Why we protest against the IDSA

IDSA guidelines:

- ignore the principles of evidence based medicine
- discourage physicians from providing treatment to severely ill patients
- dismiss extensive evidence for chronic Lyme disease
- misrepresent expert opinion as science

The result:

- thousands of patients are misdiagnosed and denied treatment
- thousands remain sick and suffer terribly
- chronically ill patients must pay out of pocket for medical treatment that is necessary
- thousands of people are devastated

Why we call upon the IDSA to 'Quit Rejecting Science'

Borrelia burgdorferi (Bb) persists following IDSA recommended antibiotic treatment

- This has been demonstrated in studies using mice, rats, hamsters, guinea pigs, gerbils, dogs, horses, and non-human primates [1,2,3,4,5,6,7]
- This has also been shown in humans on multiple occasions[3,4,5,6,7]
- Lyme spirochetes can evade host immune response and antibiotic destruction through a variety of mechanisms:
    - ⇒ Spirochetes can live intracelluarly in (including but not limited to) fibroblasts, endothelial cells, glial cells [8,9]

[1] Hodzic, E., Imai, D., Sunlian, F., Barthold, S. (2014). Resurgence of persisting non-cultivable Borrelia burgdorferi following antibiotic treatment in mice. *PLOS ONE, 9*(1), e86907.
[2] Embers, M., Barthold, S., Borda, J., Bowers, L., Doyle, L., Hodzic, E., … Philipp, M. (2012). Persistence of Borrelia burgdorferi in Rhesus Macaques following antibiotic treatment of disseminated infection. *PLOS ONE, 7*(1), e29914.
[3] Phillips, S. (2012). Active infection: Clinical definitions and evidence of persistence in Lyme disease- Contesting the underlying basis for treatment limitations for early and late Lyme disease, as well as chronic Lyme disease, alternatively known as "Post-Lyme disease syndrome."
[4] Barbour, A. (2012). Remains of Infection. *Journal of Clinical Investigation, 122*(7), 2344-2346.
[5] Lin, X., McHugh, A., Damle, N., Sikand, V., Glickstein, L., Steere, A. (2011). Burden and viability of Borrelia burdorgeri in skin and joints of patients with Erythema migrans or Lyme arthritis. *Arthritis and Rheumatism, 63*(8),2238-2247.
[6] Schmidli, J., Hunzicker, T., Moesli, P. (1988). Cultivation of Borrelia burgdorferi from joint fluid three months after treatment of facial palsy due to Lyme borreliosis. *Journal of Infectious Diseases, 158*, 905-906.
[7] Haupl, T., Hahn, G., Rittig, M., Krause, A., Schoerner, C., Schonherr, U., … Burmester, G. (1993). Persistence of B. burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis. *Arthritis and Rheumatism, 36*, 1621-1626.
[8] Jones, Charles. Rationale for prolonged antibiotic therapy in treating Lyme disease.
[9] Klempner, M., Noring, R., Rogers, R. (1993). Invasion of human skin fibroblasts by the Lyme disease spirochete, Borrelia burgdorferi. *Journal of Infectious Diseases, 67*, 1074-1081.

⇒ Some cultures of Bb divide slowly, taking up to 10 ½ months. Many antibiotics only kill dividing organisms [15]

⇒ Bb can occur in an L-form (or CWD or cyst form) or can evade immune response through biofilm formation or by altering surface protein antigens [5, „ , 15101112]

⇒ Releasing blebs and binding free antibodies is another way spirochetes can evade the immune system. These complexes are not detected by standard Lyme tests [15]

⇒ Bb can express lipoproteins that enable it to change form and function best suited to its current environment and survival [13,14]

- Bb infection establishes immunosuppressive in the host, which permits chronic infection [3]
- Some studies have demonstrated the spirochete's resistance to antibiotic classes usually prescribed for Lyme [10]
- All 4 NIH RCTs validate the existence of symptoms seen in persistent Lyme disease [15, 16, 17, 18]
- IDSA members themselves have noted this: "After weeks of disseminated infection, the Lyme disease agents may still survive in localized niches for several years." [19,3]

Current testing for Lyme is unreliable

- The current insensitive test system guarantees that over half of Lyme disease cases go undiagnosed and untreated [20]
- Serological (blood) testing of Bb is challenging due to complex antigenic composition of Bb, temporal appearance of antibodies to different antigens at successive time intervals after infection and false positive results reported especially with other spirochetal infections (EBV, HIV) [21]
- Serological testing of Lyme is not recommended in the early stage of infection because the results are usually negative. Sensitivity in patients tested at least 4-6 weeks after infection is only 44% to 56%, which is inadequate for diagnostic testing [1, 22]

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[10] Miklossy, J. (2012). Chronic or late Lyme Neuroborreliosis: Analysis of evidence compared to chronic or late Neurosyphilis. *Open Neurology Journal*, *6*, 146-157.

