Contact Us

LDA's mission does **NOT** include providing medical advice or researching your questions. We do not answer medical questions or identify ticks or rashes. Many questions can be answered by you researching the LDA site and its links to other sites. Please use the search box feature to find information on the website. We are an all volunteer organization and do our best to respond to your questions and concerns.

DO NOT use the "Contact Us" Forms for Items Below: (*We WILL NOT respond due to email volume)*

- To ask any medical questions (we do not provide any medical advice)
- To ask for information on whether chronic Lyme patients should take COVID 19 vaccine (do not know anyone who has that data)
- To ask for Doctor Referrals – use our automated system (**Click here**)

Available "Contact Us" Forms:

- General questions please **Click here**
- Website issues please **Click here**
- Dr. Referral technical questions please **Click here**

Other Contact Information

Lyme Disease Association, Inc.
PO Box 1438
Jackson, NJ 08527
888-366-6611 information line
732 938-7215 fax

www.LymeDiseaseAssociation.org

COCA/CDC Lyme Disease Conference Call – May 20th, 2020

The Clinician Outreach and Communication Activity (COCA)/Center for Disease Control is offering a conference call on May 20th, 2020: **Lyme Disease Updates and New Educational Tools for Clinicians** from 2:00–3:00 P.M. ET. See right side of page for instructions on how to join the call via zoom or phone. Advanced registration is not required.

During this COCA Call, presenters will review updates in Lyme disease epidemiology, diagnosis, treatment, and prevention and share new educational tools for both healthcare providers and their patients.

Presenters include **Grace Marx, MD, MPH** –LCDR, U.S. Public Health Service
Medical Epidemiologist, Bacterial Diseases Branch, Division of Vector-Borne Diseases, CDC

Free Continuing Education (CE) credits can be earned for this call, even if you cannot participate live. **Click here for info on CE for COCA calls/webinars**

Click here for information on the call: Lyme Disease Updates and New Educational Tools for Clinicians

Click here to view prior COCA calls/webinars

Click here for Post-Webinar Analysis by LDA

COCA provides clinicians with the most up to date information and guidance from the Center for Disease Control (CDC) regarding emergency preparedness and response and emerging public health threats.

Tick-Eating Robots Going to International Competition with VMI Team

Photo thanks: J. Occi, (PhD cand) LDA Scientific & Prof. Advisory Board

The tick rover, a robot designed to remove and kill ticks from

people’s yards, and a longtime project for Col. Jim Squire, Professor of Electrical and Computer Engineering, Virginia Military Institute, has won an award. The tick-eating robot traps ticks hiding on bushes and has been field-tested by biologists.

A team of four cadets made improvements to the rover over the winter and then entered it into a contest sponsored by the Institute of Electrical and Electronics Engineers (IEEE). Their tick-eating robot defeated several teams from the nation’s top research universities and will represent the United States and Canada in the international IEEE competition in Seville, Spain.

Next, the team hopes to license the robot and collaborate with a Dartmouth neuroscientist who wants to start a company based on it.

Read more on Virginia Military Institute’s website.

Read more about ticks, Lyme disease and the military on LDA’s website.

Study Furthers Understanding of Lyme Disease Pathogenesis

A study published in *PLOS Pathogens* by Marisela M. Davis, *et al.* furthers understanding of the *B. burgdorferi* cell envelope and pathogenesis.

The researchers found that peptidoglycan-associated protein (NapA) plays an important role in the envelope integrity and pathogenesis of the Lyme disease spirochete. The results highlight the plasticity of bacterial proteins and uncover some of the ways they may change how they perform a task despite no change in their basic biological function.

Read the study in PLOS Pathogens.

Read more Lyme disease studies on LDA's website.

Adrian Baranchuk, MD, Guest Blog – Lyme Carditis 2021 Update

May Awareness LDA Guest Blogger

Adrian Baranchuk MD, FACC, FRCPC, FCCS, FSIAC is Professor of Medicine at Queen's University, Kingston, Ontario, Canada. He is Editor-in-chief, Journal of Electrocardiology; Vice President, International Society of Holter and Non-Invasive Electrocardiology (ISHNE); Secretary, Interamerican Society of Cardiology (SIAC); Co-Director, ECG University; Past President, International Society of Electrocardiology (ISE); and Director, NET-Heart Project (Neglected Tropical Diseases and other Infectious Diseases affecting the Heart).

Lyme Carditis: Update 2021. An Evasive Diagnosis in the Time of COVID-19

Adrian Baranchuk MD, FACC, FRCPC, FCCS, FSIAC; Chang (Nancy) Wang MSc (c), MD
Department of Medicine, Kingston Health Science Center, Kingston, Ontario, Canada

Lyme disease (LD) is a tick-borne bacterial infection caused by *Borrelia burgdorferi*. Lyme carditis (LC) is an early-disseminated manifestation of LD, most commonly manifesting as a complete "shut-down" of the electrical system (high-degree atrioventricular block (AVB)) that can evolve rapidly over minutes, hours, or days producing severe symptoms like fainting, palpitations, shortness of breath, extreme dizziness, or sudden death (1-2).

Other cardiovascular manifestations include alterations of the "motor" of the heart (sinus node disease) (3), a disorganization of the cardiac rhythm that increases the risk of stroke (atrial fibrillation) (2), lesion in the distal cables of the heart (bundle branch blocks) (4), and different degrees of inflammation of the layers of the cardiac walls (myocarditis, pericarditis, and endocarditis) (2). Some of these manifestations could be so severe that a total dysfunction of the cardiac function occurs in a matter of hours, and the patient may die even if admitted to the best

ICU in the world.

The initial symptoms of LD can be mistaken by other common infections or allergic reactions. Delayed diagnosis is one of the most important risk factors to serious LD presentations including LC in all its forms. The good news is that prompt diagnosis and appropriate antibiotic therapy links to a much better prognosis. In addition, we now know that when appropriately treated with antibiotics according to guidelines (2); there is no evidence of residual disease in the heart (5).

Most conduction abnormalities caused by LC resolve with appropriate antibiotic therapy (2).

The current COVID-19 pandemic is posing a new challenge in the diagnosis of LD. There are lots of overlapping symptoms such as: fever, malaise, generalized pain, lack of energy, etc. During these times, one would advise on ruling out COVID-19 first before embarking on any other test. However, what could we recommend in terms of confirming or ruling out LD, specifically during these challenging times?

Learning how to recognize the many presentations of LD from a clinical point of view has been published several times. It is especially important to ask about outdoor activities, history of tick bites, tick removal and dermatological rashes (remember that the classic “bull eye” is only present in about 40% of cases). Extensive dermatologic examination may be necessary. Residence in an endemic region for LD is essential for risk stratification, as these recommendations should be encouraged in all ED and family doctor offices in areas of high prevalence.

Once the diagnosis is suspected, specific interrogation should be directed to cardiovascular symptoms such as: dizziness, palpitations, fainting or near fainting, chest pain and shortness of breath. If the patient recognizes any of these

symptoms, along with any other factors suggesting LD, a 12-lead ECG (the simple and unexpensive electrocardiogram) should be performed (2). Any evidence of electrical disturbance should prompt admission in hospital for a course of IV antibiotics while waiting the results of serological tests.

On the other hand, in patients presenting with unexpected high-degree AV block, clinical suspicion for LC can be assessed using the validated risk score called **SILC** (Suspicious Index in Lyme carditis) (6) where the acronym **COSTAR** (**C**onstitutional symptoms, **O**utdoor activities/endemic region, **S**ex male, **T**ick bite, **A**ge > 50, **R**ash) may help in determining the risk of presenting early disseminated LC.

In summary, use your clinical tools to suspect LD in the context of COVID-19 pandemic, order serological tests when appropriate, and remember to check for cardiovascular complications with a history, physical, and ECG. If evidence of LC, admit the patient to hospital with continuous cardiac monitoring and appropriate IV antibiotics. Decision for permanent pacemaker implantation should wait until completion of antibiotics as heart block in LC is often reversible. Most patients maintain normal rhythm on long-term follow-up. Avoiding unnecessary implants is crucial as most of these patients are young and active individuals.

References

1. Wan D, Blakely C, Branscombe P, Suarez-Fuster L, Glover B, Baranchuk A. Lyme Carditis and High-degree Atrioventricular Block. Am J Cardiol 2018; 26(5): 233-239
2. Yeung C, Baranchuk A. Diagnosis and Treatment of Lyme Carditis. J Am Coll Cardiol 2019; 73(6): 717-726
3. Gazendam N, Yeung C, Baranchuk A. Lyme carditis presenting as sick sinus syndrome. J Electrocardiol 2020; 59: 65-67
4. Maxwell N, Dryer M, Baranchuk A, Vinocur M. Phase 4 Block of the Right Bundle Branch Suggesting His-Purkinje System Involvement in Lyme Carditis. HeartRhythm Case Reports. 2020; 7(2): 112-116

5. Wang C, Baranchuk A. Long-term evolution of patients treated for early disseminated Lyme carditis. Third prize at the ICE 2021 (International Congress on Electrocardiology)
6. Besant G, Wan D, Yeung C, Blakely C, Branscombe P, Suarez-Fuster L, Redfearn D, Simpson C, Abdollah H, Glover B, Baranchuk A. Suspicious Index in Lyme Carditis (SILC): Systematic Review and Proposed New Risk Score. Clin Cardiol 2018; 41(12):1611-1616

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In summary, use your clinical tools to suspect LD in the context of COVID-19 pandemic, order serological tests when appropriate, and remember to check for cardiovascular complications with a history, physical, and ECG. If evidence of LC, admit the patient to hospital with continuous cardiac monitoring and appropriate IV antibiotics. Decision for permanent pacemaker implantation should wait until completion of antibiotics as heart block in LC is often reversible. Most patients maintain normal rhythm on long-term follow-up. Avoiding unnecessary implants is crucial as most of these patients are young and active individuals.

References

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Assessing the Safety Profile of mRNA-Based Vaccines in Patients with Autoimmune Inflammatory Rheumatic Diseases

A case series assessing the safety profile of mRNA-based vaccines in patients with autoimmune inflammatory rheumatic diseases (AIIRD) has been published in the journal *Rheumatology*. The study's authors aim to raise awareness of reactivation of herpes zoster (HZ) following the BNT162b2 mRNA vaccination in patients with AIIRD.

The researchers found the occurrence of HZ was 1.2% (n = 6) in patients with AIIRD compared with none in the control group. The 6 patients who developed HZ were females aged 49 ± 11 years with stable AIIRD: rheumatoid arthritis (n = 4), Sjogren's syndrome (n = 1), and undifferentiated connective

disease (n = 1). Five of the patients developed a first-in-a-lifetime occurrence of HZ within a short period after the first vaccine dose and in one case, HZ occurred after the second dose. Five of the patients completed the second vaccine dose with no other undesirable effects. In most of the cases, HZ infection was mild.

Additional epidemiologic studies on the safety of the mRNA-based COVID-19 vaccines in patients with AIIRD are needed to determine the association between the BNT162b2 mRNA vaccination and HZ reactivation.

Read the full study in *Rheumatology.*

Read more on LDA's COVID & Lyme Disease page.

Study Uses Lyme Patient Autopsy Specimens to Detect Borrelia Spirochetes

Frontiers in Neurology, 10 May 2021, published a study examining multiple molecular detection techniques to effectively identify *Borrelia burgdorferi* in the autopsy specimens of a patient with a history of neurocognitive disease. The individual was a post-mortem donor from the brain repository of the Lyme and Tick-Borne Diseases Research Center at the Columbia University Irving Medical Center.

The patient had a history of Lyme disease, including a well-documented erythema migrans rash with severe headache, joint pains, and a fever of 104° that seemed to have been treated successfully with antibiotics. Four years later the individual developed a neurodegenerative disorder resulting in a Lewy Body Dementia diagnosis.

The researchers describe the use of multiple overlapping techniques, such as immunofluorescence assay (IFA), RNA in *situ hybridization* (RNAscope), and PCR for detection of *Borrelia* spirochetes in post-mortem tissues. Immunofluorescent detection was found to be the most reliable method to detect spirochetes in fixed tissues.

The case study raises the question of whether *B. burgdorferi* may play a role in the development of Lewy body dementia. Future studies are anticipated to focus on testing more affected subjects in addition to more control subjects to confirm or disprove this potential link.

Study authors are S. Gadila, G. Rosoklija, A. Dwork, B. Fallon, M. Embers. The work was supported by the Steven and Alexandra Cohen Foundation and the Lyme and Tick-borne Diseases Research Center at Columbia University established by Global Lyme Alliance and the Lyme Disease Association.

Study authors Drs. Brian Fallon and Monica Embers are the Co-Directors for the upcoming LDA-Columbia Lyme & Tick-Borne Diseases 2021 Conference on Oct. 2. 2021.

Read the full study in *Frontiers in Neurology.*

Click here for the Publications for LDA-Funded Research Page to see other research funded by the LDA published in peer review.

56 Publications for LDA-Funded Research

The LDA has a long history of funding/supporting research projects that lead to real results. Below is the list of links to peer-reviewed articles that acknowledge LDA's funding/support. Click on the publication link (or just scroll down to it) to see the authors, which authors LDA provided the funding for (**green**), and the abstract and a link to the publication itself when possible. When a journal has multiple publications, click on the year in which you are interested.

