Updates in the Diagnosis and Treatment of Resistant Lyme and Chronic Disease

Lyme & TBD Congressional Town Meeting

Congressman Chris Smith

Wall Township Municipal Bldg.

May 29th, 2019

Dr. Richard Horowitz,

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Board Certified Internal Medicine

Member, HHS Tick-Borne Disease Working Group 2017-2019

Co-chair, HHS Other Tick-Borne Diseases and Co-infections 2017-2019

Disclaimer/Conflicts of Interest

- **Conflicts of Interest:**
- St Martin's Press: royalties for two books: "Why Can't I Get Better?" and "How Can I Get Better?"
- Xymogen Board of Advisors, stock, honorariums
- Grants: Bay Area Lyme Foundation, MSIDS Research Foundation
- **Disclaimer:** **The views expressed in this presentation do not represent the views of the Tick Borne Disease Working Group, HHS or the United States**

International Journal of General Medicine

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ORIGINAL RESEARCH

Precision medicine: retrospective chart review and data analysis of 200 patients on dapsone combination therapy for chronic Lyme disease/ post-treatment Lyme disease syndrome: part 1

This article was published in the following Dove Medical Press journal:
International Journal of General Medicine

Richard I Horowitz[1,2]
Phyllis R Freeman[2]

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Purpose: We collected data from an online survey of 200 of our patients, which evaluated the efficacy of dapsone (diaminodiphenyl sulfone, ie, DDS) combined with other antibiotics and agents that disrupt biofilms for the treatment of chronic Lyme disease/post-treatment Lyme disease syndrome (PTLDS). We also collected aggregate data from direct retrospective chart review, including laboratory testing for Lyme, other infections, and associated tick-borne coinfections.

healthcare

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Precision Medicine: The Role of the MSIDS Model in Defining, Diagnosing and Treating Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome and Other Chronic Illness: Part 2

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Abstract: We present a precision medical perspective to assist in the definition, diagnosis and management of Post Treatment Lyme Disease Syndrome (PTLDS)/chronic Lyme disease. PTLDS represents a small subset of patients treated for an EM rash with persistent or recurrent symptoms and functional decline. The larger population with chronic Lyme disease is less understood and well defined. Multiple Systemic Infectious Disease Syndrome (MSIDS) is a multifactorial model for treating chronic disease(s) which identifies up to 16 overlapping sources of inflammation and their downstream effects. A patient symptom survey, a retrospective chart review of 200 patients was therefore performed on those patients with chronic Lyme disease/PTLDS to identify those variables on the MSIDS model with the greatest potential effect on regaining health. Results indicate that dapsone combination therapy decreased the severity of eight major Lyme symptoms, and multiple sources of inflammation (other infections, immune dysfunction, autoimmunity, food allergies/sensitivities, leaky gut, mineral deficiencies, environmental toxins with detoxification

Why Do We Get Sick?

- **Diagnostics**: tests lack adequate sensitivity for early and late infection with multiple species of bacteria. Leads to improper diagnoses (CFS/ME, FM, A.I. dx & Neuropsychiatric disease w/dementia)
- **Persistence**: Borrelia can persist despite seemingly "adequate" antibiotics. "Persisters" have also been reported with Babesia, & multiple IC bacteria: Bartonella, Mycoplasma, Tularemia & Brucella→ chronic disease
- **Health Care Politics**: denies problems w/ diagnostics & persistence→↑ health care costs + disability

- Lee SH, et al. DNA sequencing diagnosis of off-season spirochetemia with low bacterial density in Borrelia burgdorferi and Borrelia miyamotoi infections. Int J Mol Sci. 2014 Jun 25;15(7):11364-86

The MSIDS Model is Personalized/Precision Medicine

- **"Patient centered care" & "Personalized medicine"** focus on an individual patient's risks
- One size does not fit all (limitation to guidelines)
- Paradigm shift with diagnostics/treatments
- **The 16 point MSIDS model** can efficiently screen through multifactorial etiologies contributing to chronic illness, & focus on **personalizing treatment, improving access to care**

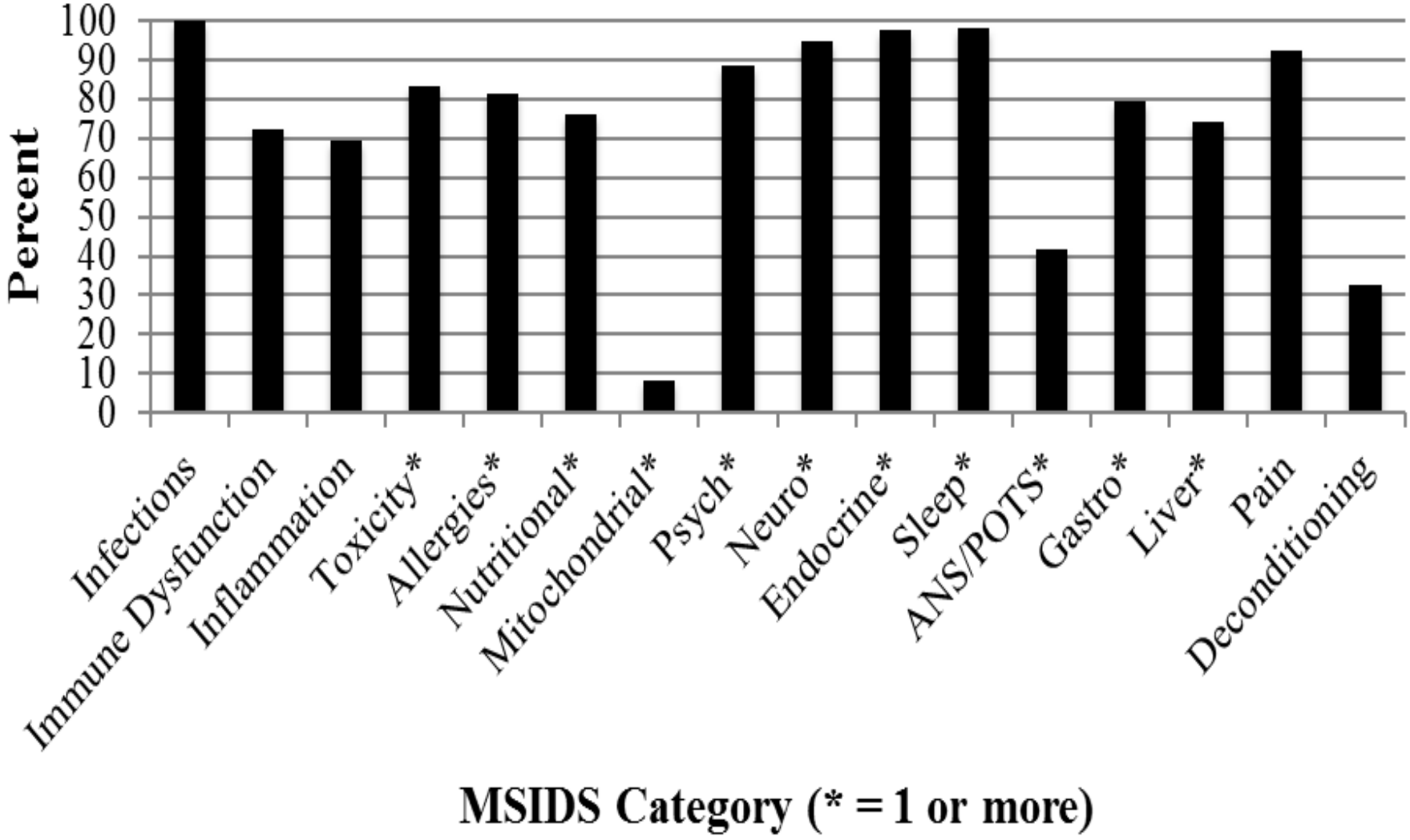
- Why Can't I Get Better? Solving the Mystery of Lyme and Chronic Disease. Dr Richard I. Horowitz. St Martin's Press, NYC. November 2013
- How Can I Get Better? An Action Plan for Treating Resistant Lyme & Chronic Disease. Dr Richard I. Horowitz. St Martin's Press, NYC. February 2017

Defining, Diagnosing & Improving The Treatment of Chronic Lyme Disease

- **Two year study: A patient symptom survey & retrospective chart review of 200 patients with "Chronic Lyme disease"/PTLDS. Three aims :**
- **Better define "Chronic Lyme disease"**
- **Evaluate the efficacy of dapsone combination therapy (DDS CT) in those with Chronic Lyme disease/PTLDS failing traditional therapy**
- **Diagnose abnormalities on the 16-point MSIDS map potentially affecting health & pinpoint overlapping sources of inflammation and their downstream effects to improve clinical outcome**

- Horowitz, et al. J Clin Exp Dermatol Res 2016, 7:3; Horowitz, R., et al. Healthcare 2018, 6, 129.

Figure 1: Percentage of Patients With MSIDS Abnormalities



16 Point MSIDS Map: Evaluate all of the Sources of Inflammation

- **Primary Sources:**
- 1) Chronic infections
- 2) G.I.: Dysbiosis of intestinal bacteria
- 3) G.I. : Leaky gut w/ Food allergies and sensitivities
- 4) Sleep disorders:↑ IL-6
- 5) Environmental toxins (heavy metals, mold…)
- 6) Nutritional Deficiencies

- **Downstream effects:**
- 7) Endocrine disorders: low T, low adrenal (f)
- 8, 9) Neurological, Psychological dysfunction
- 10) POTS/dysautonomia
- 11) Mitochondrial Dys(f)
- 11) Pain Syndromes
- 12) Liver Dysfunction
- 13) Autoimmune phen.

Laboratory Testing of MSIDS Variables

Horowitz, R., Freeman P. International Journal of General Medicine 2019:12 101–119

- Several national reference laboratories (Quest Diagnostics, LabCorp, BioReference, PacTox)
- Local state laboratories (i.e., Sunrise, NorDx, Affiliated Laboratory Inc., AccuReference)
- Specialty laboratories for tick-borne diseases (Imugen, IgeneX, MDL Laboratory, Stonybrook Lyme Disease Laboratory, Milford Molecular Diagnostics, Galaxy diagnostics, Immunosciences
- Functional medicine laboratories (Aeron Lifecycles, Labrix, Genova Diagnostics, Great Plains, Diagnos-Tech, Doctor's Data, RealTime Laboratory)

Laboratory & Clinical Evaluation

International Journal of General Medicine

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ORIGINAL RESEARCH

Empirical validation of the Horowitz Multiple Systemic Infectious Disease Syndrome Questionnaire for suspected Lyme disease

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4 September 2017
Number of times this article has been viewed