[11] Bockenstedt, L., Gonzalez, D., Haberman, A., Belperron, A. (2012). Spirochete antigens persist near cartilage after murine Lyme borreliosis therapy. *Journal of Clinical Investigation*, *122*(7), 2652-2660.

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[13] Haake, D. (2000). Spirochetal lipoproteins and pathogenesis. Microbiology, 146(7), 1491-1504.

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[17] Fallon, B., Keilp, J., Corbera, K. (2008). A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology*, *70*(13), 992-1003.

[18] Klempner, M., Hu, L., Evans, J. (2001). Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *New England Journal of Medicine*, *345*(2), 85-92.

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- Due to the nature of Lyme disease, diagnosis should be made based on a clinical diagnosis supported by a positive serological test. Clinical diagnostic criteria for Lyme disease are too stringent, with only objective signs of the disease such as an Erythema migrans rash, arthritis, meningitis, or carditis, considered relevant [2]

  ⇒ Patients with late Lyme disease may only display subjective symptoms of the disease [2]

- There are two outer surface proteins (OspA and OspB) expressed by Bb that are highly specific to Lyme disease. The CDC has neglected to include them in Lyme disease testing interpretation, though these antigens were used for the vaccines and therefore, antibodies to these antigens must be of importance [23, 24]

- Current clinically available testing cannot prove that the infection has been eradicated [25]

Treatment should be tailored to the patient and the situation

- Response of Lyme patients to the same therapy is different patient to patient [7]
- 84.8% of patients in one study showed improvement after antibiotics failed and they were treated with Hyperbaric Oxygen Therapy for chronic Lyme disease [26]
- Multiple case studies show improvement in some patients with prolonged antibiotics, with symptoms that relapse upon cessation of the treatment [27,28]
- A biostatical review of the 4 RCTs sponsored by the NIH shows that retreatment with antibiotics can be beneficial [29]
- Co-infections can complicate and exacerbate the severity of Lyme disease [5]. Co-infections can include, but are not limited to anaplasmosis, babesiosis, ehrlichiosis, bartonellosis [30], [31]
- The optimal treatment for patients with persistent symptoms from Lyme remains undefined [14]
- Physicians and insurance companies need to consider the limitations of evidence before denying antibiotic treatment for persistent Lyme symptoms [32]

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[22] Stricker, R., Johnson, L. (2011). Lyme disease: the next decade. *Infection and drug resistance, 4,* 1-9.

[23] Mason, K., Bransfield, R. (2014). Divergent opinions of proper Lyme disease diagnosis and implications for children co-morbid with autism spectrum disorder. *Medical Hypotheses, 83,* 321-325.

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[25] Green, C. (2009). Challenge to the clinical definition of late Lyme disease and post-Lyme disease syndrome. Retrieved from http://mnlyme.com/files/Green.pdf.

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[30] Rhee, H., Cameron, D. (2012). Lyme disease and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): An overview. *International Journal of General Medicine, 5,* 163-174.

[31] Stricker, R., Johnson, L. (2011). Lyme disease: The next decade. *Infection and Drug Resistance, 4,* 1-9.

- Long term antibiotic use may be an effective treatment for children with both Lyme disease and Autism Spectrum Disorder. All children in a study showed marked improvements on antibiotics and most children remained on antibiotics after completing the study [33]. 91% of children had OspA and OspA bands in testing. These two bands are very specific to Bb and were used in vaccine trials, however the CDC has neglected to include them in Lyme disease testing interpretation [34]
- Lipid replacement therapy has been successful in intractable chronic fatiguing illness and chronic Lyme disease patients [35]
- Even IDSA members have noted this: "Months to years after the initial infection with Bb, patients with Lyme disease may have chronic encephalopathy, polyneuropathy, or less commonly, leukoencephalitis. These chronic neurologic abnormalities improve with antibiotic therapy." [36]