Frontiers in Neurology 2021
(2) Frontiers in Medicine 2020, 2019
(2) Antibiotics 2020, 2017
Brain, Behavior, & Immunity – Health 2020
Meta Gene 2019
Ticks and Tick-Borne Diseases 2018
Archives of Clinical Neuropsychology 2018
(2) Psychosomatics 2018, 2013
Healthcare (Basel) 2018
Bio-Protocol 2017
(6) PLOS One 2017, 2012 (2), 2011, 2010
The FEBS Journal 2017
ACS Chemical Biology 2017
Biochemistry 2017
(2) Frontiers in Microbiology October 2016, May 2016
Park Science (NPS, Department of Interior) 2016
FEMS Microbiology Letters 2015
Clinical Infectious Disease 2014
Veterinary Sciences 2014
International Journal of Medical Sciences 2013
Northeastern Naturalist, 2013
(3) Journal of Neuropsychiatry & Clinical Neurosciences 2013, 2003, 2001
Open Neurology Journal 2012
Journal of Bacteriology 2011
Genetics 2011
Journal of Medical Entomology 2010
Neurobiology of Disease 2010
Archives General Psychiatry 2009
Gene 2009
(2) Neurology 2008, 1999
Emerging Infectious Diseases July 2008

Minerva Medica October 2008
Microbial Pathogenesis 2008
Journal of International Neuropsychological Soc. 2006
Infection & Immunity 2006
Journal of Clinical Microbiology 2005
Expert Review of Anti-Infective Therapy 2004
The Proceedings of National Academy of Science 2004
(2) JSTBD 2002, 1999
Medscape Infectious Diseases April 2000
Journal of American Medical Association (JAMA) 1999
Psychiatric Clinics of North America 1998
(2) Infection 1998, 1996

Click here to see a sample of conference presentations from researchers who have received LDA funding for their work.
Conference Presentations Resulting from LDA-Funding

Journal Articles Below

56. Frontiers in Neurology, May 10, 2021
Detecting Borrelia Spirochetes: A Case Study With Validation Among Autopsy Specimens
https://www.frontiersin.org/articles/10.3389/fneur.2021.628045/full
Shiva Kumar Goud Gadila1, Gorazd Rosoklija2,3, Andrew J. Dwork2,3,4,5, **Brian A. Fallon2*** and Monica E. Embers1*

1 Division of Immunology, Tulane National Primate Research Center, Tulane University Health Sciences, Covington, LA, United States
2 Department of Psychiatry, Columbia University, New York, NY, United States
3 Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, New York, NY, United States
4 Macedonian Academy of Sciences and Arts, Skopje, Macedonia
5 Department of Pathology and Cell Biology, Columbia University, New York, NY, United States

*Correspondence: Brian A. Fallon, baf1@cumc.columbia.edu;

Monica E. Embers, members@tulane.edu

Abstract: The complex etiology of neurodegenerative disease has prompted studies on multiple mechanisms including genetic predisposition, brain biochemistry, immunological responses, and microbial insult. In particular, Lyme disease is often associated with neurocognitive impairment with variable manifestations between patients. We sought to develop methods to reliably detect Borrelia burgdorferi, the spirochete bacteria responsible for Lyme disease, in autopsy specimens of patients with a history of neurocognitive disease. In this report, we describe the use of multiple molecular detection techniques for this pathogen and its application to a case study of a Lyme disease patient. The patient had a history of Lyme disease, was treated with antibiotics, and years later developed chronic symptoms including dementia. The patient's pathology and clinical case description was consistent with Lewy body dementia. B. burgdorferi was identified by PCR in several CNS tissues and by immunofluorescent staining in the spinal cord. These studies offer proof of the principle that persistent infection with the Lyme disease spirochete may have lingering consequences on the CNS.

55. Frontiers in Medicine (Lausanne), Oct 27, 2020
Borrelia miyamotoi Serology in a Clinical Population With Persistent Symptoms and Suspected Tick-Borne Illness
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7652925/
Shannon L. Delaney,1,2,* Lilly A. Murray,1,2 Claire E. Aasen,1 Clair E. Bennett,1,2 Ellen Brown,1,2 and **Brian A. Fallon**1,2

1 Lyme & Tick-Borne Diseases Research Center, Columbia University Irving Medical Center, New York, NY, United States
2 New York State Psychiatric Institute, Columbia University Irving Medical Center, New York, NY, United States
Edited by: Ying Zhang, Zhejiang University, China
Reviewed by: Pallab Ghosh, Harvard Medical School, United States; Raymond James Dattwyler, New York Medical College, United States

*Correspondence: Shannon L. Delaney sld2158@cumc.columbia.edu

Abstract: Eighty-two patients seeking consultation for long-term sequalae after suspected tick-borne illness were consecutively tested for Borrelia miyamotoi antibodies using a recombinant glycerophosphodiester phosphodiesterase (GlpQ) enzyme immunoassay. Twenty-one of the 82 patients (26%) tested positive on the GlpQ IgG ELISA. Nearly all of the patients (98%) had no prior B. miyamotoi testing, indicating that clinicians rarely test for this emerging tick-borne pathogen. Compared to patients who solely tested positive for Lyme disease antibodies, patients with B. miyamotoi antibodies presented with significantly more sleepiness and pain. A prospective study is needed to ascertain the relationship between the presence of B. miyamotoi antibodies and persistent symptoms.

54. Antibiotics (Basel). May 25, 2020
Effect of Borrelia burgdorferi Outer Membrane Vesicles on Host Oxidative Stress Response
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7277464/
Keith Wawrzeniak, Gauri Gaur, Eva Sapi, and **Alireza G. Senejani***

Department of Biology and Environmental Science, University of New Haven, West Haven, CT 06516, USA; kwawr1@unh.newhaven.edu (K.W.); ggaur2@unh.newhaven.edu (G.G.); ESapi@newhaven.edu (E.S.) *Correspondence: ASenejani@newhaven.edu

Abstract: Outer membrane vesicles (OMVs) are spherical bodies containing proteins and nucleic acids that are released by Gram-negative bacteria, including *Borrelia burgdorferi*, the causative agent of Lyme disease. The functional relationship between *B. burgdorferi* OMVs and host neuron homeostasis is not well understood. The objective of this study was to examine how *B. burgdorferi* OMVs impact the host cell environment. First, an in vitro model was established by co-culturing human BE2C neuroblastoma cells with *B. burgdorferi* B31. *B.*

burgdorferi was able to invade BE2C cells within 24 h. Despite internalization, BE2C cell viability and levels of apoptosis remained unchanged, but resulted in dramatically increased production of MCP-1 and MCP-2 cytokines. Elevated secretion of MCP-1 has previously been associated with changes in oxidative stress. BE2C cell mitochondrial superoxides were reduced as early as 30 min after exposure to *B. burgdorferi* and OMVs. To rule out whether BE2C cell antioxidant response is the cause of decline in superoxides, superoxide dismutase 2 (SOD2) gene expression was assessed. SOD2 expression was reduced upon exposure to *B. burgdorferi*, suggesting that *B. burgdorferi* might be responsible for superoxide reduction. These results suggest that *B. burgdorferi* modulates cell antioxidant defense and immune system reaction in response to the bacterial infection. In summary, these results show that *B. burgdorferi* OMVs serve to directly counter superoxide production in BE2C neurons, thereby 'priming' the host environment to support *B. burgdorferi* colonization.

53. Brain, Behavior, & Immunity – Health, January 7, 2020
https://www.sciencedirect.com/science/article/pii/S2666354619300158?via%3Dihub
Anti-lysoganglioside and other anti-neuronal autoantibodies in post-treatment Lyme Disease and Erythema Migrans after repeat infection
Brian A.Fallon a,b,* Barbara Strobino, a,b, SeanReim c, JulieStoner d, Madeleine W. Cunningham c

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1051 Riverside Drive, Unit 69, New York, NY, 10032, USA.

Abstract: **Background:** Molecular mimicry targeting neural tissue has been reported after Borrelia burgdorferi(Bb) infection. Herein, we investigate whether antineuronal autoantibodies are increased and whether antibody-mediated signaling of neuronal cells is elevated in a cohort of symptomatic adults with a history of Lyme Disease (LD). **Methods:** Participants (n = 179) included 24 with recent Erythema Migrans (EM) without prior LD, 8 with recent EM and prior LD (EM + prior LD), 119 with persistent post-treatment LD symptoms (PTLS), and 28 seronegative endemic controls with no prior LD history. Antineuronal immunoglobulin G (IgG) titers were measured by standard ELISA and compared with mean titers of normal age-matched sera against lysoganglioside, tubulin, and dopamine receptors (D1R and D2R). Antibody-mediated signaling of calcium calmodulin dependent protein kinase II (CaMKII) activity in a human neuronal cell line (SK-N-SH) was identified in serum. **Results:** EM + prior LD cases had higher antibody titers than controls for anti-lysoganglioside GM1 ($p = 0.002$), anti-tubulin ($p = 0.03$), and anti-D1R ($p = 0.02$), as well as higher expression in the functional antibody-mediated CaMKII Assay ($p = 0.03$). The EM cases with no prior history showed no significant differences on any measures. The PTLS cases demonstrated significantly higher titers ($p = 0.01$) than controls on anti-lysoganglioside GM1, but not for the other measures. **Conclusion:** The finding of elevated anti-neuronal autoantibodies in our small sample of those with a prior history of Lyme disease but not in those without prior Lyme disease, if replicated in a larger sample, suggests an immune priming effect of repeated infection; the CaMKII activation suggests that antineuronal antibodies have functional significance. The elevation of anti-lysoganglioside antibodies among those with PTLS is of particular interest given the established role of anti-ganglioside antibodies in peripheral and central neurologic diseases. Future prospective studies

can determine whether these autoantibodies emerge after Bb infection and whether their emergence coincides with persistent neurologic or neuropsychiatric symptoms.

52. Frontiers in Medicine, December 6, 2019
https://www.frontiersin.org/articles/10.3389/fmed.2019.00283/full

The General Symptom Questionnaire-30 (GSQ-30): A Brief Measure of Multi-System Symptom Burden in Lyme Disease

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Abstract: **Introduction:** The multi-system symptoms accompanying acute and post-treatment Lyme disease syndrome pose a challenge for time-limited assessment. The General Symptom Questionnaire (GSQ-30) was developed to fill the need for a brief patient-reported measure of multi-system symptom burden. In this study we assess the psychometric properties and sensitivity to change of the GSQ-30. **Materials and Methods:** 342 adult participants comprised 4 diagnostic groups: Lyme disease (post-treatment Lyme disease syndrome, n = 124; erythema migrans, n = 94); depression, n = 36; traumatic brain

injury, n = 51; healthy, n = 37. Participants were recruited from clinical research facilities in Massachusetts, Maryland, and New York. Validation measures for the GSQ-30 included the Patient Health Questionnaire-4 for depression and anxiety, visual analog scales for fatigue and pain, the Sheehan Disability Scale for functional impairment, and one global health question. To assess sensitivity to change, 53 patients with erythema migrans completed the GSQ-30 before treatment and 6 months after 3 weeks of treatment with doxycycline. **Results:** The GSQ-30 demonstrated excellent internal consistency (Cronbach α = 0.95). The factor structure reflects four core domains: pain/fatigue, neuropsychiatric, neurologic, and viral-like symptoms. Symptom burden was significantly associated with depression (rs = 0.60), anxiety (rs = 0.55), pain (rs = 0.75), fatigue (rs = 0.77), functional impairment (rs = 0.79), and general health (rs = −0.58). The GSQ-30 detected significant change in symptom burden before and after antibiotic therapy; this change correlated with change in functional impairment. The GSQ-30 total score significantly differed for erythema migrans vs. three other groups (post-treatment Lyme disease syndrome, depression, healthy controls). The GSQ-30 total scores for traumatic brain injury and depression were not significantly different from post-treatment Lyme disease syndrome. **Conclusions and Relevance:** The GSQ-30 is a valid and reliable instrument to assess symptom burden among patients with acute and post-treatment Lyme disease syndrome and is sensitive in the detection of change after treatment among patients with erythema migrans. The GSQ-30 should prove useful in clinical and research settings to assess multi-system symptom burden and to monitor change over time. The GSQ-30 may also prove useful in future precision medicine studies as a clinical measure to correlate with disease-relevant biomarkers.

51. Meta Gene, Volume 21, September 2019. Online May 2019 https://www.sciencedirect.com/science/article/pii/S2214540019300489

Genetic Variation in the ABCB1 Gene Associated with Post Treatment Lyme Disease Syndrome Status

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Abstract: Post Treatment Lyme Disease Syndrome (PTLDS) poses a difficult to understand health issue. This multi-centered, randomized control trial studied the possible correlation between ABCB1 (MDR1) gene variants and the incidence of PTLDS in affected patients. Genomic DNA was isolated and analyzed for four ABCB1 gene SNPs (rs1128503, rs1045642, rs2235067, and rs4148740). Significant findings include the association of rs1128503 TC variant with PTLDS status. Additionally, the rs1128503+ rs1045642+ rs2235067 SNP combination increased rs1128503 genotype TC significance to 3.83 times the rs1128503 genotype CC. The TT variant of rs4148740 in conjunction with rs1128503 reduced the odds ratio and appeared to convey a PTLDS protective status to the rs1128503 TC variant.

50. Ticks and Tick-Borne Diseases, 2018 Nov 27
https://www.ncbi.nlm.nih.gov/pubmed/30503356https://www.ncbi.nlm.nih.gov/pubmed/30503356

Regional prevalences of Borrelia burgdorferi, Borrelia bissettiae, and Bartonella henselae in Ixodes affinis, Ixodes pacificus and Ixodes scapularis in the USA.

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ABSTRACT: The objective of this work was to determine the prevalence of Borrelia and Bartonella species in Ixodes spp. ticks collected from 16 USA states. Genus PCR amplification and sequence analysis of Bartonella and Borrelia 16SsRNA-23SsRNA intergenic regions were performed on DNA extracted from 929 questing adult ticks (671 Ixodes scapularis, 155 Ixodes affinis, and 103 Ixodes pacificus). Overall, 129/929 (13.9%) Ixodes ticks were PCR positive for Borrelia burgdorferi sensu stricto, 48/929 for B. bissettiae whereas 23/929 (2.5%) were PCR positive for a Bartonella henselae. Borrelia bissettiae or B. burgdorferi s.s. and B. henselae co-infections were found in I. affinis from North Carolina at a rate of 4.5%; in a single I. scapularis from Minnesota, but not in I. pacificus. For both bacterial genera, PCR positive rates were highly variable depending on geographic location and tick species, with Ixodes affinis (n = 155) collected from North Carolina, being the tick species with the highest prevalence’s for both Borrelia spp. (63.2%) and B. henselae (10.3%). Based on the results of this and other published studies, improved understanding of the enzootic cycle, transmission dynamics, and vector competence

of Ixodes species (especially I. affinis) for transmission of Borrelia spp. and B. henselae should be a public health research priority.