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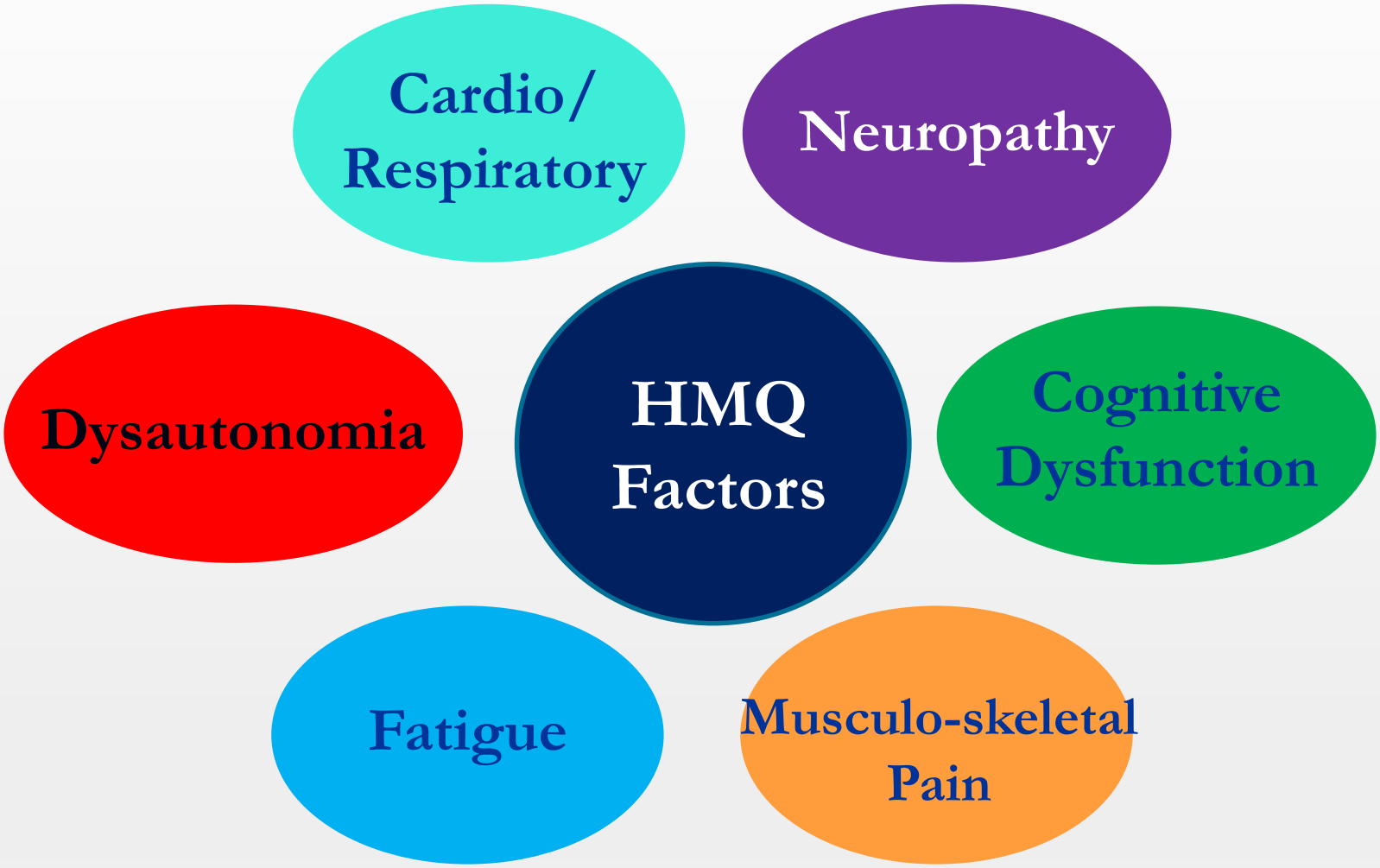
Purpose: Lyme disease is spreading worldwide, with multiple *Borrelia* species causing a broad range of clinical symptoms that mimic other illnesses. A validated Lyme disease screening questionnaire would be clinically useful for both providers and patients. Three studies evaluated such a screening tool, namely the Horowitz Multiple Systemic Infectious Disease Syndrome (MSIDS) Questionnaire. The purpose was to see if the questionnaire could accurately distinguish between Lyme patients and healthy individuals.

Methods: Study 1 examined the construct validity of the scale examining its factor structure and reliability of the questionnaire among 537 individuals being treated for Lyme disease. Study


Cardio/
Respiratory
Neuropathy
Dysautonomia
HMQ
Factors
Cognitive
Dysfunction
Fatigue
Musculo-skeletal
Pain

Percentage of Patients with EM Rashes & Positive Lyme Testing

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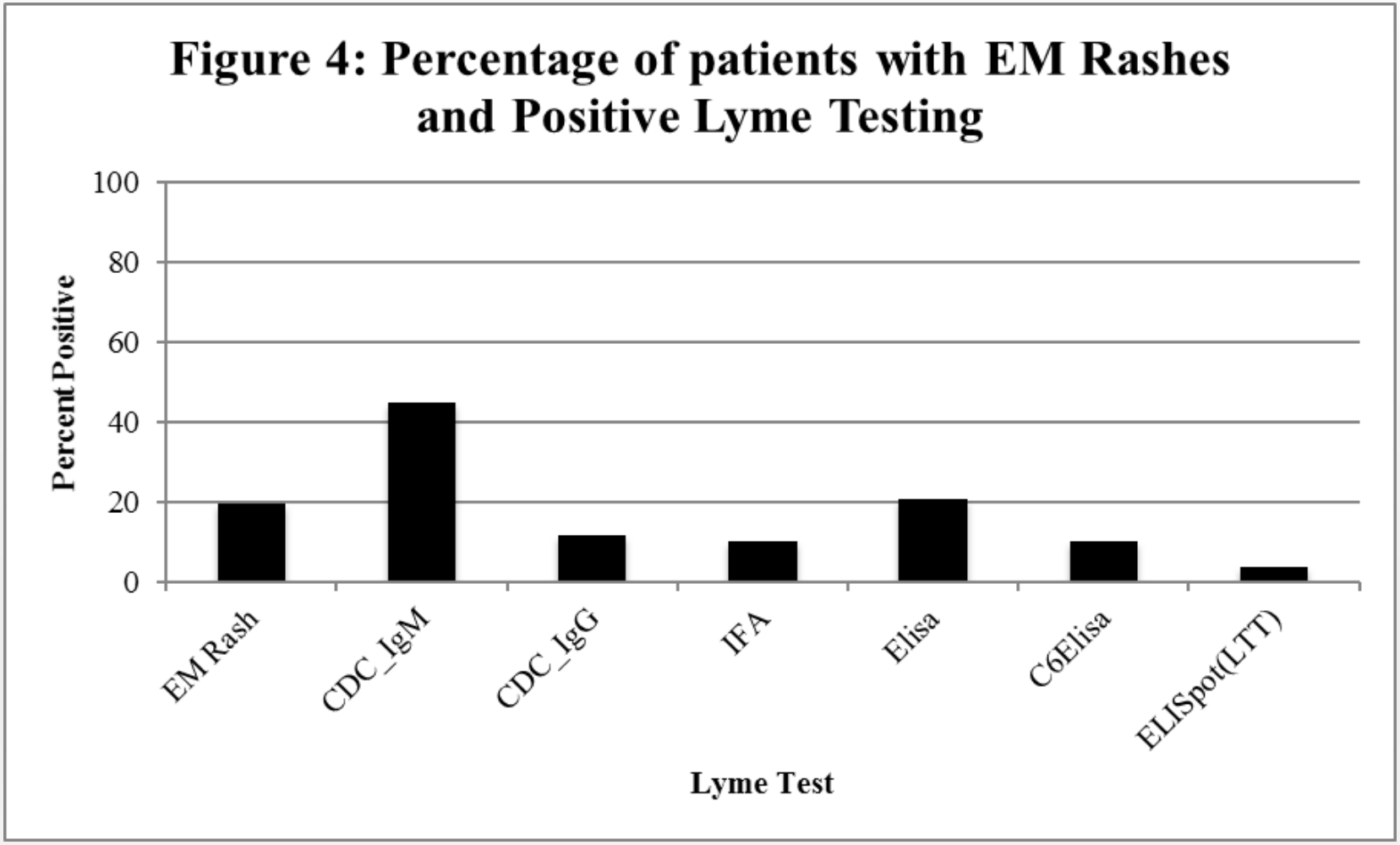

Testing: Positive IgM Western Blot Bands in 200 Patients with LD

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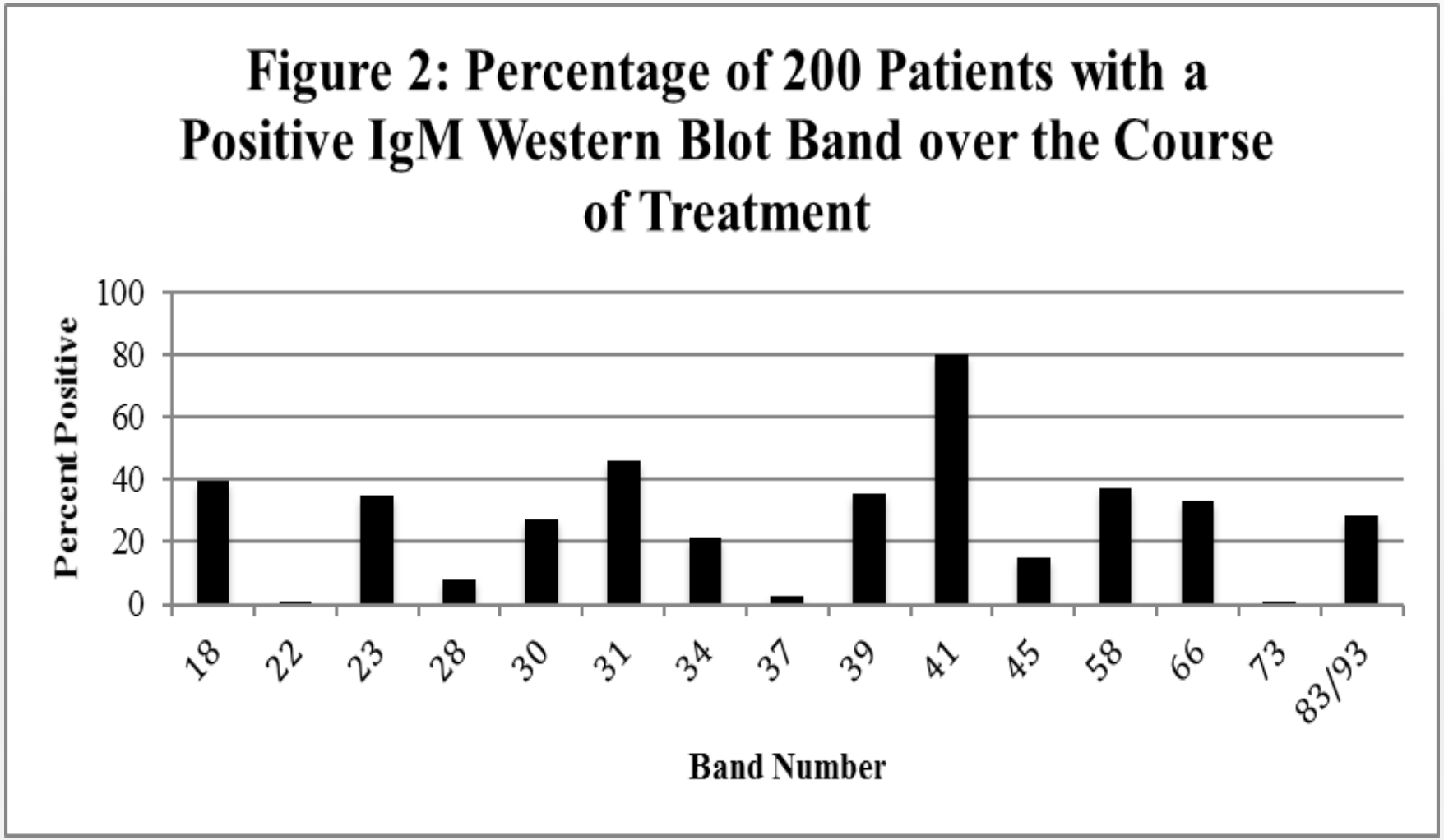