Lyme disease is a political, ethical, and economical issue

- Two highly specific Lyme proteins, OspA and OspB were eliminated from all testing procedures at the Dearborn Conference. These proteins only show in the blood after exposure to Bb, and their presence in the blood grows after infection [3]
    - ⇒ Four years later, two Lyme vaccines were available. Both relied on OspA. The patent holder of OspA, one of the vaccine inventors, and Steere all were on the voting panel at Dearborn. OspA was eliminated for financial gain [3]
- The CDC case definition was tailored by the CDC, the FDA, and SmithKline Beecham to facilitate the clinical trials of their Lyme vaccine[14] Lymerix. This case definition has also been used in forming the IDSA's Lyme treatment guidelines
- November 1, 2006: The IDSA published their Lyme treatment guidelines
    - ⇒ Most of the treatment guidelines, including Lyme, are based on expert opinion, nonrandomized trials, and case studies. Only 15% are based on randomized controlled trials (RCTs) which are considered the highest level of evidence. More than half were based on expert opinion or not supported by RCTs [37]
    - ⇒ The majority of the studies used by the IDSA to support their ideas require an Erythema migrans (EM) rash for enrollment. This rash typically appears within a month of a tick bite, if at all. These studies treated Lyme early. Other studies show that if Lyme is treated

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[32] Cameron, D. (2009). Insufficient evidence to deny antibiotic treatment to chronic Lyme disease patients. *Medical Hypotheses, 72*(6), 688-691.
[33] Mason, K., Grave, S., Bransfield, R., Harris, S. (2012). Long term antibiotic therapy may be an effective treatment for children co-morbid with Lyme disease and Autism Spectrum Disorder. *Medical Hypotheses, 78*, 606-615.
[34] Mason, K., Bransfield, R. (2014). Divergent opinions of proper Lyme disease diagnosis and implications for children co-morbid with autism spectrum disorder. *Medical Hypotheses, 83*, 321-325.
[35] Nicolson, G., Settineri, R., Ellithorpe, R. (2012). Lipid replacement therapy with a Glycohospholipid formulation with NADH and CoQ10 signficantly reduces fatigue in intractable chronic fatiguing illnesses and chronic Lyme disease patients. *International Journal of Clinical Medicine, 3*, 163-170.
[36] Logigian, E., Kaplan, R., Steere, A. (1990). Chronic neurologic manifestations of Lyme disease. *New England Journal of Medicine, 323*, 1438-1444.
[37] Keller, D. (2009). Infectious disease treatment guidelines weakened by paucity of evidence. Retrieved from http://www.medscape.com/viewarticle/712341.

early, there is less of a chance of a relapse after completing the IDSA recommended short-course antibiotics, this totally alienates those who do not get the EM rash or are not diagnosed early [3]

- November 16, 2006: Connecticut Attorney General Blumenthal conducted an investigation into the conflicts of interest surrounding the Lyme treatment guidelines. His findings were troubling (see table below)[3]

    ⇒ The authors of the Lyme treatment guidelines and those that served on the panels at Dearborn and to review the IDSA guidelines have numerous connections to drug companies, related patents, and related diagnostic tests, several were also being paid by insurance companies to corroborate treatment plans that denied long-term treatment for Lyme disease [38, 14]

- May 1, 2008: The IDSA settles with Blumenthal and agrees to re-review the guidelines with a panel free of conflicts of interest

    ⇒ January 9, 2009: The IDSA announces its review panel. There are no Lyme clinicians on the panel, and only academic researchers were allowed. The panelists selected had previous connections to the IDSA or preexisting bias towards chronic Lyme [39]

    ⇒ The IDSA makes it extremely difficult for the public, patient's organizations, and physicians to submit documentation for review. They also failed to notify presenters of participation or location a month before the hearing date. They finally postponed the hearing and instead decided to air it live over the IDSA website, available to view through a complex registration system. Over 1600 pages of peer-reviewed research supporting chronic Lyme are submitted. [35]

    ⇒ At the hearing, the IDSA limits testimony to one day and only 2 patient advocates are given 15 minutes each to speak. Press is limited to IDSA-selected journalists [35]

    ⇒ Immediately after the hearing, the IDSA president states: "IDSA's signing the agreement was not, as [Blumenthal] alleges, an admission of guilt, but an effort to end a fruitless investigation."…"**The notion that the authors had conflicts of interest is absurd…"** [35]

[38] Ferguson, J. (2012). Cure Unwanted? Exploring the chronic Lyme disease controversy and why conflicts of interest in practice guidelines may be guiding us down the wrong path. *American Journal of Law & Medicine, 38*, 196-224.
[39] History of IDSA Investigation. (2009). Retrieved from http://underourskin.com/sites/default/files/images/2010/01/IDSA_Investigation_Timeline-Feb_2010.pdf

⇒ The people listed below have made decisions regarding the diagnosis and treatment of Lyme that have impacted hundreds of thousands, if not millions of people