49. Archives of Clinical Neuropsychology, Nov 12, 2018
https://academic.oup.com/acn/advance-article-abstract/doi/10.1093/arclin/acy083/5173742?redirectedFrom=PDF
Neurocognition in Post-Treatment Lyme Disease and Major Depressive Disorder
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Dr. John Keilp, senior neuropsychologist for the Columbia Lyme & Tick-borne Diseases Research Center', reports that the cognitive profile of patients with post treatment Lyme disease is meaningfully different from the profile of patients with major depression. This is a neurocognitive biomarker or fingerprint of post-treatment Lyme disease. Although both groups might have fatigue and mental fogginess, the Lyme group more often reports problems with verbal memory and verbal fluency while the depressed (non-Lyme) group more often reports slower processing speed and poor attention. These results highlight the value of neurocognitive testing in helping to tease out the potential causes of cognitive

problems in patients with post-treatment Lyme disease.

48. Psychosomatics 59(5) · Sept/Oct 2018
https://www.ncbi.nlm.nih.gov/pubmed/29606281
Depressive Symptoms and Suicidal Ideation Among Symptomatic Patients with a History of Lyme Disease Versus Two Comparison Groups
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ABSTRACT: Background: Depression has been reported in 8–45% of patients with posttreatment Lyme symptoms (PTLS), but little is known about suicidal ideation in these patients. Method: Depression and suicidal ideation were assessed using the Beck Depression Inventory (BDI-II). Scores from the PTLS group (n = 81) were compared to those from 2 other groups: HIV+ patients being treated for fatigue (n = 70), and a nonpatient comparison group (NPCG; n = 44). ANOVA and t-tests were used to compare groups; logistic regression was used to identify the strongest correlates of suicidal ideation. Results: Mean BDI-II scores fell in the mildly depressed range for PTLS and HIV+ patients, with both groups having higher depression scores than the NPCG. Suicidal ideation was reported by 19.8% of the PTLS patients and 27.1% of the HIV+ patients, a nonsignificant difference. Among those with mild or no depression, suicidal ideation was uncommon (6.5% PTLS and 11.9% HIV+). Among the patients with moderate-to-severe depression, suicidal ideation was more common (63.2% of 19 PTLS and 50% of 28 HIV+); among these, 2 with PTLS and 1 with HIV+ expressed suicidal intent. Further, 4.5% (n = 2) of the

NPCG had suicidal ideation, each had scores in the moderate-to-severe depression range. Higher scores on the cognitive symptoms subscale of the BDI-II predicted greater likelihood of suicidal ideation across patient groups. Conclusion:As expected, suicidal ideation is increased among patients who are depressed. The fact that 1 in 5 patients with PTLS reported suicidal ideation highlights the importance of screening for depression and suicidality to optimize patient care.

47. Healthcare (Basel) 2018 Jun; 6(2): 69.
A Community Study of Borrelia burgdorferi Antibodies among Individuals with Prior Lyme Disease in Endemic Areas
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6023339/

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Abstract: The objective was to examine the prevalence of Borrelia antibodies among symptomatic individuals with recent

and past Lyme disease in endemic communities using standard assays and novel assays employing next-generation antigenic substrates. Single- and two-tiered algorithms included different anti-Borrelia ELISAs and immunoblots. Antibody prevalence was examined in sera from 32 individuals with recent erythema migrans (EM), 335 individuals with persistent symptoms following treatment for Lyme disease (PTLS), and 41 community controls without a history of Lyme disease. Among convalescent EM cases, sensitivity was highest using the C6 ELISA (93.8%) compared to other single assays; specificity was 92.7% for the C6 ELISA vs. 85.4–97.6% for other assays. The two-tiered ELISA-EUROLINE IgG immunoblot combinations enhanced case detection substantially compared to the respective ELISA-IgGWestern blot combinations (75.0% vs. 34.4%) despite similar specificity (95.1% vs. 97.6%, respectively). For PTLS cohorts, two-tier ELISA-IgG-blot positivity ranged from 10.1% to 47.4%, depending upon assay combination, time from initial infection, and clinical history. For controls, the two-tier positivity rate was 0–14.6% across assays. A two-tier algorithm of two-ELISA assays yielded a high positivity rate of 87.5% among convalescent EM cases with specificity of 92.7%. For convalescent EM, combinations of the C6 ELISA with a second-tier ELISA or line blot may provide useful alternatives to WB-based testing algorithms.

46. Bio-Protocol. Vol 7, Iss 23, December 05, 2017 DOI: 10.21769/BioProtoc.2643.
https://bio-protocol.org/e2643

Lentiviral Knockdown of Transcription Factor STAT1 in Peromyscus leucopus to Assess Its Role in the Restriction of Tick-borne Flaviviruses

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ABSTRACT: Cellular infection with tick-borne flaviviruses (TBFVs) results in activation of the interferon (IFN) signaling pathway and subsequent upregulation of numerous genes termed IFN stimulated genes (ISGs) (Schoggins et al., 2011). Many ISGs function to prevent virus pathogenesis by acting in a broad or specific manner through protein-protein interactions (Duggal and Emerman, 2012). The potency of the IFN signaling response determines the outcome of TBFV infection (Best, 2017; Carletti et al., 2017). Interestingly, data from our lab show that TBFV replication is significantly restricted in cells of the reservoir species Peromyscus leucopus thereby suggesting a potent antiviral response (Izuogu et al., 2017). We assessed the relative contribution of IFN signaling to resistance in P. leucopus by knocking down a major transcription factor in the IFN response pathway. Signal transducer and activator of transcription 1 (STAT1) was specifically targeted in P. leucopus cells by shRNA technology. We further tested the impact of gene knockdown on the ability of cells to respond to IFN and restrict virus replication; the results indicate that when STAT1 expression is altered, P. leucopus cells have a decreased response to IFN stimulation and are significantly more susceptible to TBFV replication.

45. FEBS J. 2017 Nov;284(21):3662-3683. Epub 2017 Sep 30.
https://www.ncbi.nlm.nih.gov/pubmed/28892294

Nuclease activity gives an edge to host-defense peptide piscidin 3 over piscidin 1, rendering it more effective against persisters and biofilms.

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ABSTRACT: Host-defense peptides (HDPs) feature evolution-tested potency against life-threatening pathogens. While piscidin 1 (p1) and piscidin 3 (p3) are homologous and potent fish HDPs, only p1 is strongly membranolytic. Here, we hypothesize that another mechanism imparts p3 strong potency. We demonstrate that the N-termini of both peptides coordinate Cu^{2+} and p3-Cu cleaves isolated DNA at a rate on par with free Cu^{2+} but significantly faster than p1-Cu. On planktonic bacteria, p1 is more antimicrobial but only p3 features copper-dependent DNA cleavage. On biofilms and persister cells, p3-Cu is more active than p1-Cu, commensurate with stronger peptide-induced DNA damage. Molecular dynamics and NMR show that more DNA-peptide interactions exist with p3 than p1, and the peptides adopt conformations simultaneously poised

for metal- and DNA-binding. These results generate several important conclusions. First, homologous HDPs cannot be assumed to have identical mechanisms since p1 and p3 eradicate bacteria through distinct relative contributions of membrane and DNA-disruptive effects. Second, the nuclease and membrane activities of p1 and p3 show that naturally occurring HDPs can inflict not only physicochemical but also covalent damage. Third, strong nuclease activity is essential for biofilm and persister cell eradication, as shown by p3, the homolog more specific toward bacteria and more expressed in vascularized tissues. Fourth, p3 combines several physicochemical properties (e.g., Amino Terminal Copper and Nickel binding motif; numerous arginines; moderate hydrophobicity) that confer low membranolytic effects, robust copper-scavenging capability, strong interactions with DNA, and fast nuclease activity. This new knowledge could help design novel therapeutics active against hard-to-treat persister cells and biofilms.

44. ACS Chem. Biol., 2017, 12 (5), pp 1170–1182 Publication Date (Web): March 29, 2017
https://pubs.acs.org/doi/abs/10.1021/acschembio.7b00237

Membrane Oxidation in Cell Delivery and Cell Killing Applications

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ABSTRACT: Cell delivery or cell killing processes often

involve the crossing or disruption of cellular membranes. We review how, by modifying the composition and properties of membranes, membrane oxidation can be exploited to enhance the delivery of macromolecular cargoes into live human cells. We also describe how membrane oxidation can be utilized to achieve efficient killing of bacteria by antimicrobial peptides. Finally, we present recent evidence highlighting how membrane oxidation is intimately engaged in natural biological processes such as antigen delivery in dendritic cells and in the killing of bacteria by antimicrobial peptides. Overall, the insights that have been recently gained in this area should facilitate the development of more effective delivery technologies andantimicrobial therapeutic approaches.

43. Biochemistry, 2017, 56 (10), pp 1403–1414 Publication Date (Web): February 22, 2017
https://pubs.acs.org/doi/abs/10.1021/acs.biochem.6b01046
Exploration of the Innate Immune System of Styela clava: Zn2+ Binding Enhances the Antimicrobial Activity of the Tunicate Peptide Clavanin A
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ABSTRACT: Tunicates have been used as primitive models for understanding cellmediated and humoral immunity. Clavanin A (ClavA) is one member of a family of antimicrobial peptides produced by the solitary tunicate *Styela clava*. In this work, we demonstrate that ClavA utilizes Zn2+ ions to potentiate its antimicrobial activity not only by reducing the concentration at which the peptide inhibits the growth of bacteria but also by

increasing the rate of killing. Membrane depolarization, β-galactosidase leakage, and potassium leakage assays indicate that ClavA is membrane active, forms small pores, but induces cell death by targeting an intracellular component. ClavA and ClavA-Zn2+ added to *Escherichia coli* and imaged by confocal microscopy translocate across the cell membrane. *E. coli* mutants lacking the functional Zn2+ import system are less susceptible to ClavA, suggesting that the synergistic activity between ClavA and Zn2+ has a cytoplasmic target, which is further supported by its nucleolytic activity. Overall, these studies identify a remarkable new mechanism by which zinc contributes to the immune response in the tunicate *S. clava.*

42. PLoS One, June 26, 2017;12(6)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5484488/
Interferon Signaling in Peromyscus Leucopus Confers a Potent and Specific Restriction to Vector-borne Flaviviruses
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Abstract: Tick-borne flaviviruses (TBFVs), including Powassan virus and tick-borne encephalitis virus cause encephalitis or hemorrhagic fevers in humans with case-fatality rates ranging

from 1-30%. Despite severe disease in humans, TBFV infection of natural rodent hosts has little noticeable effect. Currently, the basis for resistance to disease is not known. We hypothesize that the coevolution of flaviviruses with their respective hosts has shaped the evolution of potent antiviral factors that suppress virus replication and protect the host from lethal infection. In the current study, we compared virus infection between reservoir host cells and related susceptible species. Infection of primary fibroblasts from the white-footed mouse (Peromyscus leucopus, a representative host) with a panel of vector-borne flaviviruses showed up to a 10,000-fold reduction in virus titer compared to control Mus musculus cells. Replication of vesicular stomatitis virus was equivalent in P. leucopus and M. musculus cells suggesting that restriction was flavivirus-specific. Step-wise comparison of the virus infection cycle revealed a significant block to viral RNA replication, but not virus entry, in P. leucopus cells. To understand the role of the type I interferon (IFN) response in virus restriction, we knocked down signal transducer and activator of transcription 1 (STAT1) or the type I IFN receptor (IFNAR1) by RNA interference. Loss of IFNAR1 or STAT1 significantly relieved the block in virus replication in P. leucopus cells. The major IFN antagonist encoded by TBFV, nonstructural protein 5, was functional in P. leucopus cells, thus ruling out ineffective viral antagonism of the host IFN response. Collectively, this work demonstrates that the IFN response of P. leucopus imparts a strong and virus-specific barrier to flavivirus replication. Future identification of the IFN-stimulated genes responsible for virus restriction specifically in P. leucopus will yield mechanistic insight into efficient control of virus replication and may inform the development of antiviral therapeutics.

41. Antibiotics, March 22, 2017
http://www.mdpi.com/2079-6382/6/1/10/pdf
Activity of Sulfa Drugs and Their Combinations against

Stationary Phase B. burgdorferi In Vitro

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Abstract: Lyme disease is a most common vector-borne disease in the US. Although the majority of Lyme patients can be cured with the standard two- to four-week antibiotic treatment, at least 10%–20% of patients continue to suffer from prolonged post-treatment Lyme disease syndrome (PTLDS). While the cause for this is unclear, one possibility is that persisting organisms are not killed by current Lyme antibiotics. In our previous studies, we screened an FDA drug library and an NCI compound library on B. burgdorferi and found some drug hits including sulfa drugs as having good activity against B. burgdorferi stationary phase cells. In this study, we evaluated the relative activity of three commonly used sulfa drugs, sulfamethoxazole (Smx), dapsone (Dps), sulfachlorpyridazine (Scp), and also trimethoprim (Tmp), and assessed their combinations with the commonly prescribed Lyme antibiotics for activities against B. burgdorferi stationary phase cells. Using the same molarity concentration, dapsone, sulfachlorpyridazine and trimethoprim showed very similar activity against stationary phase B. burgdorferi enriched in persisters; however, sulfamethoxazole was the least active drug among the three sulfa drugs tested. Interestingly, contrary to other bacterial systems, Tmp did not show synergy in drug combinations with the three sulfa drugs at their clinically relevant serum concentrations against B. burgdorferi. We found that sulfa drugs combined with other antibiotics were more active than their respective single drugs and that four-drug combinations were more active than three-drug combinations. Four-drug combinations dapsone + minocycline + cefuroxime + azithromycin and dapsone + minocycline + cefuroxime + rifampin showed the best activity against stationary phase B. burgdorferi in these sulfa drug combinations. However, these four-sulfa-drug–containing combinations still had considerably less activity against B. burgdorferi stationary phase cells than the Daptomycin +

cefuroxime + doxycycline used as a positive control which completely eradicated B. burgdorferi stationary phase cells. Future studies are needed to evaluate and optimize the sulfa drug combinations in vitro and also in animal models.