Testing: Positive IgG Western Blot Bands in 200 Patients with LD

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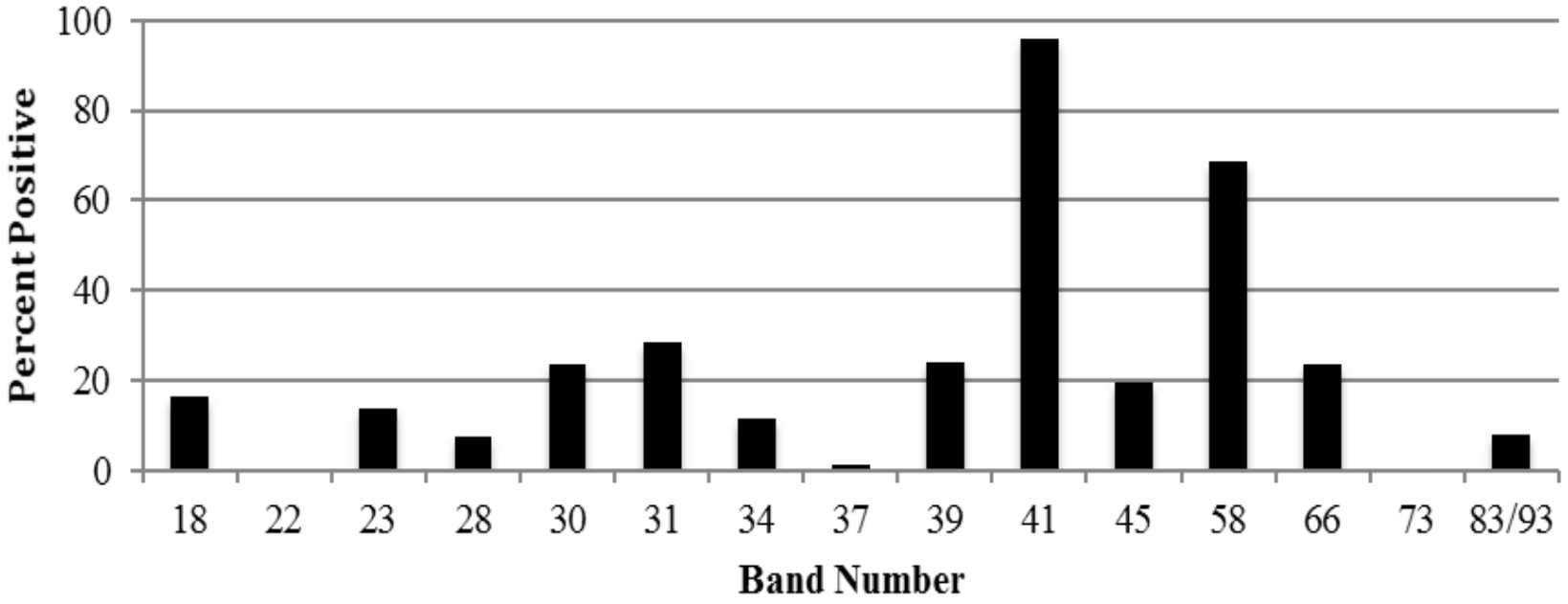
Figure 3: Percentage of 200 Patients with a Positive IgG Western Blot Band over the Course of Treatment



Bands 31 (OspA) + 34 (OspB): Markers of Borreliosis

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Table 2: Frequency and Percentage of Positive CDC IgG and IgM Western Blots with Positive Bands 31 and 34 kDa and a Negative ELISA or Negative C6 ELISA Test

		Negative Tests	
		ELISA *(N=31)*	C6 ELISA *(N=49)*
IgG Western Blot	*Band 31*(+)	4 (12.9%)	16 (32.7%)
	Band 34(+)	4 (12.9%)	8 (16.3%)
	CDC (+)	1 (3.2%)	7 (14.3%)
IgM Western Blot	*Band 31*(+)	12 (38.7%)	19 (38.8%)
	Band 34(+)	8 (25.8%)	10 (20.4%)
	CDC (+)	7 (22.6%)	23 (46.9%)

Other Diagnostic Key Points: Don't Forget the Co-infections!!

- **Expand Babesia testing**: Use a panel approach (IFA, FISH (IgeneX), PCR) including a Babesia WA-1 (duncani)
- **Expand the "net" for other TBD's**, i.e. rickettsial infections (Q-fever, RMSF, Typhus), Ehrlichia, Anaplasma, Bartonella, Mycoplasma species, Tularemia, Brucella as well as tick borne viral infections. Some of these can be fatal in the very young, old, or those patients with compromised immune systems

- Curcio Sabino R., et al. Seroprevalence of Babesia microti in Individuals with Lyme Disease Vector-Borne and Zoonotic Diseases. October 2016. doi:10.1089/vbz.2016.2020; Rickettsia Parkerii: Journal of Medical Entomology, 2017, 1–7 doi: 10.1093/jme/tjx138

viruses

MDPI

Article

Co-Infection Patterns in Individual *Ixodes scapularis* Ticks Reveal Associations between Viral, Eukaryotic and Bacterial Microorganisms

Shaun T. Cross [1], Marylee L. Kapuscinski [1], Jacquelyn Perino [1], Bernadette L. Maertens [1], James Weger-Lucarelli [1,2], Gregory D. Ebel [1] and Mark D. Stenglein [1,*]

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Abstract: *Ixodes scapularis* ticks harbor a variety of microorganisms, including eukaryotes, bacteria and viruses. Some of these can be transmitted to and cause disease in humans and other vertebrates. Others are not pathogenic, but may impact the ability of the tick to harbor and transmit pathogens.

Number of Coinfections

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- Participants tested positive for exposure to between 0 and 16 coinfections (M=5.87, SD=2.29)
- 0.5% had no evidence of coinfections
- 26% had between 2-4 coinfections
- 64% had between 5-8 coinfections
- 8% had between 9-12 coinfections
- 1.5% had more than 12 coinfections
- Most Frequent: Babesia, Bartonella, Chlamydia pneumonia, EBV, HHV6, and Mycoplasma

Coinfections: Indirect/Direct Testing

- Bacteria: Anaplasma (13.5%), Bartonella (B. henselae and B. quintana [N=93, + titer, PCR, FISH, VEGF 46.5%), Brucella (10%), Chlamydia Pneumonia (51%), Ehrlichia (14.5%), H. pylori (7.5%), Mycoplasma (M. pneumonia, M. fermentans, M. penetrans (82%), Q-Fever (Coxiella burnetti [8.5%), Rocky Mountain Spotted Fever (10%), tularemia (16.5%), typhus (10,5%)
- Parasites: Babesia (B. microti and B. duncani [N=104, 52%]), Toxoplasmosis (N=23, 11.5%)
- Viruses: HSV1 (23%), HSV2 (11.5%), HHV6 (81%), CMV (37%), Coxsackie, (7.5%) EBV (80%), Parvovirus (11.5%), WNV (6.5%)

Co-infection Status N=200 Dapsone

64% of patients had between 5-8 coinfections

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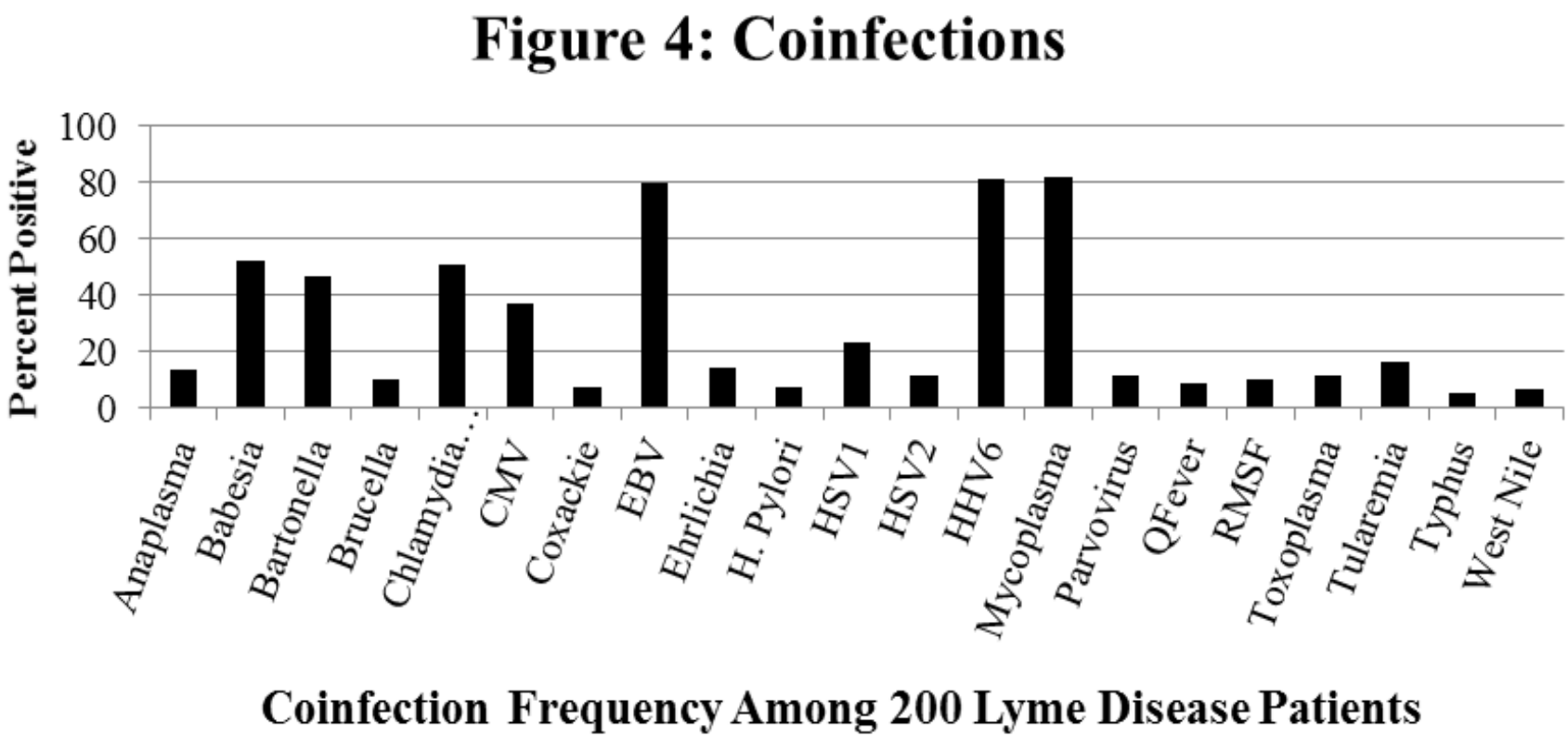

Serologic Evidence of Powassan Virus Infection in Lyme Patients = 10.4%

CDC A-Z INDEX

EMERGING INFECTIOUS DISEASES®

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Volume 23, Number 8—August 2017

Dispatch

Serologic Evidence of Powassan Virus Infection in Patients with Suspected Lyme Disease

Holly M. Frost[1], Anna M. Schotthoefer, Angela M. Thomm, Alan P. Dupuis, Sue C. Kehl, Laura D. Kramer, Thomas R. Fritsche, Yvette A. Harrington, and Konstance K. Knox

