thayer J. Analysis of False and Misleading Information about Lyme Disease. April 2017. Technical paper for NIH forensic audit of grant misappropriations.
- [60] Web Source: <http://www.nationalacademies.org/hmd/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust/Standards.aspx>. Accessed 08.20.2017.
- [61] Web source: <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2008147879&recNum=1&maxRec=&office=&prevFilter=&sortOption=&queryString=&tab=PCTDescription> Patent no. WO/2008/147879 filed with the World Intellectual Property Organisation (WIPO) in 2007. Inventor Ryan Golhar states "The present invention provides methods and devices for the identification of bioagents via the presence of their nucleic acids. In the context of the present invention, a "bioagent" is any organism, living or dead, or a nucleic acid derived from such an organism ... Bacterial biological warfare bioagents capable of being detected by the present methods include, but are not limited to, *Bacillus anthracis* (anthrax), *Yersinia pestis* (pneumonic plague), *Francisella tularensis* (tularemia), *Brucella suis* ... *Borrelia burgdorferi* (Lyme disease)."
- [62] Web source http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Positions_on_Health_Reform/Statements/IDSA%20concerning%20Project%20BioShield.pdf. Accessed 09.20.2017.
- [63] Web Source http://www.ilads.org/ilads_news/wp-content/uploads/2015/09/EvidenceofPersistence-V2.pdf. Accessed 08.20.2017.
- [64] Web source <http://www.ohchr.org/Documents/Publications/Factsheet31.Pdf>. Accessed 08.20.2017.
- [65] Web source <http://www.ohchr.org/Documents/Issues/ESCR/Health/RightToHealthWHOFS2.pdf>. Accessed 08.20.2017.
- [66] Source is the CDC. (2013) International Conference on Lyme Borreliosis and other Tick-borne Diseases. 18 Aug 2013.
- [67] Web Source <https://downloads.globalchange.gov/sap/sap4-6/sap4-6-final-report-all.pdf>. Accessed 08.20.2017.
- [68] Adrion ER, Aucott J, Lemke KW, Weiner JP. Health care costs, utilization and patterns of care following Lyme disease. *PLOS ONE*. 2015;10(2):e0116767.
- [69] The full report on the ICD11 Revision Conference in Tokyo, Japan is available at web source: <http://who.int/classifications/network/meeting/2016/ICD-11RevisionConferenceReportTokyo.pdf?ua=1>. Accessed 08.20.2017.
- [70] Haut Conseil de la Santé Publique. Borréliose de Lyme. Etat des connaissances. 23 mars 2014. Avis & Rapports. www.hcsp.fr (in French).
- [71] Lee DJ, Vielmeyer O. Analysis of overall level of evidence behind Infectious Diseases Society of America practice guidelines. *Arch Intern Med*. 2011; 171: 18-22.
- [72] Shadick NA, Phillips CB, Logigian EL et al. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. *Ann Intern Med*. 1994; 121: 905-8.
- [73] Asch ES, Bujak DI, Weiss M et al. Lyme disease: an infectious and postinfectious syndrome. *J Rheumatol*. 1994; 21: 454-61.
- [74] Skogman BH, Glimaker K, Nordwall M, et al. Long-term clinical outcome after Lyme neuroborreliosis in childhood. *Pediatrics*. 2012; 130: 262-9.
- [75] Eikeland R, Mygland A, Herlofson K, Ljostad U. European neuroborreliosis: quality of life 30 months after treatment. *Acta Neurol Scand*. 2011; 124: 349-54.
- [76] Cairns V, Godwin J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. *Int J Epidemiol*. 2005; 34: 1340-5.
- [77] Fallon BA, Lipkin RB, Corbera KM, Yu S, Nobler MS, Keilp JG, Petkova E, Lisanby SH, Moeller JR, Slavov I, Van Heertum R, Menseh BD, Sackeim HA. Regional cerebral blood flow and metabolic rate in persistent Lyme encephalopathy. *Arch Gen Psychiatry*. 2009; 66: 554-63.
- [78] Ziska MH, Donta ST, Demarest FC. Physician preferences in the diagnosis and treatment of Lyme disease in the United States. *Infection*. 1996; 24: 182-6.
- [79] Institute of Medicine (US) Committee on quality of health care in America. Crossing the quality chasm: a new healthsystem for the 21st century. National Academies Press; Washington DC, USA. 2001. P. 360.
- [80] Stricker RB. Counterpoint: long term antibiotic therapy improves persistent symptoms associated with Lyme disease. *Clin Infect Dis*. 2007; 45: 149-57.
