Overview of Evidence Supporting the Need to Update the Infectious Disease Society of America's Guidelines Regarding the Treatment of Lyme Disease

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Abstract

The Lyme disease epidemic is spreading and in order to effectively treat this disease, further investigation needs to be completed in testing, prevention, and treatment. The political and social controversy surrounding the disease is detrimental to patients seeking relief from their illness. The epicenter of this controversy seems to be the treatment guidelines established by the Infectious Diseases Society of America (IDSA). These guidelines were established using an extremely flawed system allowing extensive conflicts of interest and faulty data. Reviewing the evidence regarding these allegations, it is clear that the IDSA needs to revise the outdated guidelines physicians are referencing in treating patients—in some cases it is a matter of life or death. Many patients exhibit symptoms of Lyme disease after treatment with short-course antibiotics. In some cases these symptoms are debilitating. When accessed on February 24, 2014, the IDSA's website itself states "*Every 12 to 18 months following publication, IDSA reviews its guidelines to determine whether an update is required. This guideline was last reviewed and deemed current as of 10/2011*." Thus, a review is well over due according to the ISDA's own guidelines. An inclusive panel of clinicians, researchers, patients, and government officials should be established to re-evaluate and review the approach to Lyme disease, including opposing viewpoints (Stricker, 2014). A standard for Lyme disease testing should be established, using the OspA or OspB proteins to ensure reliability, sensitivity, and specificity. Further randomized trials of antibiotic therapy should be conducted, considering the new diagnostic criteria and the implications of treating a Lyme disease infection immediately versus with a diagnostic delay. Other forms of treatment should also be considered.

Lyme disease may be one of the most controversial epidemics both politically and socially of our time. It is often compared to the AIDS epidemic due to its volatility. As the most common tick-borne illness in the United States, the actual number of Lyme disease cases is believed to be 10 times higher than the number of cases actually reported to the Centers for Disease Control (or CDC). Yearly, 300,000 cases are reported, and many more are missed due to inaccurate reporting by healthcare practitioners and flawed criteria for diagnosis, among other reasons (Cameron, 2010) . Lyme disease is often overlooked as an insignificant ailment easily cured by a short-course of antibiotics. However, there are many peer-reviewed articles and evidence that undermines this belief. The epicenter of this controversy seems to be the treatment guidelines established by the Infectious Diseases Society of America (IDSA). Reviewing the evidence regarding these allegations, it is clear that the IDSA needs to revise the outdated guidelines physicians are referencing in treating patients—in some cases it is a matter of life or death.

The organism that causes Lyme disease, the spirochete, is extremely complex when compared to similar organisms of the same type. In comparison to the spirochete that causes syphilis, *T. Pallidum,* which contains 22 genes, the Lyme spirochete, *B. Burgdorferi* contains at least 132 genes (Porcella, 2001). This makes for an extremely complex organism that can wreak havoc on multiple organs and vital body processes, in turn making it extremely difficult to both treat and diagnose. Lyme disease may also be accompanied by an extensive list of co-infections, including anaplasmosis, babesiosis, and ehrlichiosis (Rhee, 2012).

Symptoms in an affected person can persist, weeks, months, and even years after treatment. These multi-systemic symptoms may include pain, impaired cognition, and fatigue (Jarefors, 2007). Repeated manifestations of similar symptoms during the course of infection prevent

reliable classification of "early" versus "late" stage infection, making it extremely difficult to determine the longevity of the illness (Barbour, 2012). Many symptoms change or develop or disappear throughout the course of the illness, some even mimicking the symptoms of other diseases. Some believe that the spirochete itself can persist in tissue after treatment. The organism hides in areas that increase its resistance to the immune system. Experiments have shown that residues of the bacteria cause symptoms long after the bacterium is killed and elude standard diagnostic tests (Barbour, 2012). These studies demonstrate that the spirochete is not eradicated with the 2 to 4 weeks of antibiotic therapy recommended by the Infectious Diseases Society of America (IDSA) guidelines for treating Lyme disease. In 2006, Shapiro, Wormser, and Dattwyler confirm that approximately 30% of people treated with 2-4 weeks of a single antibiotic for Lyme disease will have persistent or recurring symptoms (Green, 2009). Additionally, four government-sponsored National Institutes of Health (NIH) randomized controlled trials have validated the existence and severity of chronic Lyme disease (Cameron, 2010). However, these findings have not influenced treatment guidelines or the research priorities of governmental funding agencies (Barbour, 2012), possibly due to the rampant conflicts of interest in play while developing and maintaining these treatment guidelines at the IDSA.

How is Lyme disease diagnosed as a multi-systemic illness?