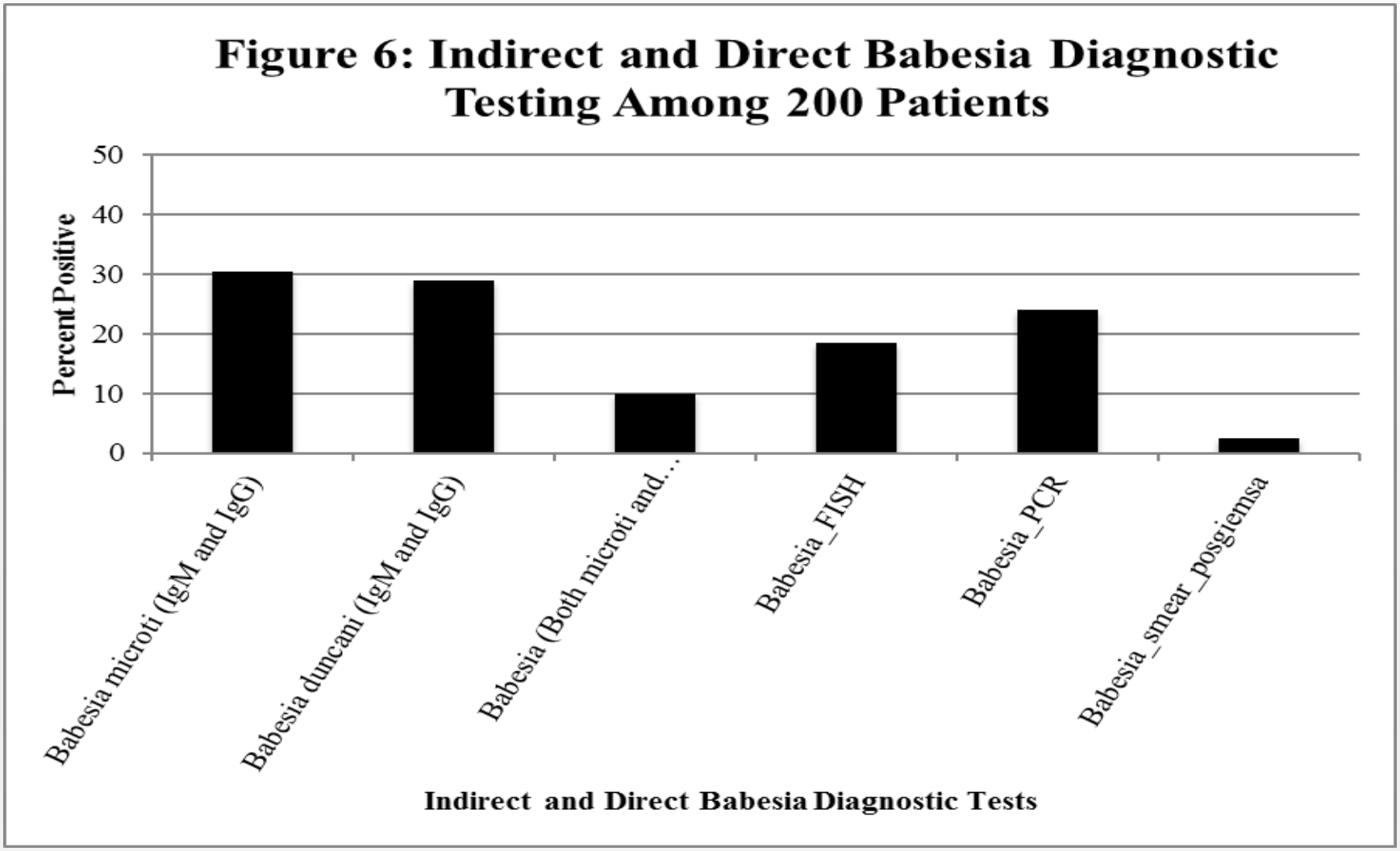
Author affiliations: Marshfield Clinic Research Foundation, Marshfield, Wisconsin, USA (H.M. Frost, A.M. Schotthoefer, T.R. Fritsche); Coppe Laboratories, Waukesha, Wisconsin, USA (A.M. Thomm, Y.A. Harrington, K.K. Knox); New York State Department of Health, Slingerlands, New York, USA (A.P. Dupuis II, L.D. Kramer); Medical College of Wisconsin, Milwaukee, Wisconsin, USA (S.C. Kehl)

Suggested citation for this article

Abstract

Powassan virus (POWV) lineage II is an emerging tickborne flavivirus with an unknown seroprevalence in humans. In a Lyme disease–endemic area, we examined the seroreactivity to POWV in 2 patient cohorts and described the clinical features of the POWV-seroreactive patients. POWV disease might be less neuroinvasive than previously thought.

Babesia Testing: Antibody, PCR, FISH, Giemsa Stain



Babesia Testing: The Need For A Broad Screening Approach

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- Seropositive: B. microti (N=51, 25.5%)
- Seropositive: B. duncani (N=56, 28%)
- Some patients had evidence of antibody titers for both species (N=20, 10%)
- Seronegative: Among 32 patients who were seronegative for B. microti and/or B. duncani, 37.5% were + by direct testing (PCR, FISH)
- One was PCR +(3%) and 11 were FISH positive (34.5%)

Antibody Positive Babesia duncani cases by Home State in 200 Patients

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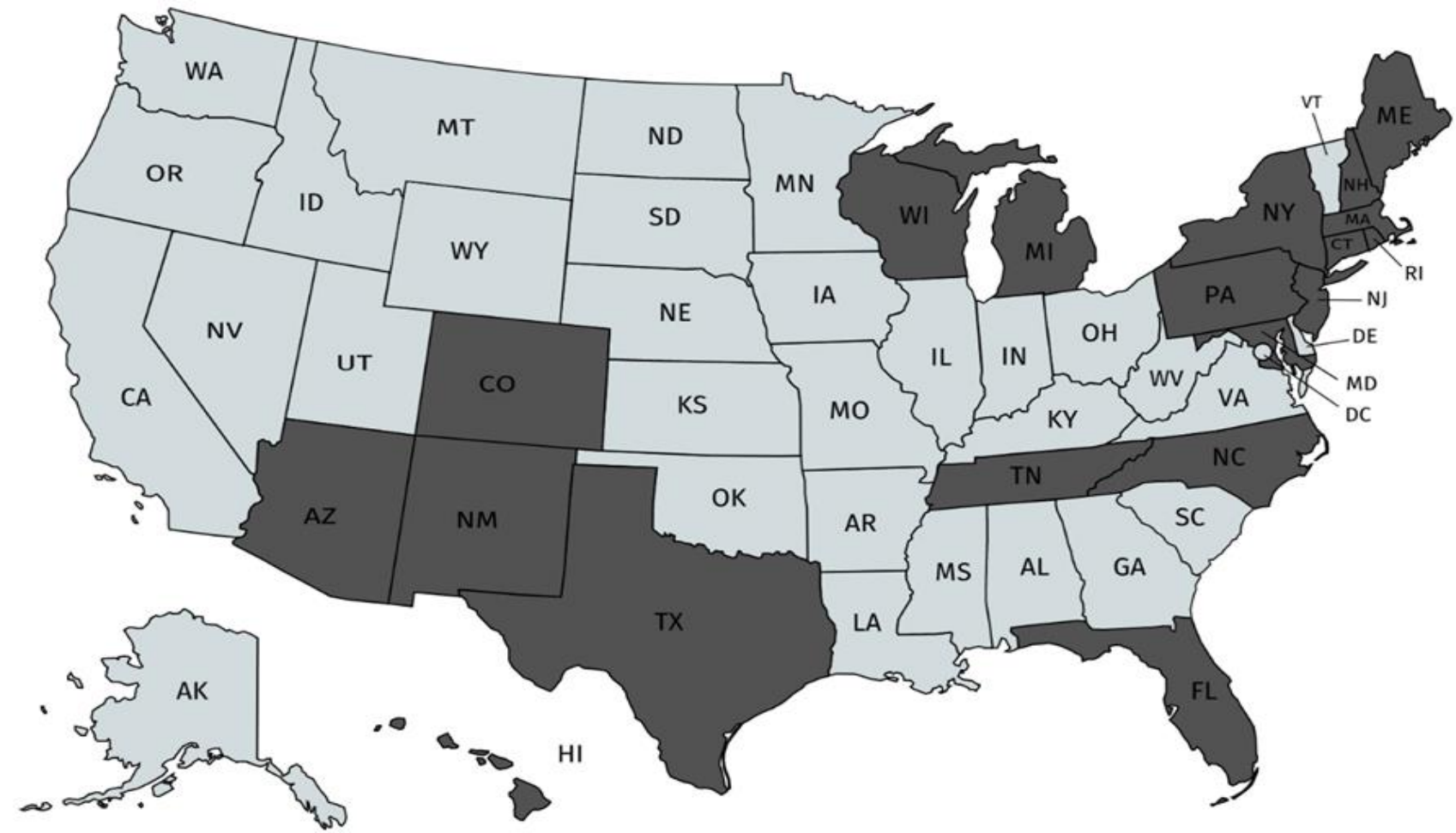

Treatment Failures Due to Persistence of Lyme Borreliosis:

- Skin: fibroblasts (Klempner) J Infect Dis 1992;166: 440-444
- Eye: (Preac-Mursic, Meier) Infection 1989;17:355-359.
- Ligamentous tissue: (Haupl) Arthritis Rheum 1993;36:1621-1626
- Joints: (Priem, Bradley, Fitzpatrick) Ann Int Med 1994;487-9
- Endothelial cells and macrophages: Ma et al, Infect Immun 1991 Feb;59(2):671-8
- CNS: (Coyle, Leigner) Eur Neurol. 1995;35:113-117
- Biofilms (Sapi, McDonald) Am J Clin Pathol 2008; 129: 988
- **Treatment failures are also seen w/persistence of Babesia, Bartonella, Tularemia, Brucella, Mycoplasma species**

Retrospective Study of 200 Patients on DDS: Proof of Persistence by PCR, FISH

Horowitz, Freeman: International Journal of General Medicine 2019:12 101–119

- Borrelia burgdorferi: **14.5%** of patients were PCR + despite "adequate" antibiotic therapy for months or years prior to DDS CT (N=29, 14.5%).
- Babesia spp.: **+ PCR/FISH** despite M+Z, C+Q
- Bartonella henselae: **+ PCR, + FISH**
- Other: tularemia (4x ↑titers), Brucella (+ agglut)
- M. fermentans (**2.5% + PCR**), M. penetrans (**1%**)
- Viruses: **HHV6 PCR +, 4x ↑ titers**

- Lemieux, J. E. et al. A global map of genetic diversity in Babesia microti reveals strong population structure and identifies variants associated with clinical relapse. Nat. Microbiol. 2016, 1, 16079

Problems with Treatment: Chronic Persistent Infection Despite Intensive Antibiotics (6)

- Bradley JF,et al, The Persistence of Spirochetal Nucleic Acids in Active Lyme Arthritis. Ann Int Med 1994;487-9
- Bayer ME, Zhang L, Bayer MH. Borrelia burgdorferi DNA in the urine of treated patients with chronic Lyme Disease symptoms. A PCR study of 97 cases. Infection 1996. Sept-Oct;24(5):347-53
- Diringer MN, et al, Lyme meningoencephalitis- report of a severe, penicillin resistant case. Arthritis & Rheum, 1987;30:705-708
- Donta, ST, Tetracycline therapy in chronic Lyme disease. Chronic Infectious Diseases, 1997; 25 (Suppl 1): 552-56
- Fitzpatrick JE, et al. Chronic septic arthritis caused by Borrelia burgdorferi. Clin Ortho 1993 Dec;(297):238-41
- Georgilis K, Peacocke M, & Klempner MS. Fibroblasts protect the Lyme disease spirochete, Borrelia burgdorferi, from ceftriaxone in vitro. J Infect Dis 1992;166: 440-444

Chronic Persistent Infection with Bb Despite Intensive Antibiotics: 5 Studies

- Fallon BA, et al. Repeated antibiotic treatment in chronic Lyme disease, Journal of Spirochetal and Tick-borne Diseases, 1999; 6 (Fall/Winter):94-101
- Fraser DD, et al. Molecular detection of persistent Borrelia burgdorferi in a man with dermatomyositis. Clinical and Exper Rheum. 1992;10:387-390
- Fried MD et al, Borrelia burdorferi persists in the gastrointestinal tract of children and adolescents with Lyme Disease, JNL of Spirochetal and Tick-borne Diseases, Spring/Summer 2002; 9:11-15
- Girschick HJ, et al. Intracellular persistence of Borrelia burgdorferi in human synovial cells. Rheumatol Int 1996;16(3):125-132
- Hassler D, et al. Pulsed high-dose cefotaxime therapy in refractory Lyme Borreliosis (letter). Lancet 1991;338:193