40. Frontiers in Microbiology, October 19, 2016
http://journal.frontiersin.org/article/10.3389/fmicb.2016.01744/pdf
Ceftriaxone Pulse Dosing Fails to Eradicate Biofilm-like Microcolony B. burgdorferi Persisters Which Are Sterilized by Daptomycin/Doxycycline/Cefuroxime Drug Combination without Pulse Dosing
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Abstract: Although the majority of Lyme disease patients can be cured, at least 10-20% of the patients continue to suffer from persisting symptoms such as fatigue, muscular and joint pain, and neurologic impairment after standard 2-4 week antibiotic treatment. While the causes for this post-treatment Lyme disease symptoms are unclear, one possibility is due to B. burgdorferi persisters that are not effectively killed by current antibiotics such as doxycycline or amoxicillin used to treat Lyme disease. A previous study showed that four rounds of ceftriaxone pulse dosing treatment eradicated B. burgdorferi persisters in vitro using a relatively young late log phase culture (5 day old). In this study, we investigated if ceftriaxone pulse dosing could also eradicate B. burgdorferi persisters in older stationary phase cultures (10 day old) enriched with more resistant microcolony form of persisters. We found that ceftriaxone pulse dosing could only eradicate planktonic log phase B. burgdorferi spirochetal forms and round body forms but not more resistant aggregated biofilm-like microcolony persisters enriched in stationary phase cultures. Moreover, we found that not all drugs are suitable for pulse dosing, with bactericidal drugs ceftriaxone and cefuroxime being more appropriate for pulse dosing than bacteriostatic drug doxycycline and persister drug daptomycin. We also showed that drug combination pulse dosing treatment was more effective than single drug pulse dosing. Importantly, we demonstrate that pulse dosing treatment impaired the activity of the persister drug daptomycin and its drug combination against B. burgdorferi persisters and that the most effective way to kill the more resistant biofilm-like microcolonies is the daptomycin/doxycycline/ceftriaxone triple drug combination without pulse dosing. Our findings indicate pulse dosing may not always work as a general principle but rather depends on the specific drugs used, with cidal drugs being more appropriate for pulse dosing than static or persister drugs, and that drug combination approach with persister drugs is more effective at killing the more resistant microcolony form of persisters than pulse dosing. These observations may have implications for more effective treatment of Lyme disease. Future studies are required to validate these findings in animal models of B. burgdorferi persistence.

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39. Frontiers in Microbiology, May 23, 2016
http://journal.frontiersin.org/article/10.3389/fmicb.2016.00743/full
A Drug Combination Screen Identifies Drugs Active against Amoxicillin-Induced Round Bodies of In Vitro Borrelia burgdorferi Persisters from an FDA Drug Library

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Abstract: Although currently recommended antibiotics for Lyme disease such as doxycycline or amoxicillin cure the majority of the patients, about 10–20% of patients treated for Lyme disease may experience lingering symptoms including fatigue, pain, or joint and muscle aches. Under experimental stress conditions such as starvation or antibiotic exposure, Borrelia burgdorferi can develop round body forms, which are a type of persister bacteria that appear resistant in vitro to customary first-line antibiotics for Lyme disease. To identify more effective drugs with activity against the round body form of B. burgdorferi, we established a round body persister model induced by exposure to amoxicillin (50 µg/ml) and then screened the Food and Drug Administration drug library consisting of 1581 drug compounds and also 22 drug combinations using the SYBR Green I/propidium iodide viability assay. We identified 23 drug candidates that have higher activity against the round bodies of B. burgdorferi than either amoxicillin or doxycycline. Eleven individual drugs scored better than metronidazole and tinidazole which have been previously described to be active against round bodies. In this amoxicillin-induced round body model, some drug candidates such as daptomycin and clofazimine also displayed enhanced activity which was similar to a previous screen against stationary phase B. burgdorferi persisters not exposure to amoxicillin. Additional candidate drugs active against round bodies identified include artemisinin, ciprofloxacin, nifuroxime, fosfomycin, chlortetracycline, sulfacetamide, sulfamethoxypyridazine and sulfathiozole. Two triple drug combinations had the highest activity against amoxicillin-induced round bodies and stationary phase B. burgdorferi persisters: artemisinin/cefoperazone/doxycycline and sulfachlorpyridazine/daptomycin/doxycycline. These findings confirm and extend previous findings that certain drug combinations have superior activity against B. burgdorferi persisters in vitro, even when pre-treated with amoxicillin. These findings may have implications for improved treatment of Lyme disease.

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38. Park Science (NPS, Department of Interior) March 2016
http://www.nature.nps.gov/ParkScience/Archive/PDF/Article_PDFs/ParkScience32(1)Summer2015_36-41_Ford_et_al_3819.pdf

Tick surveillance and disease prevention on the Appalachian Trail

(Also published in Appalachian Trail Journeys, The Magazine of the Appalachian Trail Conservancy, May/June 2014)

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Abstract: The Appalachian National Scenic Trail (AT) runs 3,520 km (2,187 mi) from northern Georgia to northern Maine, traversing 14 states where Lyme disease and other tickborne diseases are endemic or emerging. Approximately 2–3 million visitors hike the AT annually, including through-hikers who spend five to six months on the trail in spring through early fall, when common tick species are active. Disease vector tick surveillance was conducted from April through August 2013 at

42 randomly selected AT shelter areas along a south-to-north transect covering the full length of the AT. Tick abundance at shelters and tenting areas was compared with tick abundance on the AT itself, and the collected ticks were tested for common bacterial pathogens. Human-biting tick species collected comprised Ixodes scapularis, Amblyomma americanum, Amblyomma maculatum, and Dermacentor variabilis. Human pathogens Borrelia burgdorferi and Rickettsia montanensis were detected in tested ticks. Tick abundance on the trail was low overall (2.8 ticks per 1,000 m2 sampled), but exceeded tick abundance in shelters and tenting areas by 14.5 times. No ticks were collected south of Virginia or north of Massachusetts, or above 829 m (2,720 ft) in elevation, which suggests that season and elevation are significant determinants of the risk of hiker exposure to questing ticks on the AT. Such information should be included in future health messaging to hikers along with preventive measures. Management issues are discussed.

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37. FEMS Microbiology Letters Advance Access, July 24, 2015
http://femsle.oxfordjournals.org/content/early/2015/07/23/femsle.fnv120
Biofilm formation by 1 Borrelia sensu lato

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Abstract: Bacterial biofilms are microbial communities held together by an extracellular polymeric substance matrix predominantly composed of polysaccharides, proteins and nucleic acids. We had previously shown that Borrelia burgdorferi sensu stricto, the causative organism of Lyme disease in the United States is capable of forming biofilms in vitro. Here, we investigated biofilm formation by Borrelia afzelii and Borrelia garinii, which cause Lyme disease in Europe. Using various histochemistry and microscopy techniques, we show that Borrelia afzelii and Borrelia garinii form biofilms, which resemble biofilms formed by Borrelia burgdorferi sensu stricto. High-resolution atomic force microscopy revealed similarities in the ultra-structural organization of the biofilms form by three Borrelia species. Histochemical experiments revealed a heterogeneous organization of exopolysaccharides among the three Borrelia species. These results suggest that biofilm formation might be a common trait of Borrelia genera physiology.

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36. Clinical Infectious Diseases Advance Access, September 2, 2014
http://www.ncbi.nlm.nih.gov/pubmed/25182244

A comparison of Lyme disease serologic test results from four laboratories in patients with persistent symptoms after antibiotic treatment

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Summary: In patients with post-treatment Lyme syndrome, rates of positive serologic test results were generally similar among a university laboratory, a commercial laboratory, and two Lyme specialty laboratories, although interlaboratory variability was high and the IgM Western Blot performed poorly.

Abstract: Background – As the incidence of Lyme disease (LD) has increased, a number of “Lyme specialty laboratories” have emerged, claiming singular expertise in LD testing. We investigated the degree of interlaboratory variability of several LD serologic tests—whole cell sonicate (WCS) enzyme-linked immunosorbent assay (ELISA), IgM and IgG Western blots (WB), and an ELISA based on the conserved sixth region of VlsE (C6)—performed at one university laboratory, one commercial laboratory and two laboratories that specialize in LD testing.

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35. Veterinary Sciences, 2014 www.mdpi.com/2306-7381/1/1/5

Filarial Nematode Infection in Ixodes scapularis Ticks Collected from Southern

Connecticut

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Abstract: It was recently demonstrated that the lone star tick Amblyomma americanum could harbor filarial nematodes within the genus Acanthocheilonema. In this study, Ixodes scapularis (deer) ticks collected from Southern Connecticut were evaluated for their potential to harbor filarial nematodes. Non-engorged nymphal and adult stage Ixodes scapularis ticks were collected in Southern Connecticut using the standard drag method. In situ hybridization with filarial nematode specific sequences demonstrated the presence of filarial nematodes in Ixodes ticks. Filarial nematode specific DNA sequences were amplified and confirmed by direct sequencing in Ixodes nymphal and adult ticks using either general filarial nematode or Onchocercidae family specific PCR primers. Phylogenetic analysis of the 12S rDNA gene sequence indicated that the filarial nematode infecting Ixodes scapularis ticks is most closely related to the species found in Amblyomma americanum ticks and belongs to the genus of Acanthocheilonema. Our data also demonstrated that infection rate of these filarial nematode in Ixodes ticks is relatively high (about 22% and 30% in nymphal and adult Ixodes ticks, respectively). In summary, the results from our studies demonstrated that filarial nematode infection was found in Ixodes ticks similar to what has been found in Amblyomma americanum ticks.

Vet. Sci. 2014, 1, 5-15; doi:10.3390/vetsci1010005

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34. Psychosomatics 2013

http://www.psychosomaticsjournal.com/article/S0033-3182%2813%2900078-9/fulltext

Correlates of Perceived Health-Related Quality of Life in Post-treatment Lyme Encephalopathy

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ABSTRACT: Background – Marked functional impairment has been reported by patients with post-treatment Lyme disease syndrome (PTLDS). Objective: We sought to identify but the clinical features that contribute most strongly to the impaired health status associated with PTLDS. Methods: Enrolled patients had a well-documented

history of Lyme disease, prior treatment with at least 3 weeks with intravenous ceftriaxone, a positive IgG Western blot, and objective problems with memory. An index score to capture aggregate cognitive functioning, Short-Form 36 physical and mental component summer scores, and scores on other clinical and demographic measures were examined. Multiple linear regressions were performed to determine significant predictors of perceptions of impaired life functioning as delineated by theShort-Form36.Results: Fatigue was the most important contributor to perceived impairments in overall physical functioning, and fatigue and depression significantly predicted perceived impairments in overall mental functioning. Conclusions: Because fatigue and depression contribute prominently to reports of impaired physical functioning and mental functioning among patients with PTLDS, clinicians should assess patients for these symptoms and consider targeting these symptoms in the selection of treatment interventions. Future controlled studies should examine the effectiveness of such agents for patients with PTLDS.

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33. International Journal of Medical Sciences 2013
http://www.medsci.org/v10p0915.htm
Lyme Borreliosis in Human Patients in Florida and Georgia, USA
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ABSTRACT: The aim of this study was to determine the cause of illness in several human patients residing in Florida and Georgia, USA, with suspected Lyme disease based upon EM-like skin lesions and/or symptoms consistent with early localized or late disseminated Lyme borreliosis. Using polymerase chain reaction (PCR) assays developed specifically for Lyme group Borrelia spp., followed by DNA sequencing for confirmation, we identified Borrelia burgdorferi sensu lato DNA in samples of blood and skin and also in lone star ticks (Amblyomma americanum) removed from several patients who either live in or were exposed to ticks in Florida or Georgia. This is the first report to present combined PCR and DNA sequence evidence of infection with Lyme Borrelia spp. in human patients in the southern U.S., and to demonstrate that several B. burgdorferi sensu lato species may be associated with Lyme disease-like signs and symptoms in southern states. Based on the findings of this study, we suggest that human Lyme borreliosis occurs in Florida and Georgia, and that some cases of Lyme-like illness referred to as southern tick associated rash illness (STARI) in the southern U.S. may be attributable to previously undetected B. burgdorferi sensu lato infections.

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32. Northeastern Naturalist 2013; 20(1):197–204.
http://www.bioone.org/doi/abs/10.1656/045.020.0116
Distribution of Ticks & Prevalence of Borrelia burgdorferi in the Upper Connecticut River Valley of Vermont
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ABSTRACT: Ixodes scapularis (Black-legged Tick) has expanded its range in recent decades. To establish baseline data on the abundance of the Black-legged Tick and Borrelia burgdorferi (the causative agent of Lyme disease) at the edge of a putative range expansion, we collected 1398 ticks from five locations along the Connecticut River in Vermont. Collection locations were approximately evenly distributed between the villages of Ascutney and Guildhall. Relative abundance and distribution by species varied across sites. Black-legged Ticks dominated our collections (n = 1348, 96%), followed by Haemaphysalis leporispalustris (Rabbit Tick; n = 45, 3%), and Dermacentor variabilis (American Dog Tick; n = 5, <1%). Black-legged Tick abundance ranged from 6198 ticks per survey hectare (all life stages combined) at the Thetford site to zero at the Guildhall site. There was little to no overlap of tick species across sites. Phenology of Black-legged Ticks matched published information from other regions of the northeastern USA. Prevalence of B. burgdorferi in adult Black-legged Ticks was 8.9% (n = 112)

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31. J Neuropsychiatry Clin Neurosci. 2013 Feb 27. doi: 10.1176/appi.neuropsych.12090223.

http://www.ncbi.nlm.nih.gov/pubmed/23446551

Post-Treatment Lyme Syndrome and Central Sensitization.

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ABSTRACT: Central sensitization is a process that links a variety of chronic pain disorders that are characterized by hypersensitivity to noxious stimuli and pain in response to non-noxious stimuli. Among these disorders, treatments that act centrally may have greater efficacy than treatments acting peripherally. Because many individuals with post-treatment Lyme syndrome (PTLS) have a similar symptom cluster, central sensitization may be a process mediating or exacerbating their sensory processing. This article reviews central sensitization, reports new data on sensory hyperarousal in PTLS, explores the potential role of central sensitization in symptom chronicity, and suggests new directions for neurophysiologic and treatment research.