The CDC's mission is to detect and respond to new and emerging health threats, as well as tackling the biggest health problems for Americans (CDC, 2013). They track diagnoses to gain a better understanding of how an ailment is affecting the nation. The CDC created surveillance criteria to aid in reporting cases of Lyme disease, with a warning: "*This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis*." The surveillance criteria depend on the appearance of an erythema migrans rash, or the bulls-eye rash, which approximately only 40% of those infected by Lyme disease will see. Some doctors use only this rash coupled with serological testing to make a positive diagnosis, oblivious or ignorant of the issues surrounding the testing process. Many patients with late Lyme disease will only display subjective symptoms of the disease, including fatigue, pain, and cognitive problems (Stricker, 2014). A diagnosis is rare in these cases, as the serological testing seeks protein from the *Borrellia Burgdorferi* that disappears (Stricker, 2014).

Regardless of what one would like to call it—chronic Lyme disease, post-Lyme disease syndrome, or post-treatment Lyme disease—in many patients, there are symptoms that linger. The research of Allen Steere, the man who initially produced the description and definition of Lyme disease, failed to show that all symptoms diminished after a short course of antibiotics (Ferguson, 2012). European research indicates success with extended use of antibiotic treatment despite Steere's refusal to treat Lyme disease with extended use of antibiotics (Ferguson, 2012). A study by Logigian found that months to years after initial infection chronic symptoms can

occur and usually improve with antibiotic therapy (Logigian, 1990). Ironically, in contradiction to his stance that Lyme disease is a simple organism treated with short-course antibiotics, Steere co-authored this study focused on chronic presentation of the disease. A biostatistical review of antibiotic retreatment in patients with persistent Lyme disease symptoms found that retreatment can be beneficial (Delong, 2012). A study by Hook et al. found that over a three year time span, 42% of individuals diagnosed with Lyme disease remained ill for more than six months, 12% were ill for more than three years, and 36% of them were treated with antibiotics for more than eight weeks. A placebo controlled double blind re-treatment trial by Oksi demonstrated that improvement occurred with 3-10 weeks of Ceftriaxone (Green, 2009). Dr. Charles Ray Jones states that there has never been a study that demonstrates that a short course of antibiotic therapy results in eradication of the bacteria. Further investigation is needed in treatment methods utilizing long-term antibiotics, or repeated courses of antibiotics in chronic cases.

For the tick-borne infection *Coxiella burnetii*, the standard treatment is a combination of two antibiotics administered for three years (Stricker, 2006). For an infection as complex as Lyme disease, it seems that somewhere between the treatment standards of these two disease will come closer to eradication of the spirochete instead of the current IDSA guidelines (Stricker, 2006). Patients with other ongoing illnesses will receive treatment after falling out of remission and into relapse (Cameron, 2010). Why is this not the standard with Lyme disease?

Tests to confirm a diagnosis are inaccurate, insensitive, and unstandardized. The current two-tier serological testing endorsed by the IDSA has a high specificity. This means that there are very few false positives. However, this two-tier testing has a sensitivity of between 8-56%, which

means that it may miss as many as 9 out of 10 Lyme diagnoses even if the test occurs early, within 4 to 6 weeks of infection (Stricker, 2008). With increased awareness and funding, the test to discern a HIV infection has readily improved: current HIV testing has a sensitivity of 99.5%, meaning that it misses only one in 200 HIV infections (Stricker, 2008). In contrast to HIV, there is currently no reliable test or a reliable therapeutic endpoint in the treatment of Lyme disease (Stricker, 2003). It seems that the current unreliable serological tests we have now are accepted as is without question in the medical fields. It is estimated that Lyme disease is six times more common than AIDS in the United States (Sticker, 2014). The funding for Lyme disease research is approximately $25 million a year, while many of the other infectious diseases receive between $100 and $200 million annually. HIV now receives more than $3 billion a year for research (Bernstein, 2014). Similar to AIDS, in untreated or improperly treated cases Lyme disease can be fatal or severely affect quality of life. It is important to increase research in Lyme disease prevention and treatment.

As described in the NIH trials mentioned above, diagnostic delays of two years often exist (Cameron, 2010), perhaps caused by physicians using insufficient and flawed diagnostic guidelines that ignore symptoms in lieu of faulty serological tests. This delay, among other factors, may contribute to the fact that duration of illness can be between 4.7 to 9 years, as noted in the NIH trials. In addition, patients that received delayed treatment were less likely to receive relief from initial antibiotic treatment (Cameron, 2010).