Chronic Persistent Infection with Bb Despite Intensive Antibiotics: 5 Studies

- Horowitz RI. Chronic Persistent Lyme Borreliosis: PCR evidence of chronic infection despite extended antibiotic therapy: A Retrospective Review. Abstract XIII Intl Sci Conf on Lyme Disease. Mar 24-26, 2000.
- Haupl T, et al. Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis. Arthritis Rheum 1993;36:1621-1626
- Karma A, et al. Long term follow-up of chronic Lyme neuroretinitis. Retina 1996;16:505-509
- Keller TL, et al. PCR detection of Borrelia burgdorferi DNA in cerebrospinal fluid of Lyme neuroborreliosis patients. Neurology 1992;43:32-42
- Masters EJ, et al. Spirochetemia after continuous high-dose oral amoxicillin therapy. Infect Dis Clin Practice 1994;3:207-208

Chronic Persistent Infection with Bb Despite Intensive Antibiotics: 6 Studies

- Ma Y, et al. **Intracellular localization** of Borrelia burgdorferi within human **endothelial cells**. Infect Immun 1991;59:671-678
- Meier P, et al. Pars plana vitrectomy in Borrelia burgdorferi **endophthalmitis**. Klin Monatsbl Augenheilkd 1998 Dec;213(6):351-4
- Preac-Mursic V, et al. Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis. Infection 1989;17:355-359.
- Preac-Mursic V, et al. Persistence of Borrelia burdorferi and Histopathological Alterations in Experimentally Infected Animals. A comparison with Histopathological Findings in Human Lyme Disease. Infection 1990;18(6):332-341
- Straubinger RK, et al. Persistence of Borrelia burgdorferi in Experimentally Infected **Dogs** after Antibiotic Treatment. J Clin Microbiol 1997;35(1):111-116
- Embers, M. et al. Persistence of Borrelia burgdorferi in **Rhesus Macaques** following Antibiotic treatment of Disseminated Infection. PLoS ONE 7(1): e29914. doi:10.1371/journal.pone

Chronic Persistent Infection Despite Intensive Antibiotics: Xenodiagnostics

- **Mice:** Hodzic E, Barthold SW (2014) Resurgence of Persisting Non-Cultivable Borrelia burgdorferi following Antibiotic Treatment in Mice. PLoS ONE 9(1): e86907. Results confirmed previous studies: Bb could not be cultured from tissues, but low copy numbers of Bb flaB DNA were detectable in tissues up to 8 months after completion of treatment & RNA transcription of genes was seen with visualized spirochetes
- **Macaques, Embers,** 2017: evidence of persistent, intact, metabolically-active B. burgdorferi after antibiotic treatment of disseminated infection : ME, et al. (2017) Variable manifestations, diverse seroreactivity and post-treatment persistence in non-human primates exposed to Borrelia burgdorferi by tick feeding. PLoS ONE 12(12): e0189071
- **Humans**: **one patient with PTLDS had a positive result, confirming evidence of ongoing Borrelia DNA** Marques, A. et al. Xenodiagnosis to Detect Borrelia burgdorferi Infection: A First-in-Human Study. Clinical Infectious Diseases DOI: 10.1093/cid/cit939 (2014).

Post Treatment Persistence of Bb in the Animal Model: Embers 2018

PLOS ONE

RESEARCH ARTICLE

Variable manifestations, diverse seroreactivity and post-treatment persistence in non-human primates exposed to *Borrelia burgdorferi* by tick feeding

Monica E. Embers[1]*, Nicole R. Hasenkampf[1], Mary B. Jacobs[1], Amanda C. Tardo[1], Lara A. Doyle-Meyers[2], Mario T. Philipp[1], Emir Hodzic[3]

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Abstract

Post Treatment Persistence of Bb in Humans: Middleveen 2018

healthcare

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Article

Persistent Borrelia Infection in Patients with Ongoing Symptoms of Lyme Disease

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* Correspondence: rstricker@usmamed.com

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Abstract: Introduction: Lyme disease is a tickborne illness that generates controversy among medical providers and researchers. One of the key topics of debate is the existence of persistent infection with

Post Treatment Persistence of Bb & Co-infections in Humans: Horowitz 2019

International Journal of General Medicine

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ORIGINAL RESEARCH

Precision medicine: retrospective chart review and data analysis of 200 patients on dapsone combination therapy for chronic Lyme disease/ post-treatment Lyme disease syndrome: part 1

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[1]Health and Human Services, Tick-Borne Disease Working Group, Washington, DC 20201 USA; [2]Hudson

Purpose: We collected data from an online survey of 200 of our patients, which evaluated the efficacy of dapsone (diaminodiphenyl sulfone, ie, DDS) combined with other antibiotics and agents that disrupt biofilms for the treatment of chronic Lyme disease/post-treatment Lyme disease syndrome (PTLDS). We also collected aggregate data from direct retrospective chart review, including laboratory testing for Lyme, other infections, and associated tick-borne coinfections.

Data Mining of MSIDS Variables in 200 Patients on DDS CT: Inf's/Immune Dys(f)

- 1) Infections: 100%, high % Babesia (52%), significant % with IC infections, including: Bartonella (46.5%), Mycoplasma (82%), tularemia (16.5%), Brucella (10%)
- 2) Immune Dysfunction: (positive ANA, RF, HLADR2, HLADR4): 145 (72.5%) of participants had immune dysfunction, 13.5% had elevated IgM antibodies, and up to 85% had some form of immune deficiency:
- o 20.6 % had total IgG deficiency
- o 19.3% had IgM deficiency;
- o 15.9% had IgA deficiency
- 85.5% had combined IgG subclass deficiencies 1-4

Immune Dysfunction in Lyme-MSIDS

- More than 72% of the 200 pts had immune dysfunction
- Total IgG deficiency was found in 20.6%; 19.3% had IgM deficiency (13.5 % had elevated IgM antibodies); 15.9% had IgA deficiency (? ↑ food allergies) & > 85% had combined IgG subclass deficiencies 1-4.
- 85% had low IgG subclasses 1 and 3→can affect phagocytosis & antibody-dependent cellular/complement-dependent cytotoxicity
- Some patients: ↓ antibody response to a pneumovax
- Possible etiologies of immune dysfunction: Lyme, co-infections (Anaplasma), heavy metals, gliotoxins..

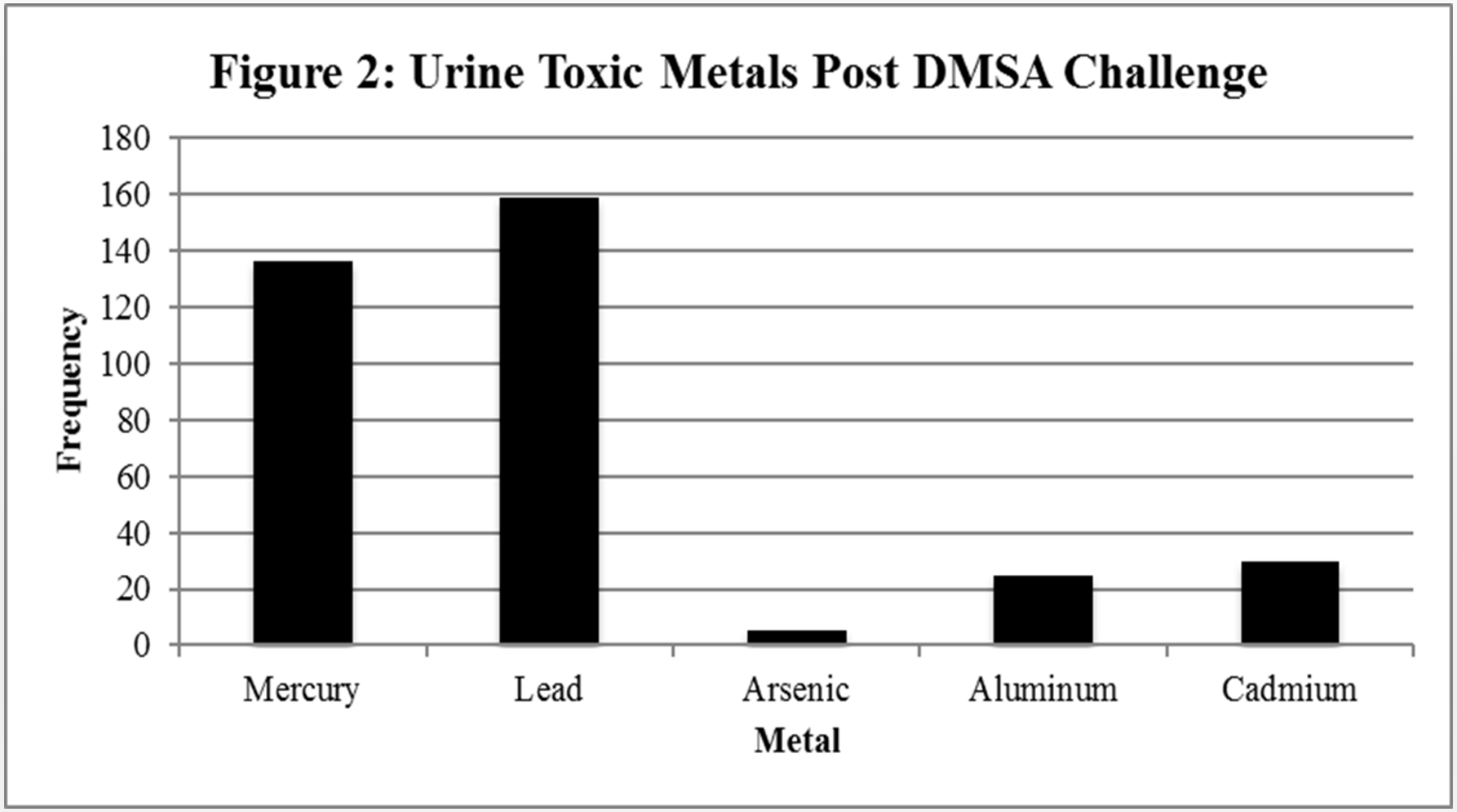
- Olano JP and DH Walker. Human Ehrlichiosis. Medical Clinics of NA. 2002. 86(2):375392.

Immune Dysfunction in Lyme Was Confirmed in Prior Animal Studies

- Nicole Baumgarth: infection with Bb in mice affects lymph nodes & production of IgG antibodies, by affecting germinal centers, ↓functional & long-lived AB responses
- Borrelia subverted a B cell response in that study & caused T cell independence → IgM skewed profile
- We found 20.6% with IgG deficiency & 7% w/CVID
- 13.5% had ↑ IgM AB's and 19.3% had an IgM deficiency: ? 2° immune complexes with active disease

- Tunev, et al. Lymphoadenopathy during Lyme Borreliosis Is Caused by Spirochete Migration-Induced Specific B Cell Activation. PLOS Pathog. 2011, 7, e1002066;
- Schutzer, S. E., et al. Sequestration of antibody to Borrelia burgdorferi in immune complexes in seronegative Lyme disease. Lancet Lond. Engl. 1990, 335, 312–315;

4. Toxicity: Urine Toxic Metals Post DMSA Challenge: Appx 85% Tested +



Data Mining of MSIDS Variables: 4. Environmental Toxins

- Mold: 30/42 (71.4%) had 1 or more ↑ mold levels
- 13/25 (52%) had elevated aflatoxins
- 18/26 (69%) had elevated ochratoxins
- 20/26 (76.9%) had elevated trichothecenes
- 17/17 (100%) had elevated gliotoxins
- 7/18 (38.9%) had "other" elevated mold (Stachybotrys exposure)
- Pesticides: 5 (2.5%) tested positive for pesticides*
- *Not all patients were tested for mold or pesticides: only those with a history of significant mold exposure and pesticide exposure were checked in those with significant chemical sensitivity and/or Parkinson's symptoms
- Edmondson, D. A.; Barrios, C. S.; Brasel, T. L.; Straus, D. C.; Kurup, V. P.; Fink, J. N. Immune Response among Patients Exposed to Molds. Int. J. Mol. Sci. 2009, 10, 5471–5484, doi:10.3390/ijms10125471.