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30. The Open Neurology Journal 2012: 6, (Suppl 1-M2) 79-87

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474942/

A Reappraisal of the U.S. Clinical Trials of Post-Treatment Lyme Disease Syndrome

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ABSTRACT: Four federally funded randomized placebo-controlled treatment trials of post-treatment Lyme syndrome in the United States have been conducted. Most international treatment guidelines summarize these trials as having shown no acute or sustained benefit to repeated antibiotic therapy. The goal of this paper is to determine whether this summary conclusion is supported by the evidence.
Methods: The methods and results of the 4 U.S. treatment trials are described and their critiques evaluated.
Results: 2 of the 4 U.S. treatment trials demonstrated efficacy of IV ceftriaxone on primary and/or secondary outcome measures.
Conclusions: Future treatment guidelines should clarify that efficacy of IV ceftriaxone for post-treatment Lyme fatigue was demonstrated in one RCT and supported by a second RCT, but that its use was not recommended primarily due to adverse events stemming from the IV route of treatment. While repeated IV antibiotic therapy can be effective, safer modes of delivery are needed.

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29. PLoS ONE 7(10) 2012: e48277. doi:10.1371/journal.pone.0048277

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0048277

Characterization of Biofilm Formation by Borrelia burgdorferi In Vitro

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ABSTRACT: Borrelia burgdorferi, the causative agent of Lyme disease, has long been known to be capable of forming aggregates and colonies. It was recently demonstrated that Borrelia burgdorferi aggregate formation dramatically changes the in vitro response to hostile environments by this pathogen. In this study, we investigated the hypothesis that these aggregates are indeed biofilms, structures whose resistance to unfavorable conditions are well documented. We studied Borrelia burgdorferi for several known hallmark features of biofilm, including structural rearrangements in the aggregates, variations in development on various substrate matrices and secretion of a protective extracellular polymeric substance (EPS)

matrix using several modes of microscopic, cell and molecular biology techniques. The atomic force microscopic results provided evidence that multilevel rearrangements take place at different stages of aggregate development, producing a complex, continuously rearranging structure. Our results also demonstrated that Borrelia burgdorferi is capable of developing aggregates on different abiotic and biotic substrates, and is also capable of forming floating aggregates. Analyzing the extracellular substance of the aggregates for potential exopolysaccharides revealed the existence of both sulfated and non-sulfated/carboxylated substrates, predominately composed of an alginate with calcium and extracellular DNA present. In summary, we have found substantial evidence that Borrelia burgdorferi is capable of forming biofilm in vitro. Biofilm formation by Borrelia species might play an important role in their survival in diverse environmental conditions by providing refuge to individual cells.

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28. PLOS One 2012

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0033280

Genome Stability of Lyme Disease Spirochetes: Comparative Genomics of Borrelia burgdorferi Plasmids

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ABSTRACT: Lyme disease is the most common tick-borne human illness in North America. In order to understand the molecular pathogenesis, natural diversity, population structure and epizootic spread of the North American Lyme agent, Borrelia burgdorferi sensu stricto, a much better understanding of the natural diversity of its genome will be required. Towards this end we present a comparative analysis of the nucleotide sequences of the numerous plasmids of B. burgdorferi isolates B31, N40, JD1 and 297. These strains were chosen because they include the three most commonly studied laboratory strains, and because they represent different major genetic lineages and so are informative regarding the genetic diversity and evolution of this organism. A unique feature of Borrelia genomes is that they carry a large number of linear and circular plasmids, and this work shows that strains N40, JD1, 297 and B31 carry related but non-identical sets of 16, 20, 19 and 21 plasmids, respectively, that comprise 33–40% of their genomes. We deduce that there are at least 28 plasmid compatibility types among the four strains. The B. burgdorferi ~900 Kbp linear chromosomes are evolutionarily exceptionally stable, except for a short ≤20 Kbp plasmid-like section at the right end. A few of the plasmids, including the linear lp54 and circular cp26, are also very stable. We show here that the other plasmids, especially the linear ones, are considerably more variable. Nearly all of the linear plasmids have undergone one or more substantial inter-plasmid rearrangements since their last common ancestor. In spite of these rearrangements and differences in plasmid contents, the overall gene complement of

the different isolates has remained relatively constant.

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27. Journal of Bacteriology 2011 http://jb.asm.org/content/193/4/1018.long
Whole-Genome Sequences of Thirteen Isolates of Borrelia burgdorferi
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ABSTRACT: Borrelia burgdorferi is a causative agent of Lyme disease in North America and Eurasia. The first complete genome sequence of B. burgdorferi strain 31, available for more than a decade, has assisted research on the pathogenesis of Lyme disease. Because a single genome sequence is not sufficient to understand the relationship between genotypic and geographic variation and disease phenotype, we determined the whole-genome sequences of 13 additional B. burgdorferi isolates that span the range of natural variation. These sequences should allow improved understanding of pathogenesis and provide a foundation for novel detection, diagnosis, and prevention strategies.

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26. PLoS ONE 6(2): e17287. doi:10.1371/journal.pone.0017287 2011
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0017287
Distinct Cerebrospinal Fluid Proteomes Differentiate Post-Treatment Lyme Disease from Chronic Fatigue Syndrome
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ABSTRACT: Neurologic Post Treatment Lyme disease (nPTLS) and Chronic Fatigue (CFS) are syndromes of unknown etiology. They share features of fatigue and cognitive dysfunction, making it difficult to differentiate them. Unresolved is whether nPTLS is a subset of CFS.

Pooled cerebrospinal fluid (CSF) samples from nPTLS patients, CFS patients, and healthy volunteers were comprehensively analyzed using high-resolution mass spectrometry (MS), coupled with immunoaffinity depletion methods to reduce protein-masking by abundant proteins. Individual patient and healthy control CSF samples were analyzed directly employing a MS-based label-free quantitative proteomics approach. We found that both groups, and individuals within the groups, could be distinguished from each other and normals based on their specific CSF proteins ($p<0.01$). CFS (n = 43) had 2,783 non-redundant proteins, nPTLS (n = 25) contained 2,768 proteins, and healthy normals had 2,630 proteins. Preliminary pathway analysis demonstrated that the data could be useful for hypothesis generation on the pathogenetic mechanisms underlying these two related syndromes. nPTLS and CFS have distinguishing CSF protein complements. Each condition has a number of CSF proteins that can be useful in providing candidates for future validation studies and insights on the respective mechanisms of pathogenesis. Distinguishing nPTLS and CFS permits more focused study of each condition, and can lead to novel diagnostics and therapeutic interventions.

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25. Genetics: Published Articles Ahead of Print, published on September 2, 2011 as 0.1534/genetics.111.130773 Copyright 2011
http://www.genetics.org/content/189/3/951.long

Pervasive Recombination and Sympatric Genome Diversification Driven by Frequency-Dependent Selection in Borrelia burgdorferi, the Lyme disease Bacterium

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ABSTRACT: How genomic diversity within bacterial populations originates and is maintained in thepresence of frequent recombination is a central problem in understanding bacterial evolution. Natural populations of Borrelia burgdorferi, the bacterial agent of Lyme disease, consist of diverse genomic groups co-infecting single individual vertebrate hosts and tick vectors. To understand mechanisms of sympatric genome differentiation in B. burgdorferi, we sequenced and compared 23 genomes representing major genomic groups in North America and Europe. Linkage analysis of over 13,500 single nucleotide polymorphisms revealed pervasive horizontal DNA exchanges. Although three times more frequent than point mutation, recombination is localized and weakly affects genome-wide linkage disequilibrium. We show by computer simulations that, while enhancing population fitness, recombination constrains neutral and adaptive divergence among sympatric genomes through periodic selective sweeps. In contrast, simulations of frequency-dependent selection with recombination produced the observed pattern of a large number of sympatric genomic groups associated with major sequence variations at the selected locus. We conclude that negative frequency-dependent selection targeting a small number of surface-antigen loci (ospC in particular) sufficiently explains the maintenance of sympatric genome diversity in B. burgdorferi without adaptive divergence. In fact, pervasive recombination makes it unlikely for local B. burgdorferi genomic groups to achieve host specialization. B. burgdorferi genomic groups in northeastern United States are thus best viewed as constituting a single bacterial species, whose generalist nature is a key to its rapid spread and
human virulence.

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24. Journal of Medical Entomology 47(1):89-94. 2010
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2837073/

Extraction of Total Nucleic Acids from Ticks for the Detection of Bacterial & Viral Pathogens

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ABSTRACT: Ticks harbor numerous bacterial, protozoal, and viral pathogens that can cause serious infections in humans and domestic animals. Active surveillance of the

tick vector can provide insight into the frequency and distribution of important pathogens in the environment. Nucleic-acid based detection of tick-borne bacterial, protozoan, and viral pathogens requires the extraction of both DNA and RNA (total nucleic acids) from ticks. Traditional methods for nucleic acid extraction are limited to extraction of either DNA or the RNA from a sample. Here we present a simple bead-beating based protocol for extraction of DNA and RNA from a single tick and show detection of Borrelia burgdorferi and Powassan virus from individual, infected Ixodes scapularis ticks. We determined expected yields for total nucleic acids by this protocol for a variety of adult tick species. The method is applicable to a variety of arthropod vectors, including fleas and mosquitoes, and was partially automated on a liquid handling robot.

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23. PLoS ONE 5(5) 2010
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0010650

Genotypic variation and Mixtures of Lyme Borrelia in Ixodes Ticks from North America and Europe

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ABSTRACT: Lyme disease, caused by various species of Borrelia, is transmitted by Ixodes ticks in North America and Europe. Studies have shown the genotype of Borrelia burgdorferi sensu stricto (s.s.) or the species of B. burgdorferi sensu lato (s.l.) affects the ability of the bacteria to cause local or disseminated infection in humans.
Methodology/Principal Findings: We used a multilocus PCR electrospray mass spectrometry assay to determine the species and genotype Borrelia from ticks collected in New York, Connecticut, Indiana, Southern Germany, and California and characterized isolates from parts of the United States and Europe. These analyses identified 53 distinct genotypes of B. burgdorferi sensu stricto with higher resolution than ospC typing. Genotypes of other members of the B. burgdorferi sensu lato complex were also identified and genotyped including B. afzelii, B. garinii, B. lusitaniae, B. spielmanii, and B. valaisiana. While each site in North America had genotypes unique to that location, we found genotypes shared between individual regions and two genotypes found across the United States. Significant B. burgdorferi s.s. genotypic diversity was observed between North America and Europe: only 6.6% of US genotypes (3 of 45) were found in Europe and 27% of the European genotypes (3 of 11) were observed in the US. Interestingly, 39% of adult Ixodes scapularis ticks from North America were infected with more than one genotype of B. burgdorferi s.s. and 22.2% of Ixodes ricinus ticks from Germany were infected with more than one genotype of B. burgdorferi s.l.
Conclusions/Significance: The presence of multiple Borrelia genotypes in ticks increases the probability that a person will be infected with more than one genotype of B. burgdorferi, potentially increasing the risks of disseminated Lyme disease. Our study indicates that the genotypic diversity of Borrelia in ticks in both North America and Europe is higher then previously reported and can have potential clinical consequences.

22. Neurobiology of Disease 2010
http://www.sciencedirect.com/science/article/pii/S0969996109003386
Inflammation and central nervous system Lyme disease.

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ABSTRACT: Lyme disease, caused by the bacterium *Borrelia burgdorferi*, can cause multi-systemic signs and symptoms, including peripheral and central nervous system disease. This review examines the evidence for and mechanisms of inflammation in neurologic Lyme disease, with a specific focus on the central nervous system, drawing upon human studies and controlled research with experimentally infected rhesus monkeys. Directions for future human research are suggested that may help to clarify the role of inflammation as a mediator of the chronic persistent symptoms experienced by some patients despite antibiotic treatment for neurologic Lyme disease.

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21. Arch Gen Psychiatry. 2009;66(5):554-563. http://archpsyc.jamanetwork.com/article.aspx?articleid=483068
Regional Cerebral Blood Flow and Metabolic Rate in Persistent Lyme Encephalopathy
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ABSTRACT: Main Outcome Measures: Patients with persistent Lyme encephalopathy were compared with age-, sex-, and education-matched controls. Fully quantified assessments of rCBF and rCMR for glucose were obtained while subjects were medication-free using positron emission tomography. The CBF was assessed in 2 resting room air conditions (without snorkel and with snorkel) and 1 challenge condition (room air enhanced with carbon dioxide, ie, hypercapnia).
Results: Statistical parametric mapping analyses revealed regional abnormalities in all rCBF and rCMR measurements that were consistent in location across imaging methods and primarily reflected hypoactivity. Deficits were noted in bilateral gray and white matter regions, primarily in the temporal, parietal, and limbic areas. Although diminished global hypercapnic CBF reactivity ($P < .02$) was suggestive of a component of vascular compromise, the close coupling between CBF and CMR suggests that the regional abnormalities are primarily metabolically driven. Patients did not differ from controls on global resting CBF and CMR measurements.
Conclusions: Patients with persistent Lyme encephalopathy have objectively quantifiable topographic abnormalities in functional brain activity. These CBF and CMR reductions were observed in all measurement conditions. Future research should address whether this pattern is also seen in acute neurologic Lyme disease.

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20. Gene 2009 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2743244/

Fast, adaptive evolution at a bacterial host-resistance locus: The PFam54 gene array in Borrelia burgdorferi”

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ABSTRACT: Microbial pathogens have evolved sophisticated mechanisms for evasion of host innate and adaptive immunities. PFam54 is the largest paralogous gene family in the genomes of Borrelia burgdorferi, the Lyme disease bacterium. One member of PFam54, the complement-regulator acquiring surface proteins 1 (BbCrasp-1), is able to abort the alternative pathway of complement activation via binding human complement-regulator factor H (FH). The gene coding for BbCRASP-1 exists in a tandem array of PFam54 genes in the B. burgdorferi genome, a result apparently of repeated gene duplications. To help elucidate the functions of the large number of PFam54 genes, we performed phylogenomic and structural analyses of the PFam54 gene array from ten B. burgdorferi genomes. Analyses based on gene tree, genome synteny, and structural models revealed rapid adaptive evolution of this array through gene duplication, gene loss, and functional diversification. Individual PFam54 genes, however, do not show high intra-population sequence polymorphisms as genes providing evasion from adaptive immunity generally do. PFam54 members able to bind human FH are not monophyletic, suggesting that human FH affinity, however strong, is an incidental rather than main function of these PFam54 proteins. The large number of PFam54 genes existing in any single B. burgdorferi genome may target different innate-immunity proteins of a single host species or the same immune protein of a variety of host species. Genetic variability of the PFam54 gene array suggests that universally present PFam54 lineages such as BBA64, BBA65, BBA66, and BBA73 may be better candidates for the development of broad-spectrum vaccines or drugs than strain-restricted lineages such as BbCRASP-1.