When patients do receive treatment without a delay, physicians often do not report cases of Lyme disease to the CDC for a multitude of reasons. The reporting criteria for Lyme disease do not include an estimated 30 to 50% of patients. Many physicians rely on the faulty serological test to confirm a positive diagnosis. Others place their trust in the bulls-eye rash—a rash that is only seen in approximately 40% of Lyme disease infections. Some physicians fail to report out of fear of repercussion from either the state health departments or insurance companies. In some cases, physicians treating patients with methods outside of the IDSA treatment guidelines have found themselves at risk of losing their licenses or of having their license suspended. A study by Nelson et al. analyzed private insurance claims related to Lyme disease for a nine-year time span and found that a large number of Lyme disease cases not reported are diagnosed and treated by healthcare providers (Sticker, 2014).

Treatment guidelines are used to create standardization of practice, minimize malpractice claims, and to save on costs. Guidelines are referred to by every part of the healthcare industry, including but not limited to physicians, researchers, pharmaceutical companies, and health insurance companies. These guidelines often take on the force of law (Ferguson, 2012). Due to the widespread blind use of these guidelines, it is vital to ensure that unbiased and empirical evidence is considered. The Institute of Medicine (IOM) defines practice guidelines as "systemically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances (IOM, 2011)" In addition; practice guidelines should reflect information that is based on the most current scientific research available. Ferguson (2012) writes that guidelines should have four important attributes: reliability and reproducibility, scientific validity, clinical applicability, and clinical flexibility. Routine

maintenance is needed to ensure that guidelines remain current with current scientific information (Ferguson, 2012).

Most clinicians rely on the treatment guidelines developed by the IDSA.

The treatment guidelines set forth by the IDSA recommend short-term antibiotics, dismissing any symptoms that may occur after the completion of the course. These guidelines offer information on the assessment, treatment, and prevention of Lyme disease and were published in 2006. In spite of the CDC's warning, the guidelines use the CDC's surveillance criteria for diagnosis. Two independent analyses presented at the 47th IDSA Annual Meeting revealed that most of the IDSA's treatment guidelines issued between 1994 and April 2009 are based only on expert opinion, nonrandomized trials, and case studies. Only about 15% of the guidelines are supported by randomized controlled trials, which are considered the highest level of evidence (Keller, 2009).

The guidelines established by the IDSA should have been used to provide benefits for patients, but instead were used by physicians and insurers as a justification for denying treatment for individuals who were still affected by Lyme disease symptoms following the ISDA recommended short-term antibiotic treatment (Ferguson, 2012). As a consequence, Richard Blumenthal, the Connecticut Attorney General, ordered an investigation on the suspected conflicts of interest infiltrating the IDSA panelists. His findings left many aghast, and the resulting apathy from the organizations involved was even more shocking. The authors of the guidelines had significant connections to drug companies, related patents, and Lyme diagnostic

tests. Several were also being paid by insurance companies to corroborate treatment plans that ended with a short course of antibiotics, and a few had received compensation for acting as expert witnesses in malpractice suits related to Lyme disease (Ferguson, 2012). These conflicts of interest left many unsuspecting patients in the hands of physicians that either are unaware, or choose to ignore, the fact that they are following faulty guidelines set forth by a panel with selfish interests. In an attempt to appease Blumenthal, the IDSA agreed to hold a review of the guidelines it had set forth. A panel convened in 2009.

Panelists were screened by an outside ethicist, who was selected and paid by the IDSA. This did not eliminate conflicts of interest. The most notable factor this ethicist screened for was anyone that earned more than $10,000 a year from treating Lyme disease (Stricker, 2012). These individuals were excluded from the panel. The panel chairperson selected a like-minded panel, set in the belief that chronic Lyme disease does not exist. In fact, 7 out of 8 of the panel members were members of the IDSA (Stricker, 2011). It is also notable that in the first panel convened by the IDSA, the only panelist with an open mind about the Lyme disease debate was removed (Ferguson, 2012). The IDSA oversight committee was not included in the panel selection process. The panel refused to accept additional panelists that did not share their viewpoint, telling them that the panel was already full, yet later expanding the panel to include other like-minded individuals (Ferguson, 2012). Patients were also turned away from participating in the panel hearing. The IDSA refused to review any evidence regarding the existence of chronic Lyme disease. More than 300 peer-reviewed articles and 1600 pages of analysis supporting the concept of chronic Lyme disease were received by the IDSA and ignored (Stricker, 2011). An improper voting procedure was used, favoring leaving the guidelines as originally presented. The

IDSA also failed to disclose its close connections to the American Academy of Neurology (AAN). The IDSA actually used the AAN guidelines to support its own guidelines and corroborate the denial of the existence of chronic Lyme disease (Ferguson, 2012). Additionally, an article published in the *New England Journal of Medicine* corroborated the findings of the IDSA, stating that chronic Lyme disease does not exist, and that even if it did, the costs to the patient's health outweigh the benefits of treating it with long-term antibiotics. It was undisclosed that 11 members of the IDSA panel were authors of this article (Stricker, 2008).