Data Mining of MSIDS Variables: 6. Nutritional/Enzyme Deficiencies

- 76% had one or more nutritional deficiencies
- 5 (2.5%) had AA and 2 (1%) had fatty acid deficiencies
- 36 (18%) had iodine deficiencies
- 14 (7%) had copper deficiencies: 3 (1.5%) had deficiencies in serum copper; 6 (3%) had deficiencies in red blood cell [RBC] copper; 5 (2.5%) had deficiencies in plasma copper
- 31 (16%) had magnesium deficiencies: 3% had deficiencies in serum magnesium; 13% had deficiencies in RBC magnesium
- 36 (18%) had zinc deficiencies: 22 (11%) had deficiencies in serum zinc; 7 (3.5%) had deficiencies in RBC zinc; 7 (3.5%) had deficiencies in plasma zinc; 105 (52.5%) had MTHFR mutations

- Prasad, A. S.; et al. Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress. Am. J. Clin. Nutr. 2007, 85, 837–844.

Data Mining of MSIDS Variables: 10. Endocrine Abnormalities

- Endocrine Abnormalities: 195 (97.5%)
- 121 (60.5%) had thyroid abnormalities
- 144 (72%) had adrenal abnormalities
- 82 (41%) had sex hormone abnormalities
- 136 (68%) had vitamin D deficiencies
- 3 (1.5%) had pregnenolone deficiencies
- 74 (37%) had DHEA abnormalities

- Berczi, I. The pituitary gland, psychoneuroimmunology and infectious disease." In Friedman, H., Klein, T. W., Friedman, A. L., eds., Boca Raton, FL: CRC Press, 1996. pp. 79–109. In Psychoneuroimmunology, Stress and Infection.; Friedman, H., Klein, T., Friedman, A., Eds.; CRC Press: Boca Raton, FL, 1996; pp. 79–109.

Data Mining of MSIDS Variables: 11. Sleep Disorders

- 98% had one or more sleep disorders:
- 23 (11.5%) had Obstructive Sleep Apnea (OSA)
- 1 (.5%) had Restless Leg Syndrome (RLS)
- 7 (3.5%) had Benign Prostatic Hyperplasia (BPH)
- 4 (2%) were in menopause/ 2 (1%) had high adrenals
- 1 (.5%) had medication induced sleep problems
- 189 (94.5%) had other sleep problems, i.e., difficulties with insomnias, hypersomnias, circadian rhythm disorders (secondary to Lyme and tick-borne diseases)

- Greenberg, H. E.; Ney, G.; Scharf, S. M.; Ravdin, L.; Hilton, E. Sleep quality in Lyme disease. Sleep 1995, 18, 912–916.

Data Mining of MSIDS Variables: 12. ANS Dysfunction/POTS

- ANS Dysfunction/POTS: 83 (41.5%) of participants
- 23 (11.5%) had mild POTS (1-10 mm Hg drop in BP, and/or 1-10-point increase in heart rate after standing)
- 41 (20.5%) had moderate POTS (11-29 mm drop in BP, and/or 11-29-point increase in heart rate after standing)
- 9 (4.5%) had severe POTS (30+ ↑ in heart rate standing)
- 19 (9.5%) had dysautonomia (e.g. gastroparesis, chronic constipation, bladder dysfunction, or dysfunction in temperature regulation) & 2 (1%) had 'other' (tremors and/or discoloration hands/feet)

- Kanjwal, K.; Karabin, B.; Kanjwal, Y.; Grubb, B. P. Postural orthostatic tachycardia syndrome following Lyme disease. Cardiol. J. 2011, 18, 63–66.

What is the Common Denominator?

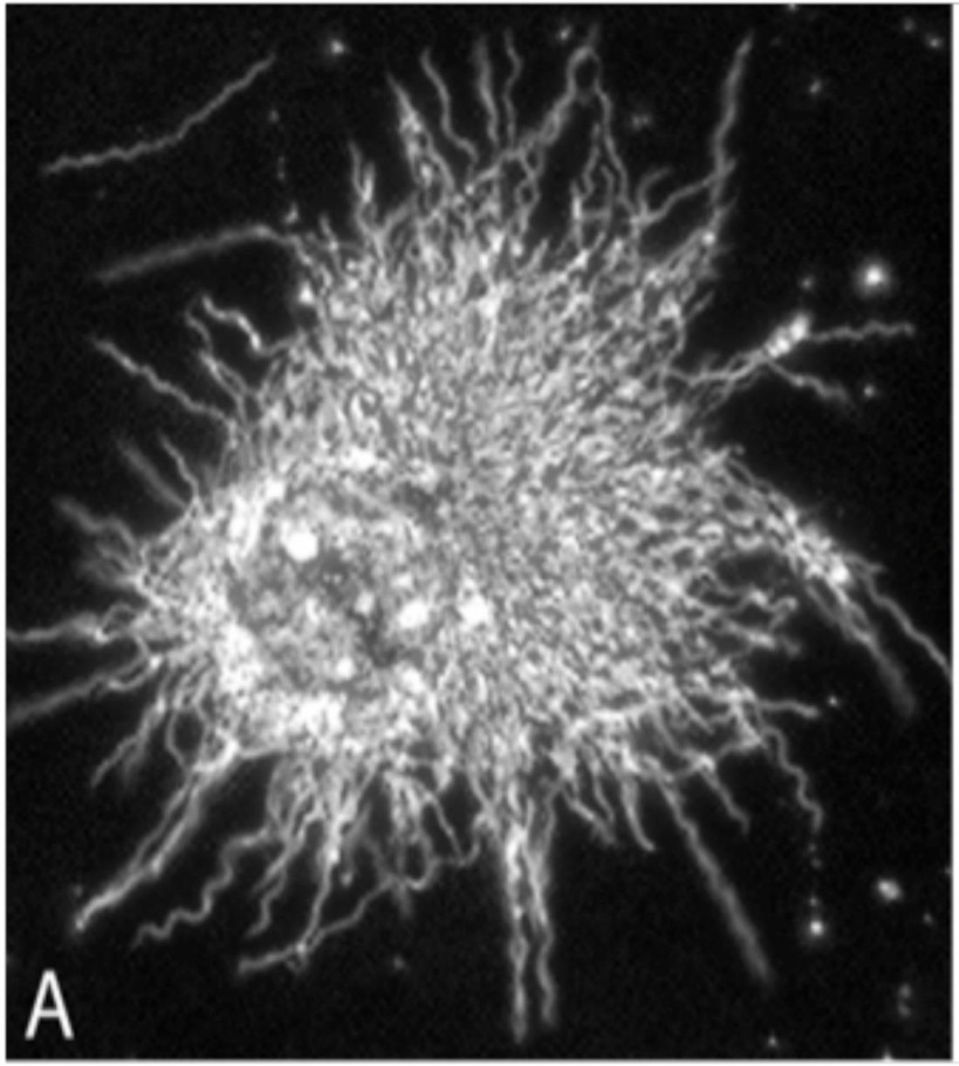
Multiple (Intracellular) Infections → Inflammation & Immune Dysfunction

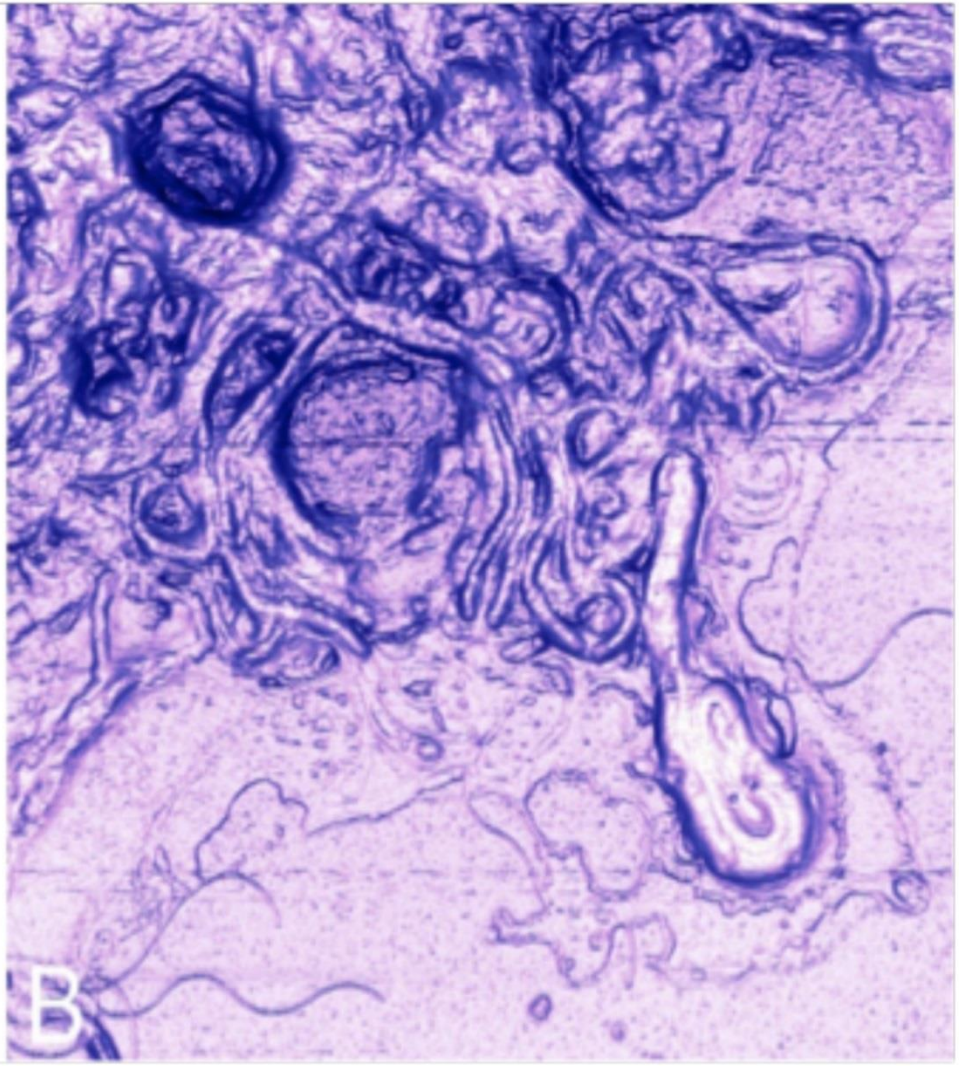
- Borrelia, Bartonella spp., Mycoplasma spp., Chlamydia, tularemia, Brucella, Ehrlichia, Anaplasma & Rickettsial infections (RMSF, Q-fever) are all intracellular infections
- Intracellular infections may be resistant to therapy & located in biofilms

- Girschick, H. J., Huppertz, H. I., Russmann, H., et al. "Intracellular persistence of Borrelia burgdorferi in human synovial cells." Rheumatol Int 16 no. 3 (1996): 125–32.
- Ma, Y., Sturrock, A., and Weis J. J. "Intracellular localization of Borrelia burgdorferi within human endothelial cells." Infect Immun 59 no. 2 (February 1991): 671–78.
- Montgomery, R. R., Nathanson, M. H., and Malawista, S. E. "The fate of Borrelia burgdorferi, the agent for Lyme disease, in mouse macrophages. Destruction, survival, recovery." J Immunol 150 no. 3 (February 1993): 909–15.