- [81] Sackett D, Straus S., Richardson W, et al. Evidence based-medicine: how to practice and teach EBM. Churchill Livingstone, Edinburgh, London. 2000.
- [82] Pediatrics 2004 Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004; 114: 874-7.
- [83] Liegner KB, Shapiro JR, Ramsay D, Halperin AJ, Hogrefe W, Kong L. Recurrent erythema migrans despite extended antibiotic treatment with minocycline in a patient with persisting *Borrelia burgdorferi* infection. *J Amer Acad Derm* 1993;28:312-4.
- [84] Meriläinen L, Herranen A, Schwarzbach A, Gilbert L. Morphological and biochemical features of *Borrelia burgdorferi* pleomorphic forms. *Microbiology*. 2015; 161: 516-27.
- [85] Sharma B, Brown AV, Matluck NE, Hu LT, Lewis K. *Borrelia burgdorferi*, the causative agent of Lyme disease, forms drug-tolerant persister cells. *Antimicrob Agents Chemother*. 2015; 59, 4616-24.
- [86] Zhang Y. Persisters, persistent infections and the yin-yang model. *Antimicrob Drug Resist*. 2013; 3.
- [87] Brorson O, Brorson SH. Transformation of cystic forms of *Borrelia burgdorferi* to normal, mobile spirochetes. *Infection*. 1997; 25: 240-6.
- [88] Brorson O, Brorson, S.H. In vitro conversion of *Borrelia burgdorferi* to cystic forms in spinal fluid, and transformation to mobile spirochetes by incubation in BSK-H medium. *Infection* 1998; 26: 144–150.
- [89] Brorson O, Brorson SH. A rapid method for generating cystic forms of *Borrelia burgdorferi*, and their reversal to mobile spirochetes, *APMIS*. 1998; 106: 1131-41.
- [90] Lewis K. Persister cells, dormancy and infectious disease. *Nature*. 2007; 5.
- [91] Straubinger RK, Summers BA, Chang YF, Appel MJ. Persistence of *Borrelia burgdorferi* in experimentally infected dogs after antibiotic treatment. *J Clin Microbiol*. 1997; 35: 111-6.
- [92] Straubinger RK. PCR-based quantification of *Borrelia burgdorferi* organisms in canine tissues over a 500-day postinfection period. *J Clin Microbiol*. 2000; 38: 2191-9.
- [93] Embers ME, Ramamoorthy R, Philipp MT. Survival strategies of *Borrelia burgdorferi*, the aetiologic agent of Lyme disease. *Microbes Infect*. 2004; 6: 312-8.
- [94] Hodzic E, Feng S, Holden K, Freet KJ, Barthold SW. Persistence of *Borrelia burgdorferi* following antibiotic treatment in mice. *Antimicrob Agents Chemother*. 2008; 52: 1728-36.
- [95] Barthold SW, Hodzic E, Imai DM et al. Ineffectiveness of tigecycline against persistent *Borrelia burgdorferi*. *Antimicrob Agents Chemother*. 2010; 54: 643-51.
- [96] Embers ME, Barthold SW, Borda JT, Bowers L, Doyle L, Hodzic E, et al. Persistence of *Borrelia burgdorferi* in Rhesus macaques following antibiotic treatment of disseminated infection. *PLoS ONE*. 2012; 7: e29914. Erratum: *PLoS ONE*. 2012; 7.

- [97] Hunfeld KP, Ruzic-Sabljić E, Norris DE, Kraiczky P, Strl F. In vitro susceptibility testing of *Borrelia burgdorferi* sensu lato isolates cultured from patients with erythema migrans before and after antimicrobial chemotherapy. *Antimicrob Agents Chemother*. 2005; 49: 1294-301.
- [98] Strle F, Preac-Mursic V, Cimperman J et al. Azithromycin versus doxycycline for treatment of erythema migrans: clinical and microbiological findings. *Infection*. 1993; 21: 83-8.
- [99] Weber K, Wilske B, Preac-Mursic V, Thurmayer R. Azithromycin versus penicillin V for the treatment of early Lyme borreliosis. *Infection*. 1993; 21: 367-72.
- [100] Haupl T, Hahn G, Rittig M et al. Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis. *Arthritis Rheum*. 1993; 36: 1621-6.
- [101] Lawrence C, Lipton RB, Lowy FD, Coyle PK. Seronegative chronic relapsing neuroborreliosis. *Eur Neurol*. 1995; 35: 113-7.