Conflicts of interest have been prevalent when it comes to Lyme disease from the start.

The Second National Conference on Lyme Disease Testing in Dearborn, Michigan was based on research by a group of scientists that included Steere. This group supported the notion that "protocol-based positive Lyme diagnoses should be based on the existence of arthritis in patients." The National Institutes for Health, or NIH, was a financial supporter of this research. The NIH had already classified Lyme as being primarily related to arthritis (Ferguson, 2012). The scientists eliminated two highly specific Lyme proteins (OspA and OspB) from all testing procedures. These proteins only appear in blood after infection and the presence of these proteins in the blood multiply as infection continues (Ferguson, 2012). The proteins that are currently included in diagnostic testing dissipate as time passes. This increases the chance of a false negative on Lyme disease test even during an active infection.

The Dearborn panel felt that it would be in their best interest to exclude these proteins from testing due to their vested interest in creating a vaccine for Lyme. Vaccines were released four

years later, all using the OspA protein. Patients vaccinated with these vaccines would test positive for the OspA protein—and this is why the scientists refused to use OspA in testing (Ferguson, 2012). Had they included the OspA protein in vaccine development, all persons vaccinated against Lyme disease would potentially test positive for active infection. Millions of dollars of funding had been provided to the scientists to develop these vaccines. Three of the panelists, including Steere, overtly had connections to these vaccines. After being placed on the market, the vaccines were pulled for causing horrible Lyme-like side effects in users. After completing the vaccination trials, Steere acknowledged the possibility that OspA may cause chronic Lyme (Ferguson, 2012).

What other factors are encouraging ignorance of Lyme sufferers?

In addition to the flawed IDSA guidelines, the Klempner (2001) and Fallon (2008) antibiotic trials were widely published and have been used by insurance companies to limit treatment options for those with chronic Lyme. Both of these studies have been criticized by many for having a barrage of issues, meaning that any conclusions drawn from the studies are not accurate. Problems with the design include a delay in treatment, inappropriate selection and lack of randomization of participants, failure to explain positive cerebrospinal fluid findings, failure to report objective cognitive tests, inadequate screening for co-infections, small sample size, lack of follow-up, and refusal to recognize that there is no current technique to verify eradication of the infection (Bransfield, 2003).

Of the seven studies used by the IDSA to support their guidelines and the notion that Lyme disease is easily treated, six of them required a physician-confirmed bulls-eye rash. This ensured the patients were treated early in the course of the infection, which increased the probability that short-course antibiotics would be successful. The only conclusion that can be drawn from these 7 studies is that if a Lyme infection is identified early and the patient has a bulls-eye rash, treating the infection for 14 to 28 days with one of four antibiotics will ensure that the patient will very rarely have recurrence of the rash (Green, 2009). Despite the shortcomings of all of the Lyme disease antibiotic trials thus far, there have been no additional antibiotic trials. An IDSA panel member actually advised against further trials (Cameron, 2010).

Research has shown that in addition to the risks posed by Lyme disease itself, complications can occur from co-infections, including Borrelia Ehrlichia, Babeosis, Anaplasmosis, and Bartonellosis, amongst others. Studies have shown at least a 20% co-infection rate in Lyme cases, adding further complications to treating the illness (Jones, 2005). *Borrelia Burgdorferi* can also transform into cystic, granular, or cell wall deficient forms in response to environmental conditions (Sapi, 2011). Spirochetes can live intracelluarly in fibroblasts, endothelial and glial cells, as well as other cells, or deflect immune detection by altering surface protein antigens. These processes can render it invincible to various therapeutic interventions (Sapi, 2011; Jones, 2005). In addition, biofilm formation increases the spirochete's survival in various conditions. The formation of biofilms can cause the failure of short-course antibiotic therapy (Stricker, 2011). *Borrelia Burgdorferi* has a complex life cycle, with some strains taking up to 10.5 months to grow. This in itself suggests that two to four weeks of antibiotics is inadequate for treatment (Jones, 2005)

The Heterogeneity of Treatment Effect (HTE) occurs when patients respond differently to the same treatment. This occurs with Lyme disease (Green, 2009). This can be due to individual responses to medication, which bodily systems are infected, presence of co-infections or duration of illness. Research trials regarding the best treatment for Lyme disease must keep this in mind. HTE can cause investigators to believe that their results are more generalizable than they actually are, resulting in patients either receiving treatment they do not need or being refused treatment they do need (Green, 2009). For example, short-course antibiotics may work for those recently infected, but not for those with a long-standing active infection. In contrast, short-course antibiotics may not work for those recently infected, but with Lyme disease as well as multiple co-infections.