Borrelia Biofilms: Eva Sapi, PhD University of New Haven

Sapi E, et al. (2012) Characterization of biofilm formation by *Borrelia burgdorferi* In vitro. PLoS ONE 7(10): e48277.





Mycobacterium Drugs + Essential Oils Affect Lyme, Co-infections & Biofilms

- Recent scientific research has identified Lyme as a "persister" bacteria, similar to TB and leprosy
- Persisters are a small fraction of quiescent bacterial cells that survive lethal antibiotics but can regrow leading to post-treatment relapse. Ex's: TB, leprosy, syphilis, endocarditis, biofilm infections

- Borrelia burgdorferi, the causative agent of Lyme disease, forms drug-tolerant persister cells. Sharma B, et al. Antimicrobial Agents And Chemotherapy, pii: AAC.00864-15. Online first, 2015 May 26
- Persisters, persistent infections and the Yin–Yang model, Ying Zhang; Emerging Microbes and Infections (2014) 3, e3; doi:10.1038/emi.2014.3;
- Zhang, Y (2015) Drug Combinations against Borrelia burgdorferi Persisters In Vitro: Eradication Achieved by Using Daptomycin, Cefoperazone and Doxycycline. PLoS ONE 10(3): e0117207
- Identification of new compounds with high activity against stationary phase Borrelia burgdorferi from the NCI compound collection. Zhang, Y. Emerging Microbes and Infections (2015) 4, e31

SciMedCentral

JSM Arthritis

Case Report

Are Mycobacterium Drugs Effective for Treatment Resistant Lyme Disease, Tick-Borne Co-Infections, and Autoimmune Disease?

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Keywords
- Lyme disease
- Bartonella
- Tularemia
- Behçet's Disease/Syndrome
- Rheumatoid arthritis
- Dapsone
- Pyrazinamide
- Persister bacteria

Abstract

Introduction: PTLDS/chronic Lyme disease may cause disabling symptoms with associated overlapping autoimmune manifestations, with few clinically effective published treatment options. We recently reported on the successful use of a mycobacterium drug, Dapsone, for those with PTLDS. We now report on the novel use of another mycobacterium drug, pyrazinamide, (PZA), in relieving resistant symptomatology secondary to Lyme disease and associated co-infections, while decreasing autoimmune manifestations with Behçet's syndrome.

Method: Disabling multi-systemic/arthritic symptoms persisted in a Lyme patient with co-infections (Bartonella, tularemia) and overlapping rheumatoid arthritis/Behçet's disease, despite several rotations of classic antibiotic and DMARD regimens. Dapsone, a published treatment protocol used for Behçet's syndrome, recently has been demonstrated to be effective in the treatment of PTLDS/chronic Lyme disease and co-infections. It was superior to prior treatment regimens in relieving some resistant chronic tick-borne/autoimmune manifestations; however, it did not effectively **treat the skin lesions and ulcers secondary to Behçet's disease, nor significantly affect** the granuloma formation, joint swelling, and pain associated with Lyme, Bartonella, and RA. PZA, in combination with Plaquenil, minocycline and rifampin, relieved her resistant symptomatology secondary to Lyme and co-infections, her Behçet's ulcers, as well as granulomatous skin changes. In addition, a quadruple intracellular combination of a tetracycline (doxycycline), combined with rifampin, Dapsone, and a quinolone **(moxifloxacin) was effective in treating reactivation of her tularemia.**

Conclusion: Further scientific studies are needed on the role of intracellular bacteria and mycobacterium drugs like Dapsone and pyrazinamide in the treatment of both chronic persistent bacterial infections and resistant autoimmune phenomena.

ABBREVIATIONS

PTLDS: Post-Treatment Lyme Disease Syndrome; RA: Rheumatoid Arthritis; AI: Autoimmune Illness; PZA: Pyrazinamide, DMARDs: Disease-Modifying Anti Rheumatic Drugs; VEGF: Vascular Endothelial Growth Factor, MSIDS: Multiple Systemic Infectious Disease Syndrome

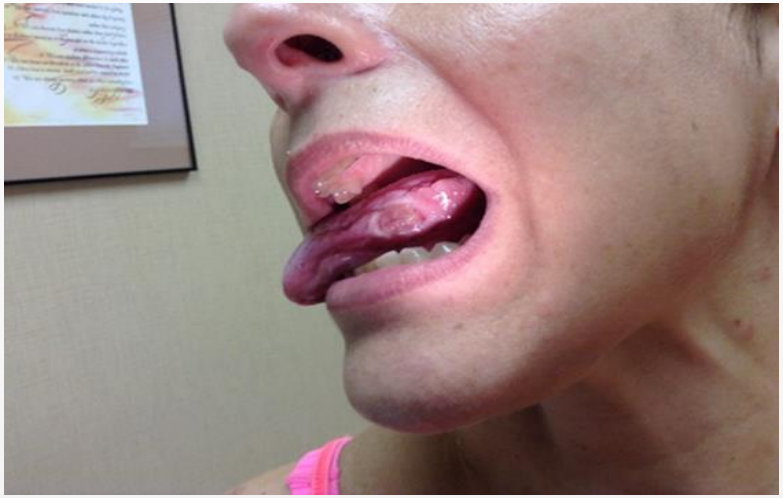
INTRODUCTION

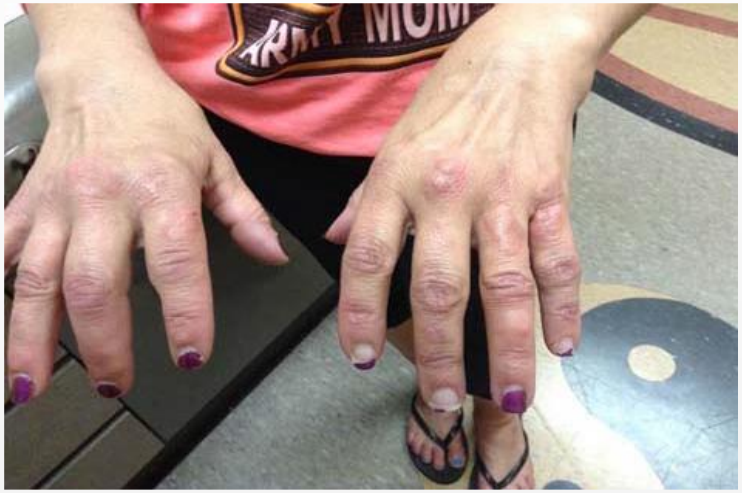
Autoimmune diseases like rheumatoid arthritis and lupus are rising in incidence in the United States and environmental factors are being implicated [1-3]. Tick-borne diseases, such as Lyme disease are also increasing in number as per recent Centers for Disease Control (CDC) studies [4,5], and have been associated with autoimmune manifestations [6]. Up to 20-25% of patients may suffer the consequences of Post- Treatment Lyme Disease Syndrome (PTLDS) [7] after a tick bite, with or without associated autoimmune disease, leading to multiple symptoms, including disabling fatigue, arthritis, and neuropathy.

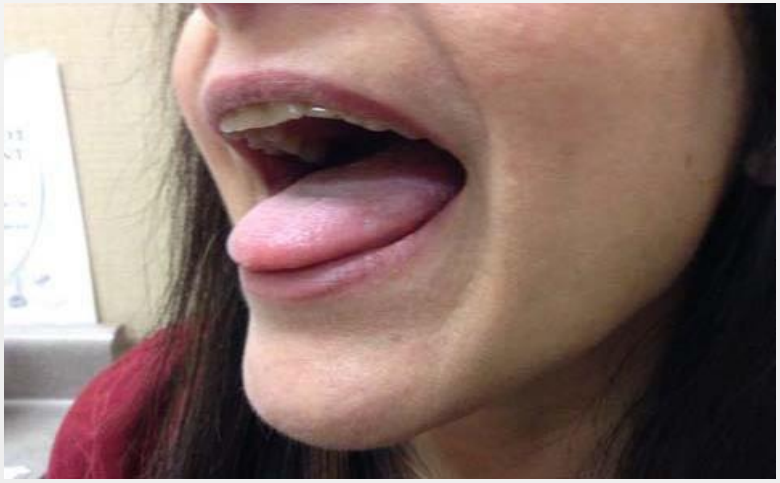
The National Science Foundation has identified Lyme disease as one of several emerging pandemic disease outbreaks that threaten global public health and world economies [8]. The CDC reported a significant increase in the number of Lyme cases in

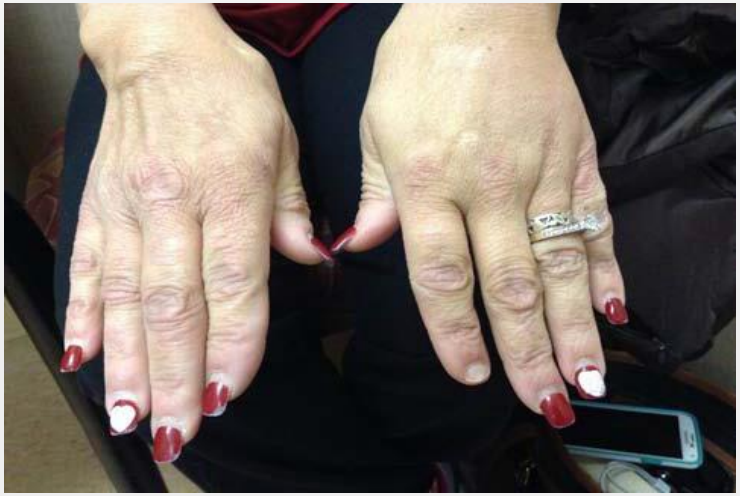
PZA in Lyme, Bartonella, Behcet's Dx:

Horowitz & Freeman JSM Arthritis, July 2016









- Evidence of persistent Bartonella, Tularemia, HHV6

antibiotics

MDPI

Article

Identification of FDA-Approved Drugs with Activity against Stationary Phase *Bartonella henselae*

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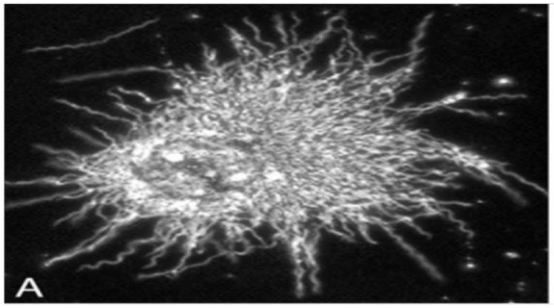
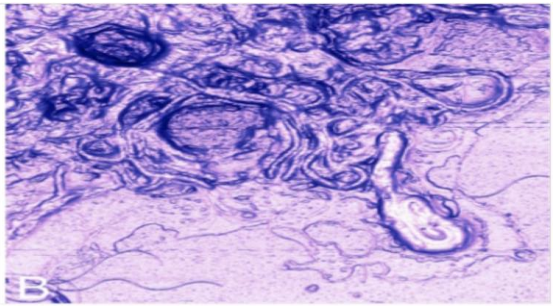
Abstract: *Bartonella henselae* can cause various infections in humans, ranging from benign and self-limiting diseases to severe and life-threatening diseases as well as persistent infections that are difficult to treat. To develop more effective treatments for persistent Bartonella infections, in this

Persistence: The Biofilm Barrier to Treatment

- **Microbial biofilms are largely responsible for the recalcitrance of many infections to conventional anti-microbial therapy (C. diff, Candida, SBE…)**
- **Up to 1000-fold decreases in antimicrobial susceptibility have been observed for biofilms**

- **Stewart PS. Mechanisms of antibiotic resistance in bacterial biofilms. Int J Med Microbiol. 2012:107–113.**
- **Sapi E, et al.(2012) Characterization of biofilm formation by Borrelia burgdorferi In vitro. PLoS ONE 7(10)**
- **Sapi E, Balasubramanian K, Poruri A, Maghsoudlou JS, Socarras KM, Timmaraju KR., et al. Evidence of in vivo existence of borrelia biofilm in borrelial lymphocytomas. Eur J Microbiol Immunol. 2016;0:1–16.**





Treat the Infections: Biofilm Busters

- **Dr Ying Zhang et al: "oregano, cinnamon bark, and clove bud completely eradicated all viable cells without any regrowth in subculture"**
- **Biofilms: Stevia, herbal extracts (Biocidin, oregano oil): liposomal formulations help ↑ penetration of herbal compounds into biofilms. Use all three!**
- **Feng J, et al. Front. Med, 11 October 2017**

Front. Med., 11 October 2017 | https://doi.org/10.3389/fmed.2017.00169

Selective Essential Oils from Spice or Culinary Herbs Have High Activity against Stationary Phase and Biofilm *Borrelia burgdorferi*

Jie Feng[1], Shuo Zhang[1], Wanliang Shi[1], Nevena Zubcevik[2],  Judith Miklossy[3] and Ying Zhang[1]*

Clinical & Experimental Dermatology Research

Horowitz and Freeman, J Clin Exp Dermatol Res
2016, 7:3
http://dx.doi.org/10.4172/2155-9554.1000345

Research Article Open Access

The Use of Dapsone as a Novel "Persister" Drug in the Treatment of Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome

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Abstract

Dapsone (diaminodiphenyl sulfone, i.e., DDS) is commonly used to treat dermatological conditions including acne, dermatitis herpetiformis, and leprosy. Mycobacterium leprae, a known "persister" bacteria, requires long-term treatment with intracellular medications including rifampin and Dapsone. Other "persister" bacteria recently have been identified, including *Borrelia burgdorferi*, the agent of Lyme disease.