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19. Neurology May 2008 http://www.neurology.org/content/70/13/992.long

A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy

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ABSTRACT: **Background**: Optimal treatment remains uncertain for patients with cognitive impairment that persists or returns after standard IV antibiotic therapy for Lyme disease.
Methods: Patients had well-documented Lyme disease, with at least 3 weeks of prior IV antibiotics, current positive IgG Western blot, and objective memory impairment. Healthy individuals served as controls for practice effects. Patients were randomly assigned to 10 weeks of double-masked treatment with IV ceftriaxone or IV placebo and then no antibiotic therapy. The primary outcome was neurocognitive performance at week 12—specifically, memory. Durability of benefit was evaluated at week 24. Group differences were estimated according to longitudinal mixed-effects models.
Results: After screening 3368 patients and 305 volunteers, 37 patients and 20 healthy individuals enrolled. Enrolled patients had mild to moderate cognitive

impairment and marked levels of fatigue, pain, and impaired physical functioning. Across six cognitive domains, a significant treatment-by-time interaction favored the antibiotic-treated group at week 12. The improvement was generalized (not specific to domain) and moderate in magnitude, but it was not sustained to week 24. On secondary outcome, patients with more severe fatigue, pain, and impaired physical functioning who received antibiotics were improved at week 12, and this was sustained to week 24 for pain and physical functioning. Adverse events from either the study medication or the PICC line were noted among 6 of 23 (26.1%) patients given IV ceftriaxone and among 1 of 14 (7.1%) patients given IV placebo; these resolved without permanent injury.
Conclusion: IV ceftriaxone therapy results in short-term cognitive improvement for patients with posttreatment Lyme encephalopathy, but relapse in cognition occurs after the antibiotic is discontinued. Treatment strategies that result in sustained cognitive improvement are needed.

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18. Emerging Infectious Diseases Volume 14, Number 7—July 2008
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2600328/
Wide Distribution of a High-Virulence Borrelia burgdorferi Clone in Europe & North America.
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ABSTRACT: The A and B clones of Borrelia burgdorferi sensu stricto, distinguished by outer surface protein C (ospC) gene sequences, are commonly associated with disseminated Lyme disease. To resolve phylogenetic relationships among isolates, we sequenced 68 isolates from Europe and North America at 1 chromosomal locus (16S–23S ribosomal RNA spacer) and 3 plasmid loci (ospC,dbpA, and BBD14). The ospC-A clone appeared to be highly prevalent on both continents, and isolates of this clone were uniform in DNA sequences, which suggests a recent trans-oceanic migration. The genetic homogeneity of ospC-A isolates was confirmed by sequences at 6 additional chromosomal housekeeping loci (gap, alr, glpA, xylB, ackA, and tgt). In contrast, the ospC-B group consists of genotypes distinct to each continent, indicating geographic isolation. We conclude that the ospC-A clone has dispersed rapidly and widely in the recent past. The spread of the ospC-A clone may have contributed, and likely continues to contribute, to the rise of Lyme disease incidence.

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17. Minerva Medica October 2008;99(5):489-96.
http://www.ncbi.nlm.nih.gov/pubmed/18971914
Severity of Lyme disease with persistent symptoms. Insights from a double-blind placebo-controlled clinical trial
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ABSTRACT: Lyme disease is a global health concern and is the world's leading tick borne infection caused by the spirochete, Borrelia burgdorferi, that has been

associated with numerous neurologic, rheumatologic and psychiatric manifestations. The symptoms of Lyme disease have been characterized as either severe or ”related to the aches and pains of daily living.” A randomized double-blind, placebo-controlled clinical trial (RCT) was conducted in a primary internal medicine practice in Westchester County, New York, USA. A total of 84 adults with Lyme disease with persistent symptoms (LDPS) were studied; 52 received amoxicillin and 34 received placebo. The subjects received either placebo or amoxicillin 3 g per day orally for 3 months. The SF-36 was used as the outcome measure of the patient’s perceived Quality of Life (QOL). For subjects enrolling in this RCT, the average SF-36 physical component summary (PCS) of QOL (40+/-9, range 29-44) and mental component summary (MCS) of QOL (39+/-14, range 23-46) were worse than the general USA population and worse than individuals with diabetes, heart disease, depression, osteoarthritis or rheumatoid arthritis. The improvements in the SF-36 measure of QOL for subjects randomized to amoxicillin vs. placebo was significant (46% vs 18%, P=0.007). It is important for clinicians to be aware that LDPS can be severe. A significant gain in the QOL for subjects randomized to amoxicillin in this RCT without serious adverse events is consistent with the goal of improving patient’s QOL and consequently worthy of further study.

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16. Microbial Pathogenesis Nov-Dec 2008
http://www.sciencedirect.com/science/article/pii/S0882401008001253
Profiling the humoral immune response to Borrelia burgdorferi infection with protein microarrays
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ABSTRACT: To determine the cell envelope proteins of Borrelia burgdorferi recognized by immune sera of patients with late Lyme disease, we developed a Borrelia microarray containing proteins encoded by 90 cell envelope genes and their homologs described in the annotated genomic sequence of B. burgdorferi, strain B31. The protein microarray was used to profile the humoral immune response using sera from 13 patients with late Lyme disease and four normal controls. Although there was considerable heterogeneity in the individual sera responses, 25 of the cell envelope proteins were recognized by seven or more samples. Sera from non-infected individuals lacked reactivity against any of the proteins on the array. Among the most antigenic envelope proteins, BLAST search revealed little sequence homology to known microbial proteins from other species. The proteins that were highly seropositive included several members of the Erp gene families, BBA24 (decorin binding protein A (DbpA)) and members of the Borrelia gene family Pfam113 that code for the Mlp lipoprotein gene family. Several novel, uncharacterized B. burgdorferi antigens identified in this study were BBA14, BBG23, BB0108, BB0442 and BBQ03. The accurate diagnosis of Lyme disease depends on correlating objective clinical abnormalities with serological evidence of exposure to B. burgdorferi. A protein array of the envelope proteins of Borrelia burgdorferi may be very useful in specifically identifying patients with Lyme disease. This approach could contribute to a more rapid discovery of antigens not expressed in vitro that may be useful for the development of vaccine and diagnostics.

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15. Infection and Immunity, January 2006
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1346608/
Identification of Borrelia burgdorferi outer surface proteins

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ABSTRACT: Several Borrelia burgdorferi outer surface proteins have been identified over the past decade that are up-regulated by temperature- and/or mammalian host-specific signals as this spirochete is transmitted from ticks to mammals. Given the potential role(s) that these differentially up-regulated proteins may play in B. burgdorferi transmission and Lyme disease pathogenesis, much attention has recently been placed on identifying additional borrelial outer surface proteins. To identify uncharacterized B. burgdorferi outer surface proteins, we previously performed a comprehensive gene expression profiling analysis of temperature-shifted and mammalian host-adapted B. burgdorferi. The combined microarray analyses revealed that many genes encoding known and putative outer surface proteins are down-regulated in mammalian host-adapted B. burgdorferi. At the same time, however, several different genes encoding putative outer surface proteins were found to be up-regulated during the transmission and infection process. Among the putative outer surface proteins identified, biochemical and surface localization analyses confirmed that seven (Bb0405, Bb0689, BbA36, BbA64, BbA66, BbA69, and BbI42) are localized to the surface of B. burgdorferi. Furthermore, enzyme-linked immunosorbent assay analysis using serum from tick-infested baboons indicated that all seven outer surface proteins identified are immunogenic and that antibodies are generated against all seven during a natural infection. Specific antibodies generated against all seven of these surface proteins were found to be bactericidal against B. burgdorferi, indicating that these newly identified outer surface proteins are prime candidates for analysis as second-generation Lyme disease vaccinogens.

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14. J Int Neuropsychol Soc. 2006 Jan;12(1):119-29
http://www.ncbi.nlm.nih.gov/pubmed/16433951

WAIS-III and WMS-III performance in chronic Lyme disease

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ABSTRACT: There is controversy regarding the nature and degree of intellectual and memory deficits in chronic Lyme disease. In this study, 81 participants with rigorously diagnosed chronic Lyme disease were administered the newest revisions of the Wechsler Adult Intelligence Scale (WAIS-III) and Wechsler Memory Scale (WMS-III), and compared to 39 nonpatients. On the WAIS-III, Lyme disease participants had poorer Full Scale and Performance IQ's. At the subtest level, differences were restricted to Information and the Processing Speed subtests. On the WMS-III, Lyme disease participants performed more poorly on Auditory Immediate, Immediate, Auditory Delayed, Auditory Recognition Delayed, and General Memory indices. Among WMS-III subtests, however, differences were restricted to Logical Memory (immediate and delayed) and Family Pictures (delayed only), a Visual Memory subtest. Discriminant analyses suggest deficits in chronic Lyme are best characterized as a combination of memory difficulty and diminished processing speed. Deficits were modest, between one-third and two-thirds of a standard deviation, consistent with earlier studies. Depression severity had a weak relationship to processing speed, but little other association to test performance. Deficits in chronic Lyme disease are consistent with a subtle neuropathological process affecting multiple performance tasks, although further work is needed to definitively rule out nonspecific illness effects. (JINS, 2006, 12, 119-129.).

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13. Journal of Clinical Microbiology, February 2005 http://jcm.asm.org/content/43/2/850.long

Evidence of Borrelia Autoimmunity-Induced Component of Lyme Carditis and Arthritis.

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ABSTRACT: We investigated the possibility that manifestations of Lyme disease in certain hosts, such as arthritis and carditis, may be autoimmunity mediated due to molecular mimicry between the bacterium Borrelia burgdorferi and self-components. We first compared amino acid sequences of Streptococcus pyogenes M protein, a known inducer of antibodies that are cross-reactive with myosin, and B. burgdorferi and found significant homologies with OspA protein. We found that S. pyogenes M5-specific antibodies and sera from B. burgdorferi-infected mice reacted with both myosin and B. burgdorferi proteins by Western blots and enzyme-linked immunosorbent assay. To investigate the relationship between self-reactivity and the response to B. burgdorferi, NZB mice, models of autoimmunity, were infected. NZB mice infected with B. burgdorferi developed higher degrees of joint swelling and higher anti-B. burgdorferi immunoglobulin M cross-reactive responses than other strains with identical major histocompatibility complex (DBA/2 and BALB/c). These studies reveal immunological cross-reactivity and suggest that B. burgdorferi may share common epitopes which mimic self-proteins. These implications could be important for certain autoimmunity-susceptible individuals or animals that become infected with B. burgdorferi.

12. Expert Review Anti-Infective Therapy 2004
http://www.ilads.org/lyme/ILADS_Guidelines.pdf
Evidence-based guidelines for the management of Lyme disease
International Lyme & Associated Diseases Society Lyme Disease Treatment Guidelines
ILADS Working Group: Dan Cameron, MD, MPH-1 [Internal Medicine and Epidemiology, Mt. Kisco, New York]; Andrea Gaito, MD [Rheumatology, Basking Ridge, New Jersey]; Nick Harris, PhD [Immunology, Palo Alto, California]; Gregory Bach, DO [Family and Integrative Medicine, Colmar, Pennsylvania]; Sandra Bellovin, MD [Family Practice, Portsmouth, Virginia]; Kenneth Bock, MD [Family Practice, Rhinebeck, New York]; Steven Bock, MD [Family Practice, Rhinebeck, New York]; Joseph Burrascano, MD [Internal Medicine, East Hampton, New York]; Constance Dickey, RN [Registered Nurse, Hampden, Maine]; Richard Horowitz [Internal Medicine, Hyde Park, New York]; Steven Phillips, MD [Internal Medicine, Ridgefield, Connecticut]; Lawrence Meer-Scherrer MD [Internal Medicine, Flamatt, Switzerland]; Bernard Raxlen, MD [Psychiatry, Greenwich, Connecticut]; Virginia Sher, MD [Psychiatry, Holland, Pennsylvania]; Harold Smith, MD [Emergency Medicine, Danville, Pennsylvania]; Pat Smith [President, Lyme Disease Association]*; Ray Stricker MD [Hematology and Immunotherapy, San Francisco, California]

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***Pat Smith, LDA, was co-author on article**

ABSTRACT: This report, completed in November 2003, is intended to serve as a resource for physicians, public health officials and organizations involved in the evaluation and treatment of Lyme disease.

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11. Proceedings of the National Academy of Science, Sept. 2004
http://www.pnas.org/content/101/39/14150.long
Genetic exchange and plasmid transfers in Borrelia burgdorferi sensu stricto revealed by three-way genome comparisons and multilocus sequence typing.
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ABSTRACT: Comparative genomics of closely related bacterial isolates is a powerful method for uncovering virulence and other important genome elements. We determined draft sequences (8-fold coverage) of the genomes of strains JD1 and N40 of Borrelia burgdorferi sensu stricto, the causative agent of Lyme disease, and we compared the predicted genes from the two genomes with those from the previously sequenced B31 genome. The three genomes are closely related and are evolutionarily approximately equidistant (0.5% pairwise nucleotide differences on the main chromosome). We used a Poisson model of nucleotide substitution to screen for genes with elevated levels

of nucleotide polymorphisms. The three-way genome comparison allowed distinction between polymorphisms introduced by mutations and those introduced by recombination using the method of phylogenetic partitioning. Tests for recombination suggested that patches of high-density nucleotide polymorphisms on the chromosome and plasmids arise by DNA exchange. The role of recombination as the main mechanism driving B. burgdorferi diversification was confirmed by multilocus sequence typing of 18 clinical isolates at 18 polymorphic loci. A strong linkage between the multilocus sequence genotypes and the major alleles of outer-surface protein C (ospC) suggested that balancing selection at ospC is a dominant force maintaining B. burgdorferi diversity in local populations. We conclude that B. burgdorferi undergoes genome-wide genetic exchange, including plasmid transfers, and previous reports of its clonality are artifacts from the use of geographically and ecological isolated samples. Frequent recombination implies a potential for rapid adaptive evolution and a possible polygenic basis of B. burgdorferi pathogenicity.