- [102] Lee SH, Vigliotti JS, Vigliotti VS, Jones W, Shearer DM. Detection of *Borreliae* in archived sera from patients with clinically suspect Lyme disease. *Int J Mol Sci*. 2014; 15: 4284-98.
- [103] Masters E, Lynxwiler P, Rawlings J. Spirochetemia after continuous high-dose oral amoxicillin therapy. *Infect Dis Clin Pract*. 1994; 3: 207-8
- Murgia R, Cinco M. Induction of cystic forms by different stress conditions in *Borrelia burgdorferi*. *APMIS*. 2004; 112: 57-62.
- [104] Oksi J, Nikoskelainen J, Viljanen MK. Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. *Eur J Clin Microbiol Infect Dis*. 1998; 17: 715-9.
- [105] Oksi J, Marjamaki M, Nikoskelainen, Viljanen MK. *Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. *Ann Med*. 1999; 31: 225-32.
- [106] Pfister HW, Preac-Mursic V, Wilske B, et al. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. *J Infect Dis*. 1991; 163: 311-8.
- [107] Phillips SE, Mattman LH, Hulinska D, Moayad H. A proposal for the reliable culture of *Borrelia burgdorferi* from patients with chronic Lyme disease, even from those previously aggressively treated. *Infection*. 1998; 26: 364-7.
- [108] Preac-Mursic V, Weber K, Pfister HW. Survival of *Borrelia burgdorferi* in antibiotic-treated patients with Lyme borreliosis. *Infection*. 1989; 17: 355-9.
- [109] Preac-Mursic V, Pfister HW, Spiegel et al. First isolation of *Borrelia burgdorferi* from an iris biopsy. *J Clin Neuroophthalmol*. 1993; 13: 155-61.
- [110] Preac-Mursic V, Pfister HW, Spiegel H, Burk R, Wilske B, Reinhardt S, et al. Formation and cultivation of *Borrelia burgdorferi* spheroplast-L-form variants. *Infection*. 1996; 24: 218-26.
- [111] Schmidli J, Hunziker T, Moesli P, Schaad UB. Cultivation of *Borrelia burgdorferi* from joint fluid three months after treatment of facial palsy due to Lyme borreliosis. *J Infect Dis*. 1988; 158: 905-6.
- [112] Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. *Expert Rev Anti Infect Ther*. 2014; 12: 1103-35.
- [113] Perronne C. Critical review of studies trying to evaluate the treatment of chronic Lyme disease. *Presse Med*. 2015.
- [114] Donta ST. Tetracycline therapy for chronic Lyme disease. *Clin Infect Dis*. 1997; 25: S52-6.
- [115] Donta ST. Macrolide therapy of chronic Lyme disease. *Med Sci Monit*. 2003; 9: 136-42.
- [116] Clarissou J, Song A, Bernede C, Guillemot D, Dinh A, Ader F, Perronne C, Salomon J. Efficacy of a long-term antibiotic treatment in patients with a chronic tick associated poly-organic syndrome (TAPOS). *Med Mal Infect*. 2009; 39: 108-15.
- [117] Horowitz RI, Freeman P. The use of dapsone as a novel "persister" drug in the treatment of chronic Lyme disease/post treatment Lyme disease syndrome. *J Clin Exp Dermatol Res*. 2016.
- [118] Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, et al. Study and treatment of post-Lyme disease (STOP-LD). A randomized double masked clinical trial. *Neurology*. 2003; 60: 1923-30.
- [119] Fallon BA, Keilp JG, Cordera KM, Petkova E, Britton CB, Dwyer E, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology*. 2008; 70: 992-1003.
- [120] Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, Norton D, Levy L, Wall D, McCall J, Kosinski M, Weinstein A. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001; 345: 85-92.
- [121] Berende A, Hofstede HJM, Vos FJ, van Midendorp H., Vogelaar ML, Tromp M et al. N Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. *Engl J Med*. 2016; 374: 1209-20.
- [122] DeLong AK, Blossom B, Maloney EL, Phillips SE. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: a biostatistical review of randomized, placebo-controlled, clinical trials. *Contemp Clin Trials*. 2012; 33: 1132-42. *Front. Med.*, 14 December 2017 | <https://doi.org/10.3389/fmed.2017.00224>.
- [123] Rebman A, Bechtold K, Ynag T, Mihm E, Novak C, Aucott J. The Clinical, Symptom, and Quality-of-Life Characterization of a Well-Defined Group of Patients with Posttreatment Lyme Disease Syndrome. *Front. Med.*, 14 December 2017.