Mark S. Klempner, MD	Research grants from CDC and NIH
Eugene D. Shapiro, MD	**Lyme treatment guidelines author.** Board member of the ALDF, received compensation for testifying in Lyme cases by insurance companies
Allen Steere, MD	**Lyme treatment guidelines author.** Attended the Dearborn conference to set guidelines for diagnosis. Attended the Vaccines and related Biological Products Advisory Committee to approve Lymerix, the OspA dependent vaccine. Lead researcher for SmithKline Beecham Lyme vaccine, Lymerix, on the consulting staff of a biotechnology company that depends on the success of the OspA vaccine. Steere published articles regarding the extreme adverse events for the OspA vaccine, yet still worked to have the vaccine approved at the 1998 FDA hearing. He has also been employed at the CDC and Yale University.
Adriana Marques, MD	Co-inventor on patent application for Bb antibody testing, grants from DIR, NIAID, NIH.
Raymond J. Dattwyler, MD	**Lyme treatment guidelines author.** Attended the Dearborn conference to set guidelines for diagnosis. Attended the Vaccines and related Biological Products Advisory Committee to approve Lymerix, the OspA dependent vaccine. Research grants from NIH, has stock in Biopeptides Corp., has received compensation for testimony in malpractice cases, holds patents on vaccine and diagnostic technology, has worked with pharmaceutical companies as a consultant and investigated on recommended antibiotics for Lyme.
John J. Halperin, MD	Testified in Lyme cases and has equity in 4 medical product companies
Gary P. Wormser, MD	**Lyme treatment guidelines author**. Research grants from CDC, the NIH, and 4 other institutions, holds equity in medical product company and has received compensation for testimony in Lyme malpractice cases, is a board member of ALDF, consultant to Baxter for Lyme vaccine development
Alan Barbour, MD	Attended the Dearborn conference to set guidelines for diagnosis. Patent holder on: OspA and OspB, 66 kDa antigen from Bb, Borrelia antigen, Flagella-less Borrelia, OspA proteins of Bb subgroups,cloning and expression of soluble truncated variants of OspA, OspB, and Vmp7, diagnostic tests for a new spirochete, virulence associated proteins in Bb. Inventor of vaccine technology used to manufacture Aventis Lyme vaccines
Barbara Johnson, PhD	Attended the Dearborn conference to set guidelines for diagnosis Works for the CDC, inventor on work using protein antigens that can be used for future generations of the OspA vaccine.

- February 1, 2009: the Freedom of Information Act reveals that the IDSA violated the agreement with Blumenthal

    ⇒ Internal IDSA memos reveal a divided panel on whether testing should be made mandatory for a diagnosis of Lyme, but the improper voting procedures used by the IDSA let the guidelines stand as they were [35]

- IDSA procedural violations delay a change in the guidelines for years, allowing the authors to pursue commercial interests (vaccines and tests) supported by flawed science

    ⇒ Several IDSA members have financial ties to the new Lyme vaccine that caught the media's attention recently including Alan Barbour, Raymond Dattwyler, and Benjamin Luft

- Lack of profitable treatment options has limited pharmaceutical involvement [5]
- The cost to society is billions[29], the cost to patients is in the tens of thousands
- Physicians are fearful of treating patients with persistent symptoms. Insurance companies, state health departments sometimes investigate and remove the licenses of physicians willing to treat outside the IDSA guidelines [29]

This is a serious problem that needs immediate attention

- The CDC has increased their estimate of Lyme cases from 30,000, to 300,000, to 1,000,000 [40]

What we need

- Revise the guidelines to follow Kathleen Lohr's four important attributes of clinical practice guidelines [34]

    1. Reliability and reproducibility
    2. Scientific validity
    3. Clinical applicability
    4. Clinical flexibility
    5. "Routine maintenance" to ensure guidelines are relevant and reflective of current scientific information

- The guidelines should be revised with the following in mind:

    ⇒ An inclusive panel of clinicians, researchers, patients, and government officials to be established to determine a new approach to Lyme disease using panel balancing recommended by government guidelines for controversial diseases [36]

[40] Stricker, R., Johnson, L. (2014). Lyme disease: Call for a "Manhattan Project" to combat the epidemic. *PLOS Pathogens, 10*(1), e1003796.

⇒ A uniform standard for Lyme disease testing with an emphasis on a "gold standard" culture or PCR test for the spirochete [36]

⇒ Further trials of antibiotic therapy should be conducted once better testing is in place, with emphasis on combination antimicrobial therapy and encouragement of pharmaceutical industry participation [36]

⇒ Alternative treatments should not be dismissed; treatment decisions should be made on a case-by-case basis between the patient and the physician

"**The fact that there is a disagreement is not a valid reason for physicians to turn away or ignore patients with persistent Lyme disease symptoms." -Daniel Cameron, MD, MPH**