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10. The Journal of Neuropsychiatry & Clinical Neurosciences. 2003
http://neuro.psychiatryonline.org/article.aspx?articleid=101812
Regional Cerebral Blood Flow and Cognitive Deficits in Chronic Lyme Disease.
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ABSTRACT: This study examined brain functioning in patients with Lyme encephalopathy. Eleven patients underwent neuropsychological tests and Xenon133-regional cerebral blood flow (rCBF) studies, using an external detector system. Each rCBF scan was age- and sex-matched to two archival, normal controls. While few differences were noted on gray-matter flow indices (ISI, fg), Lyme patients demonstrated significant flow reductions in white matter index (k2) (p=.004), particularly in the posterior temporal and parietal lobes bilaterally (p=.003). Flow reductions in white matter areas were significantly associated with deficits in memory (r=.66, p=.027) and visuospatial organization (r=.62, p=.041). Results suggest that Lyme encephalopathy may be a disease primarily affecting the cerebral white matter.

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9. Journal of Spirochetal and Tick-borne Diseases. Spring/Summer 2002
https://www.ilads.org/wp-content/uploads/2018/10/JSTBD-VOL9-SPRING-SUMMER-02-1.pdf
Borrelia burgdorferi Persists in the Gastrointestinal Tract of Children and Adolescents with Lyme Disease.
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ABSTRACT: This study documents the persistence of B burgdorferi DNA in the gastrointestinal tract of pediatric patients who have already been treated with antibiotics for Lyme disease. Ten consecutive patients between the ages of 9 and 13 years presented with an erythema migrans (EM) rash, a positive western blot for Lyme disease, chronic abdominal pain, heartburn, or bright red blood in the stool.

Endoscopy assessed the gastrointestinal (GI) mucosa for inflammation and biopsies were examined for B burgdorferi using a Dieterle stain and with polymerase chain reaction (PCR) to the outer surface protein A (Osp A) of B burgdorferi. As controls, 10 consecutive patients with chronic abdominal pain were also tested by GI biopsies and with PCR. B burgdorferi persisted in the GI tract in all 10 patients with Lyme disease as shown by Dieterle stain of biopsies and with PCR. None of the control subjects' biopsies were PCR positive for B. burgdorferi. Chronic gastritis, chronic duodenitis, and chronic colitis were found in Lyme disease patients and associated with the detection of B burgdorferi DNA in the GI tract despite prior antibiotic treatments. We have concluded that the DNA of B burgdorferi persisted in patients with Lyme disease even after antibiotic treatment.

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8. Journal of Neuropsychiatry and Clinical Neurosciences. 2001 13:500-5-7
http://neuro.psychiatryonline.org/doi/pdf/10.1176/jnp.13.4.500
A Controlled Study of Cognitive Deficits in Children with Chronic Lyme Disease.
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ABSTRACT: Although neurologic Lyme disease is known to cause cognitive dysfunction in adults, little is known about its long-term sequelae in children. Twenty children with a history of new-onset cognitive complaints after Lyme disease were compared with 20 matched healthy control subjects. Each child was assessed with measures of cognition and psychopathology. Children with Lyme disease had significantly more cognitive and psychiatric disturbances. Cognitive deficits were still found after controlling for anxiety, depression, and fatigue. Lyme disease in children may be accompanied by long-term neuropsychiatric disturbances, resulting in psychosocial and academic impairments. Areas for further study are discussed.

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7. Medscape Infectious Diseases 2(1) April 2000
Preliminary in Vitro and in Vivo Findings of Hyperbaric Oxygen Treatment in Experimental Bb Infection.
http://www.medscape.com/viewarticle/432883#4
Charles Pavia, PhD

NY Medical College School of Medicine. NYCOM Microbiology and Immunodiagnostic Laboratory of NYIT.

ABSTRACT: In these studies, we evaluated repeated HBOT for its ability to kill Bb in vitro, and in vivo, in a murine model of Lyme disease. Several North American tick-derived and recently obtained patient isolates were studied separately in our assay systems. To test for in vitro susceptibility, one-half to one million Bb were cultured in a small volume (0.1 – 0.2 ml) of BSK media using small snap-cap test tubes. With the caps removed, these cultures were then exposed, for one hour (twice daily for 2 consecutive days), to pure, filtered oxygen pressurized to 2-3 times normal atmospheric conditions. This was achieved using a specially constructed, miniaturized cylindrical chamber (length = 12 inches; diameter = 8 inches), equipped to accept any pressurized gas mixture through its portal opening. After the final

HBOT, all cultures received an additional 0.5 ml of BSK media (making the final volume now 0.6 – 0.7 ml), and their caps were snapped shut. Matching control cultures received no HBOT. All cultures were incubated at 33° C for 2-3 days and were examined microscopically for live Bb. Our results showed that 14 of 17 strains of Bb had their growth inhibited by 33-94%, while there was little or no inhibition of 3 Bb strains. For the in vivo studies, separate groups of C3H or CO1 mice were infected intradermally with 100,000 Bb. Two to 4 weeks later, one group of infected mice received two, 1.0-1.5 hour HBO exposures, for two consecutive or alternating days. The treated mice were sacrificed one day after the last treatment, and extract cultures of their urinary bladders were prepared in BSK media. It was found that no Bb grew out of 80% of these extract cultures, whereas live Bb organisms were recoverable from 90% of extract cultures prepared from matched, infected control mice not treated with HBO. These data suggest that HBOT may be considered as a clinically useful form of adjunct therapy in the treatment of Lyme disease.

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6. Journal of Spirochetal and Tick-borne Diseases Fall/Winter 1999
Repeated Antibiotic Treatment in Chronic Lyme Disease.
https://www.ilads.org/wp-content/uploads/2018/10/JSTBD-VOL6-FALL-WINTER-99-3.pdf
Brian A. Fallon, MD, Felice Tager, PhD, John Keilp, PhD, Nicola Weiss, PhD, Michael R. Liebowitz, MD,
New York State Psychiatric Institute and Columbia University Department of Psychiatry, New York, New York; Lesley Fein, MD, Private Practice, West Caldwell, New Jersey; Kenneth Liegner, MD, Private Practice, West Caldwell, New Jersey.

ABSTRACT: Patients with chronic Lyme disease who experience persistent cognitive deficits despite having received the recommended antibiotic treatment pose a therapeutic dilemma. This pilot study was designed to assess whether additional antibiotic therapy is beneficial.

Enrolled in the study were 23 patients with complaints of persistent memory problems who had previously received 4-16 weeks of intravenous antibiotic therapy. Patients were tested at baseline and 4 months later. During this interval, the private physician determined treatment (intravenous, intramuscular, oral, or none). Assessments included standardized measures of cognition, depression, anxiety, and functional status.

Between times 1 and 2, 5 patients were given no antibiotics and 18 were given additional antibiotics: 7 intravenously, 4 intramuscularly, and 7 orally. At time 1, there were no statistically significant group differences in cognition, depression, or anxiety between those who later received antibiotics and those who didn’t. At time 1, the 23 patients were also functionally disabled. At time 2, compared with patients who received no antibiotics, patients given antibiotics scored better on overall and individual measures of cognition. Patients given intravenous antibiotics showed the greatest functional improvement (pain, physical functioning, energy) and the most cognitive improvement, even when controlling for baseline differences in cognition between the treatment groups. Patients who did not have a reactive Western blot currently or historically were just as likely to improve cognitively as patients with reactive Western blot results.

This uncontrolled study suggests that repeated antibiotic treatment can be beneficial, even among patients who have been previously treated and even among patients who are currently Western blot negative, with the intravenous route of treatment being the most effective. A double-blind placebo-controlled study is

needed to confirm these results.

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5. JAMA, Nov. 24, 1999, Vol.282, No.20
http://jama.jamanetwork.com/article.aspx?articleid=192130
Borrelia Burgdorferi–Specific Immune Complexes in Acute Lyme Disease.
Steven E. Schutzer, MD; P. K. Coyle, MD; Patrick Reid, MS; Bart Holland, PhD

Author Affiliations: Department of Medicine, Division of Allergy and Immunology (Dr Schutzer and Mr Reid) and Department of Preventive Medicine (Dr Holland), University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark (Dr Schutzer and Mr Reid); and the Department of Neurology, State University of New York, Stony Brook (Dr Coyle).

ABSTRACT: Context Diagnosis of infection with Borrelia burgdorferi, the cause of Lyme disease (LD), has been impeded by the lack of effective assays to detect active infection.
Objective: To determine whether B burgdorferi specific immune complexes are detectable during active infection in LD.
Design, Setting, and Patients: Cross-sectional analysis of serum samples from 168 patients fulfilling Centers for Disease Control and Prevention surveillance criteria for LD and 145 healthy and other disease controls conducted over 8 years. Tests were performed blinded.
Main Outcome Measure Detection of B burgdorferi immune complexes by enzyme-linked immunosorbent assay and Western blot.
Results: The B burgdorferi immune complexes were found in 25 of 26 patients with early seronegative erythema migrans (EM) LD; 105 of 107 patients with seropositive EM LD; 6 of 10 patients who were seronegative with culture-positive EM; 0 of 12 patients who were treated and recovered from LD; and 13 of 13 patients with neurologic LD without EM. Among 147 controls, B burgdorferi immune complex was found in 0 of 50 healthy individuals; 0 of 40 patients with persistent fatigue; 0 of 7 individuals with frequent tick exposure; and 2 of 50 patients with other diseases.
Conclusion: These data suggest that B burgdorferi immune complex formation is a common process in active LD. Analysis of the B burgdorferi immune complexes by a simple technique has the potential to support or exclude a diagnosis of early as well as active LD infection
Funding/Support: This work was supported in part by grants A41518, NS34092, AI31561, and AR40470 from the National Institutes of Health and grant U50/CCU206582 from the Centers for Disease Control and Prevention, and by the Lyme Disease Association of New Jersey.

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4. Neurology, Oct 12, 1999 http://www.neurology.org/content/53/6/1340.long
Absence of Borrelia Burgdorferi-specific immune complexes in chronic fatigue syndrome.
Schutzer SE-1, Natelson BH.

1 Department of Medicine, University of Medicine and Dentistry, New Jersey Medical School, Newark 07103, USA. schutzer@umdnj.edu

ABSTRACT: Chronic fatigue syndrome (CFS) and Lyme disease often share clinical features, especially fatigue, contributing to concern that Borrelia burgdorferi (Bb), the cause of Lyme disease, may underlie CFS symptoms. We examined 39 CFS

patients and 40 healthy controls with a Bb immune complex test. Patients and controls were nonreactive. Centers for Disease Control and Prevention-defined CFS patients lacking antecedent signs of Lyme disease—erythema migrans, Bell's palsy, or large joint arthritis—are not likely to have laboratory evidence of Bb infection.

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3. The Psychiatric Clinics of North America Vol. 21,#3, 9/98

http://www.psych.theclinics.com/article/S0193-953X%2805%2970032-0/fulltext

The Underdiagnosis of Neuropsychiatric Lyme Disease in Children and Adults.

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1-Department of Psychiatry, Columbia University Medical Center and the Lyme Disease Research Program, New York, New York (BAF), 2-private practice, Armonk, New York (JMK), 3-Department of Medicine, Seton Hall University, and private practice, Basking Ridge, New Jersey (AG), 4-Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (JAN)

ABSTRACT: Lyme disease is a tick-borne illness caused by the spirochete Borrelia burgdorferi. Reported throughout the United States, the greatest incidence of Lyme disease occurs in certain areas, such as the Northeast, the upper Midwest, and the Pacific Coastal states. It has been dubbed "The New Great Imitator" because, like another spirochetal illness neurosyphilis-the original Great Imitator, Lyme disease has a vast array of multisystem manifestations, including neuropsychiatric ones.18 Failure to recognize Lyme disease early in its course can result in the development of a chronic illness that is only temporarily or partially responsive to antibiotic therapy. The goal of this article is to present the typical and atypical manifestations of Lyme disease in children and adults in order to help the clinician more rapidly unmask the correct diagnosis behind the puzzling presentations of some patients.

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2. Infection. 1998 Nov-Dec:26(6):364-7

http://www.ncbi.nlm.nih.gov/pubmed/9861561?dopt=Abstract

A proposal for the reliable culture of Borrelia burgdorferi from patients with chronic Lyme disease, even from those previously aggressively treated.

Phillips SE-1, Mattman LH, Hulinska D, Moayad H

1Greenwich Hospital, CT 06830, USA.

ABSTRACT: Since culture of Borrelia burgdorferi from patients with chronic Lyme disease has been an extraordinarily rare event, clarification of the nature of the illness and proving its etiology as infectious have been difficult. A method for reliably and reproducibly culturing B. burgdorferi from the blood of patients with chronic Lyme disease was therefore sought by making a controlled blood culture trial

studying 47 patients with chronic Lyme disease. All had relapsed after long-term oral and intravenous antibiotics. 23 patients with other chronic illness formed the control group. Positive cultures were confirmed by fluorescent antibody immuno-electron microscopy using monoclonal antibody directed against Osp A, and Osp A PCR. 43/47 patients (91%) cultured positive. 23/23 controls (100%) cultured negative. Although persistent infection has been, to date, strongly suggested in chronic Lyme disease by positive PCR and antigen capture, there are major problems with these tests. This new method for culturing B. burgdorferi from patients with chronic Lyme disease certainly defines the nature of the illness and establishes that it is of chronic infectious etiology. This discovery should help to reestablish the gold standard in laboratory diagnosis of Lyme disease.