The cost to society is in the billions. Patients are forced to see Lyme-literate doctors that cannot accept health insurance out of fear of repercussion. These patients spend thousands of dollars out-of-pocket. The pharmaceutical industry has not shown any initiative in approaching this epidemic. Since the treatment options for Lyme disease do not look to be profitable, and the controversy surrounding the disease, the pharmaceutical industry has steered clear of any involvement (Stricker, 2011). Once the medical community unites on its stance towards chronic Lyme disease, the pharmaceutical industry will have more motivation for involvement in creating complex antibiotic regimens to aid in recovery.

The IDSA guidelines are posted online with a disclaimer: ”*It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situation. IDSA considers adherence to the guidelines listed below to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances*” (Accessed February 24 2014). Although the IDSA states that the guidelines are flexible and should be accommodating on a patient-by-patient basis, doctors that treat Lyme disease with long-term antibiotics often find themselves in legal battles. IDSA members have acted as expert witnesses in malpractice suits related to Lyme disease (Ferguson, 2012).

California, Connecticut, Massachusetts, Minnesota, New Hampshire, New York and Rhode Island have taken legal action to protect doctors that are willing to treat patients based on clinical diagnosis and using methods other than the short-term antibiotics stated in the IDSA guidelines (Jemseck, 2006). This has provided some security for those treating patients and patients that are diagnosed in these states. Some patients travel across the country to receive care from these doctors, who are more prone to take insurance than doctors who are not protected from insurance companies by state-ordered legal regulations.

The Red Cross is taking precautions with donations, fearing that the Babesia parasite will be transmitted through blood transfusions. The CDC has increased its estimate of Lyme disease cases to 300,000 and even increased their budget to research this devastating illness by 3%.

Some states are taking legal action to ensure the safety of practitioners treating Lyme disease. Recent reports show that Lyme disease is likely to be sexually transmitted. It seems that the realization that Lyme disease is a serious threat is widespread; however, the IDSA still chooses to ignore the devastation its guidelines have caused. Even after Blumenthal ordered the hearing on the IDSA's regulations, no changes were made.

As all of this is coming to light, the IDSA is pressuring the Obama administration to focus on reducing antibiotic resistant infections. This includes stricter regulations on antibiotic use, which would add friction to the already strained treatment of chronic Lyme disease. It is notable that a long-term course of Doxycycline is routinely given to patients with acne. Doxycycline is also an antibiotic that targets Lyme disease. It is remarkable that long-term antibiotics will be prescribed for acne—an affliction that does not affect activities of daily living. Doxycycline will not be prescribed long-term for Lyme disease—an affliction that can easily affect activities of daily living. Research has shown that under the guidance of a professional clinician, the risk of using long-term antibiotics is significantly reduced.

<u>The risk and prevention of human transmission of Lyme disease require further studies.</u>

Further investigation into the use of long-term antibiotics and other alternative methods of treatment need to be pursued. These studies should be long-term, randomized, and placebo-controlled to ensure the scientific validity of the results (Bransfield, 2003). Research also must investigate the delay to diagnosis, failure to respond to short-course antibiotics, and relapse within the patient population (Green, 2009). This epidemic is spreading and in order to

effectively treat the disease, further investigation needs to be completed. The information currently being used to make treatment decisions for ill patients is outdated. In fact, when accessed on February 24, 2014, the IDSA's website itself states "**Every 12 to 18 months following publication, IDSA reviews its guidelines to determine whether an update is required. This guideline was last reviewed and deemed current as of 10/2011*." Thus, a review is well over due according to even the ISDA's own guidelines. An inclusive panel of clinicians, researchers, patients, and government officials should be established to re-evaluate and review the approach to Lyme disease, including opposing viewpoints (Stricker, 2014). A standard for Lyme disease testing should be established, using the OspA or OspB proteins to ensure reliability, sensitivity, and specificity. Further randomized trials of antibiotic therapy should be conducted, considering the new diagnostic criteria and the implications of treating a Lyme disease infection immediately versus with a diagnostic delay. Other forms of treatment should also be considered. Guidelines must emphasize the importance of clinical judgment in individual cases and be readily available to primary care doctors, who are most likely to see a presenting Lyme patient first (Green, 2009).

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