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1. Infection 24 (1996) #5 http://www.ncbi.nlm.nih.gov/pubmed/8923044

Borrelia burgdorferi DNA in the Urine of Treated Patients with Chronic Lyme Disease

Symptom: A PCR Study of 97 Cases

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Author affiliation: Fox Chase Cancer Center, Philadelphia, PA 19111, USA

ABSTRACT: All patients had shown erythema chronica migrans following a deer tick bite. Most of the patients had been antibiotic-treated for extended periods of time. …Of the 97 patients, 72 (74.2%) were found with positive PCR and the rest with negative PCR. The 62 healthy volunteers were PCR negative. It is proposed that a sizeable group of patients diagnosed on clinical grounds as having chronic Lyme disease may still excrete Borrelia DNA, and may do so in spite of intensive antibiotic treatment.

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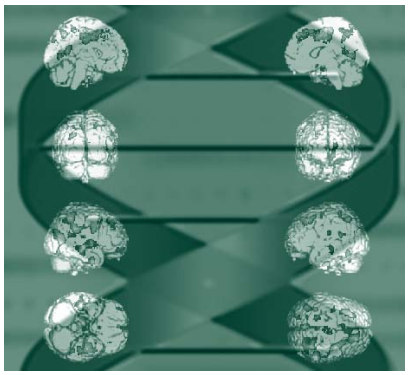
Lyme Disease Association, Inc. June 2015
PO Box 1438 Jackson, NJ 08527
www.LymeDiseaseAssociation.org
888-366-6611

Lyme Disease Association

(LDA) Grant Program

The LDA's grant program is divided into three categories: Research, Education, and LymeAid 4 Kids grants. Click here for the summary of stats on grants awarded through 2020.

Research



Since the LDA officially opened its doors in 1992, it has awarded 122 research grants from coast to coast. The Lyme Disease Association is one of the largest sources of private, nonprofit tick-borne diseases research funding in the United States. We strive to fund the most relevant research and cutting-edge research aimed at investigating the prevention and treatment of tick-borne diseases. We choose projects led by top scientists who are able to publish in peer review to move the field forward.

LDA in partnership with an affiliate endowed the first center in the world to study chronic Lyme disease, which opened at Columbia University in 2007. The Center brings together researchers from various disciplines and from around the US.

Since 1999, the LDA has sponsored 20 scientific/medical conferences, eighteen jointly with Columbia University Vagelos College of Physicians and Surgeons. All provided Continuing Medical Education (CME) credits for physicians. LDA has funded cutting-edge research projects with over 36 different researchers and institutions throughout the country, such as: Columbia University College of Physicians & Surgeons, NJ Medical School, Fox Chase Cancer Center, University of California, Davis, University of Pennsylvania, Bringham & Woman's Hospital, NY Medical College, Rockefeller University, Tulane Regional Primate Center, University of North Florida, NIH/NASA and UDSA.

The results of LDA's research projects have been published in 56 peer-reviewed scientific journals to date, such as: Journal of the American Medical Association (JAMA), The Proceedings of the National Academy of Science, The Psychiatric Clinics of North America, Infection, Psychiatric Clinics of North America, Neurology, JSTBD, Journal of Clinical Microbiology, Journal of International Neuropsychological Society and Infection and Immunology, Emerging, Infectious Diseases (CDC), Journal of Neuropsychiatry & Clinical Neurosciences, Journal of International, Neuropsychological Society, Infection & Immunity, Gene, Genetics, Journal of Bacteriology, Journal of Entomology, and PLOS 1.

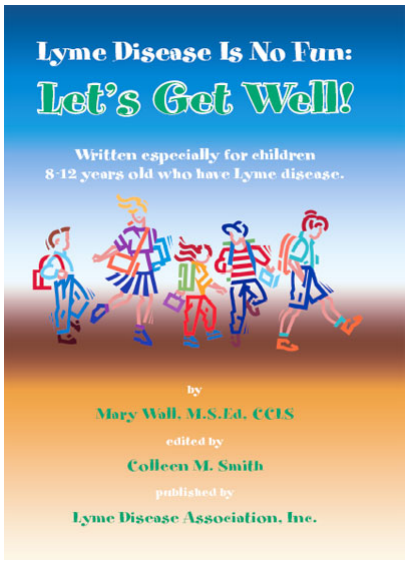
One project resulted in data used to apply for/receive $4.7 million NIH grant. Significant genome mapping initially funded by LDA, has shown that different strains of Borrelia have the ability to exchange genetic material among themselves, a trait greatly benefiting their survival and probably confounding the body's ability to eradicate the organism.

Other areas of work include: Testing, Treatment trials, Persistence of tick-borne diseases in GI tract, Mapping the genome of Borrelia strains, Brain imaging in the study of Lyme disease, PCR studies, Endocrine studies of Lyme, Underdiagnosis of neuropsychiatric Lyme disease in children and adults, Natural tick control, Identifying organisms in ticks nationwide, Immune complexes, Magnetic field effects on Borrelia, Infection rate of mammals, and Protein arrays.

Currently, there are more than a half-dozen projects that are ongoing. The researchers, projects, and science are ready to find a cure. Now we need the funding to make it a reality.

(Image of PET Scan overlay above courtesy of Brian Fallon, MD, Columbia University)

Education



To help increase awareness and education throughout the country, the LDA believes it is essential to work with and assist other Lyme organizations and individuals.

To date, LDA has awarded 155 educational grants. 95 educational scholarships to the LDA/Columbia continuing medical education conferences were awarded. Other grants have been to groups from across the country and some to universities. Many of the grants were used to support the following types of activities: publications (including *Compendium of Tick-Borne Disease: A Thousand Pearls*, "Lyme Times," "The Basics," TX Lyme Disease brochure), school curriculum project, Lyme disease websites, distribution of materials to school nurses, host various educational projects in schools, support medical conferences including several offering CME awards, sponsor physicians for CME medical conferences, sponsor Lyme disease symposia, provide educational in-service meetings for schools, companies, and general public.

Diagnosis/Treatment for children without insurance

About LymeAid 4 Kids (LA4K) – The Lyme Disease Association started LA4K fund in 2004 and has helped children all over the U.S. and in Canada. Developed with the help of author Amy Tan, the fund is for children who do not have/receive insurance coverage for Lyme disease treatment for children and have economic difficulties. Donations can be made

online to LDA help this LA4K fund as there are so many applicants, the fund does run out of money frequently. **Total Funds distributed since 2004 totals $400,400.**

Click here for LymeAid 4 Kids Grant Application

The LDA is an all-volunteer 501(c)(3) organization that has raised ~$6.4 million dollars for Lyme disease research, prevention, and education.

About the LDA

The Lyme Disease Association, Inc. (LDA) is designated by the IRS as a 501(c)(3) non-profit, a charity focusing on research, education, prevention and patient support.

History

The Lyme Disease Association began as Lyme Disease Association of Central Jersey in 1991 and then became Lyme Disease Association of New Jersey in 1993. Formed by patients and doctors who saw the need to organize, fund research and educate people, by 1997, it had influence far beyond NJ borders. In 2000, the Board changed the name to Lyme Disease Association, Inc. (LDA) with a broader mission expanding research funding (LDA-funded research has appeared in 56 scientific journal publications to date) and including expanded patient support (LA4K). At that time, LDA decided to remain an all volunteer organization without paid employees so that almost all of its incoming revenue would be dedicated to the mission. It remains volunteer-run with some professional consultants who provide specific expertise when needed.

Mission Statement

The Lyme Disease Association, Inc. (LDA) has been granted 501(c)(3) non-

profit status by the IRS. Its mission is promoting awareness of and controlling the spread of Lyme and other tick-borne diseases (TBD) and their complications through education and other means; raising and distributing funds for Lyme and tick-borne diseases (TBD) research, education and other related Lyme and TBD issues; assisting underprivileged patients in connection with Lyme and other TBD.

Accomplishments

On average, 97% of funds raised go directly to programs. LDA presents fully accredited annual scientific/medical conferences, funds research nationally, provides monies for children without insurance coverage for Lyme, provides free literature, has free information line, hosts free online doctor referral and heads an umbrella organization, LDAnet, of 45 associated organizations nationwide that work together on national issues. The LDA is a GuideStar Exchange Platinum participant, signifying GuideStar's highest level of transparency. LDA has also been designated as a federally approved national charity for workplace giving in the Combined Federal Campaign. (CFC) for 15 years. Additionally, LDA is an EPA partner in its PESP program to safely eradicate tick populations and reduce the risk of pesticides and is a part of an integrated pest management tick working group with government and public members. To that end, it helped in the planning of the EPA's prevention conference and spoke at and co-hosted a session of the conference with the Centers for Disease Control (CDC). The LDA President was also a co-author of the article produced from a network developed under EPA, Network to Reduce Lyme Disease in School Aged Children. The article "You Can Make A Difference to A Child by Reducing the Risk of Lyme Disease appeared in the May 2010 journal of the National Association of School Nurses.

In its search for a cure for chronic Lyme disease and for prevention, the LDA has funded dozens of research projects coast-to-coast at institutions including Columbia University College of Physicians & Surgeons (NY), New Jersey Medical School (NJ), University of Washington (WA), Northeast Wildlife DNA Laboratory (PA), University of California, Davis (CA), Georgia Southern University Research & Service Foundation (GA), Johns Hopkins University (MD), Kendall County Health Department (IL), University of New Haven (CT), and Stony Brook University (NY), New York Medical College (NY), Boston Medical (MA), Rockefeller University (NY), University of North Florida (FL), and Shanandoah School of Pharmacy (VA). Much of LDA-funded research has been featured in peer-reviewed journal publications (54 to date), e.g., Journal of the American Medical Association, Proceedings of the National Academy of Science,

Emerging Infectious Diseases, Psychiatric Clinics of North America, Infection, Journal of Neuropsychiatry & Clinical Neurosciences, Journal of Clinical Microbiology, Journal of International Neuropsychological Society, Neurology, Immunology, Open Neurology Journal, PLOS One, & Genetics. 122 research grants have been awarded since LDA's inception.

Genome work initially funded by LDA has shown that different strains of Borrelia have the ability to exchange genetic material among themselves, a trait greatly benefiting their survival and probably confounding the body's ability to eradicate the organism. LDA funding of genome mapping has led to 17 strains being mapped.

In 2007, Columbia University announced the opening of the Lyme & Tick-Borne Diseases Research Center in New York, the first in the world devoted to the study of chronic Lyme disease. LDA co-funded the Center. LDA has given a grant to create a tissue bank there to store samples for Lyme disease research, now ongoing. The LDA has funded cutting edge published work with University of New Haven into the presence of *Borrelia burgdorferi* biofilms, which may be one of the survival mechanisms of the Lyme organism even after long-term treatment and loaned the University specialized equipment for its work.

The LDA has presented 20 fully CME accredited (continuing medical education) scientific conferences for researchers, doctors, and health care providers, featuring international speakers on the topic of Lyme and other tick-borne diseases, most jointly sponsored by Columbia University Vagelos College of Physicians and Surgeons. The 14th LDA conference was held in Minnesota in 2013, the first CME conference in the Upper Midwest and the 15th and 16th were held in Providence, RI in 2014 and 2015. The 2016 conference was held in St. Paul, Minnesota, the 2017 conference was held in Philadelphia, Pennsylvania, and the 2018 conference was held in Providence, Rhode Island. The 20th LDA conference was held on Sept 21 & 22, 2019 in Philadelphia, Pennsylvania. The LDA website contains video clips of the various conferences. A few conferences have had certifications for other professionals such as social workers, psychologists, dentists, nurses.

Since children ages 5-14 are at the highest risk of acquiring Lyme disease, the LDA created LymeAid 4 Kids, a fund that helps children without insurance. Initiated in conjunction with internationally acclaimed author Amy Tan, a Lyme victim, the LDA fund has awarded $399,400 in grants. LDA has compiled a website section, Lyme in the Schools, containing tools which can be accessed for free by schools, parents, and

the general public. Resource articles, statistics, and an LDA educational PowerPoint, How A Tick Can Make You Sick, can be run for free in the classroom from the computer as can a prevention video for kids that the UMDNJ created in partnership with the LDA under an EPA grant. LDA's book for children with chronic Lyme, Lyme Disease Is No Fun, Let's Get Well! can be ordered on the site as can free pamphlet for parents and educators, The ABCs of Lyme Disease.

The LDA's extensive resource list also includes free materials (postage charge as of 2014) such as newly updated LymeR Primer, Tickmark, and Tick Card; National Case Map, Case Number graphs, Personal & Property Prevention Posters, Symptoms Lists and at cost materials including conference DVDs, and books. The site also houses an extensive collection of tick and rash pictures and tick-borne microbes. Finding doctors who are experienced in treating tick-borne diseases is difficult, thus LDA created an automatic doctor referral system to help people nation wide.

LDA has educated through public, school, corporate and government seminars. It has developed billboards including an electronic one on Times Square in 2012 featuring the spread of chronic Lyme. Annually, LDA awards education grants to many other Lyme groups, universities and other organizations to further their mission against tick-borne diseases. 155 education grants have been awarded to date. 95 educational conference scholarships to the LDA/Columbia continuing medical education conferences were awarded.

LDA reps have been asked to testify in many states, and been invited to be a part of press conferences with congressmen, governors and other officials. LDA had led the charge on the introduction and passage of many pieces legislation at the federal and state levels, including the 2014 Lyme bill that passed the House, and has been successful in meeting with officials at all levels of government. The LDA President testified before the US House of Representatives Foreign Affairs Global Health & Human Rights Subcommittee Lyme hearing in 2012 and before the US House of Representatives Energy & Commerce Health Subcommittee in 2013. LDA has been twice invited to meet with the Vector-Borne Division of the CDC in Ft. Collins, CO, to discuss the spread of tick-borne diseases and other issues. LDA led the team to negotiate the Lyme language which passed in the the 21st Century Cures Act in 2016 which creates a federal Tick-Borne Diseases Working Group which has a patient voice at the table. The LDA President was appointed a ~3 year term on the Congressionally Directed Medical Research Program panel to oversee disbursements of funds for Lyme disease research. Most recently, the LDA President was appointed as a committee

member to the Federal Health and Human Services (HHS) Tick-borne Disease Working Group which presented it’s first report to Congress in November of 2018.