Objectives: We tested the efficacy of DDS in patients with chronic Lyme disease/PTLDS with tick-borne co-infections including Babesiosis, who failed commonly used antibiotic and antimalarial protocols.

Methods: 100 patients with Lyme disease, 56 of who were Babesia positive, were placed on Dapsone and folic acid in combination with either one or two other intracellular drugs, including rifampin, tetracyclines, and/or macrolide antibiotics. Several patients also took cephalosporins, and all patients were on protocols to treat cystic forms of Borrelia and biofilms.

Results: Patients completed a symptom severity survey before beginning treatment with Dapsone and then again after at least one month of treatment scoring their complaints from 0 indicating "none" to 4 indicating "severe" for symptoms including fatigue, joint and/or muscle pain, disturbed sleep, and cognitive difficulties. Results demonstrated that Dapsone significantly improved all patients' clinical symptoms except for headache, where changes did not reach statistical significance. In addition, Dapsone, known to have anti-malarial effects, helped resistant Babesia symptoms of sweats, chills, and flushing. Lyme positive, Babesia positive patients also demonstrated significant changes in pain, disturbed sleep, and cognitive difficulties. Side effects included macrocytic anemia and rare cases of methemoglobinemia, which resolved by either decreasing the dose of Dapsone or increasing folic acid.

Conclusion: Dapsone is a novel and effective "persister" drug for those with PTLDS and associated tick-borne co-infections who have failed classical antibiotic protocols. Further prospective trials must determine the DDS dose, length of treatment and best combination antibiotic therapy in order to effect a long-term health benefit.

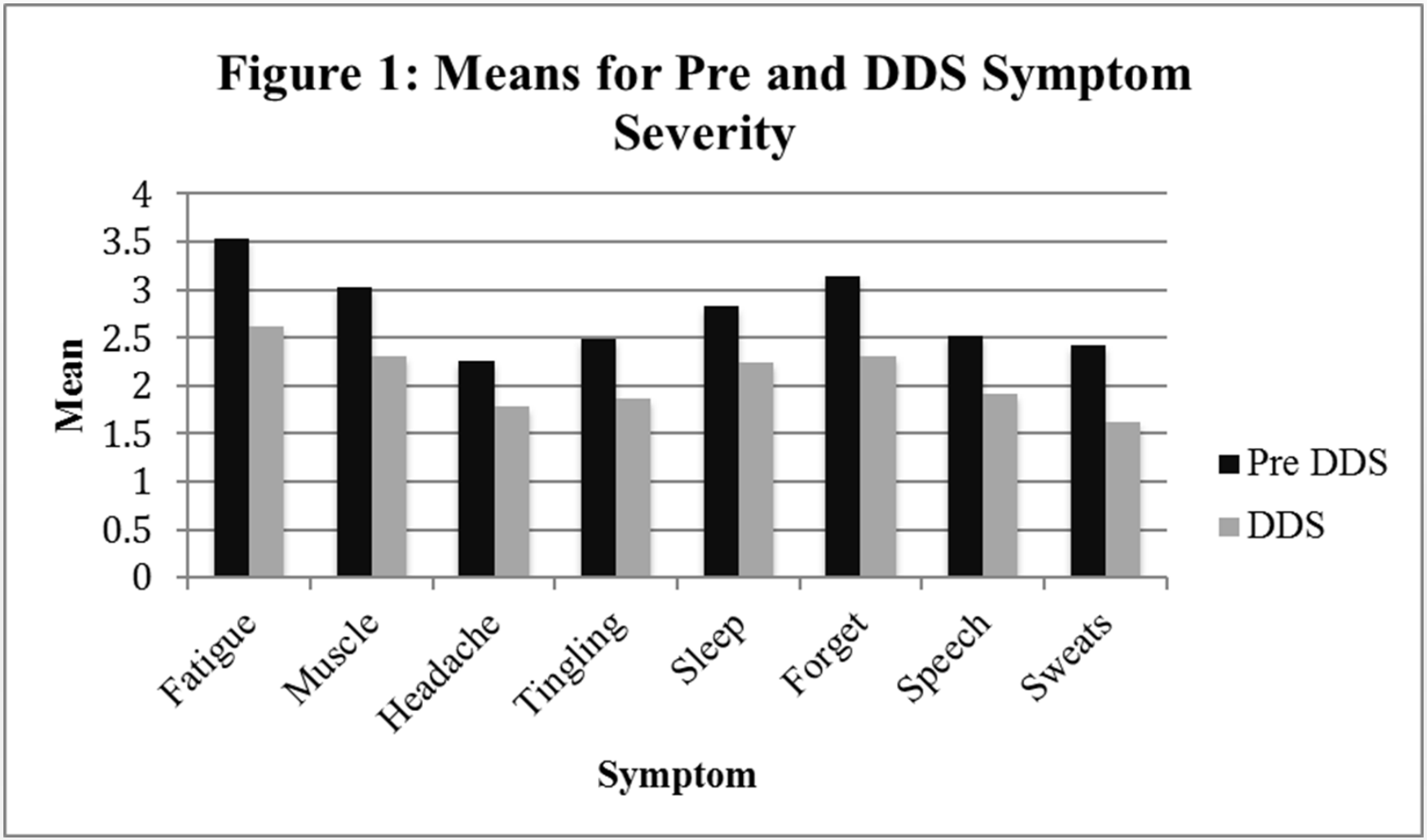
Paired-samples t-tests for 200 Patients w/ LD: Pre-DDS and DDS

Horowitz, Freeman, International Journal of General Medicine 2019:12 101–119

- Fatigue and/or Tiredness: $t(164)=10.69$, $p < .001$
- Muscle and/or Joint Pain: $t(164)=8.13$, $p < .001$
- Headache: $t(164)=5.35$, $p < .001$
- Tingling and/or Numbness and/or Burning of Extremities: $t(164)=6.71$, $p < .001$
- Sleep Problems: $t(164)=6.17$, $p < .001$
- Forgetfulness and/or Brain Fog: $t(164)=9.84$, $p < .001$
- Difficulty with Speech/Writing: $t(164)=8.70$, $p < .001$
- Day Sweats and/or Night Sweats and/or Flushing: $t(164)=8.36$, $p < .001$

Figure 1: Means for Pre & DDS Symptom Severity

Horowitz, Freeman, International Journal of General Medicine 2019:12 101–119



Neurocognitive Deficits in PTLDS and Lyme-MSIDS

- In a recent 2018 study on cognitive decline in 124 patients with PTLDS, 92% of patients had some level of cognitive difficulty, yet 50% had no statistically or clinically relevant cognitive decline, & only 26% had significant cognitive decline on measures of memory
- In 165 patients with "Lyme-MSIDS" who reported their symptoms before DDS and on at least 6 months on DDS: almost 91 % of patients self-reported some level of cognitive difficulty (similar #'s) but the group w/ mod, mod severe, or severe cognitive impairment (forgetfulness/brain fog) was 3X higher at 78%.

- Touradji, P.; Aucott, J. N.; Yang, T.; Rebman, A. W.; Bechtold, K. T. Cognitive Decline in Post-treatment Lyme Disease Syndrome. Arch. Clin. Neuropsychol., doi:10.1093/arclin/acy051.

Neurocognitive Deficits in Lyme-MSIDS

Horowitz & Freeman: pre-publication 2018

- Despite multiple overlapping etiologies ↑ inflammation w/ immune dysfunction (72%), the DDS group w/ significant cognitive deficits statistically improved w/ p values < .001
- Success of DDS: good CNS penetration; antibacterial effects (stopping RNA and protein production by bacteria); works against a broad range of pathogens; efficacy against different forms of borrelia, including round body, stationary phase and biofilm forms
- Dapsone also has an anti-inflammatory effect, by converting myeloperoxidase (MPO) into its inactive prod.

- an Zyl, J. M.; Basson, K.; Kriegler, A.; van der Walt, B. J. Mechanisms by which clofazimine and dapsone inhibit the myeloperoxidase system: A possible correlation with their anti-inflammatory properties. Biochem. Pharmacol. 1991, 42, 599–608, doi:10.1016/0006-2952(91)90323-W.

Effect of Dapsone and its Antimicrobial Combinations on *Borrelia burgdorferi* Biofilms

[1]Amber Fearnley, [1]Khusali Gupta M. S. cand., [2]Phyllis R. Freeman Ph.D., [2]Richard I. Horowitz M.D. and [1]Eva Sapi Ph.D.
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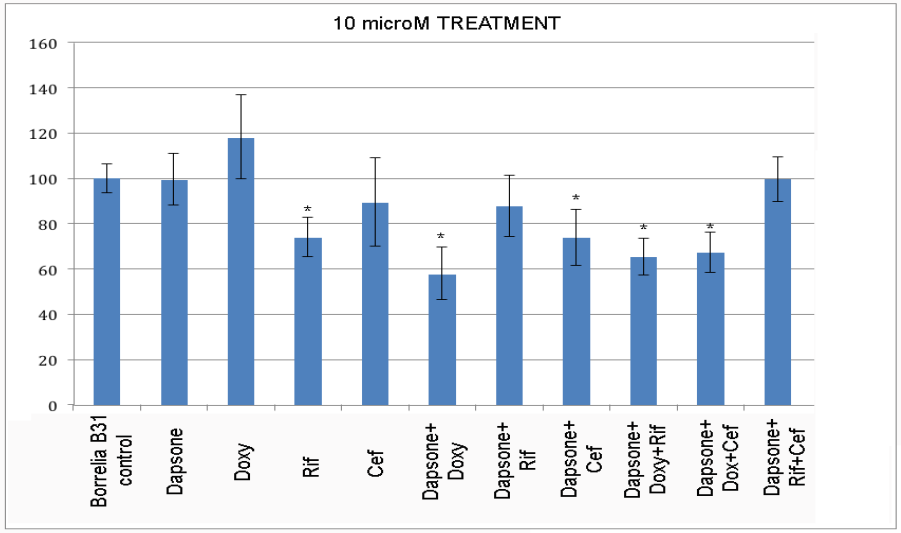
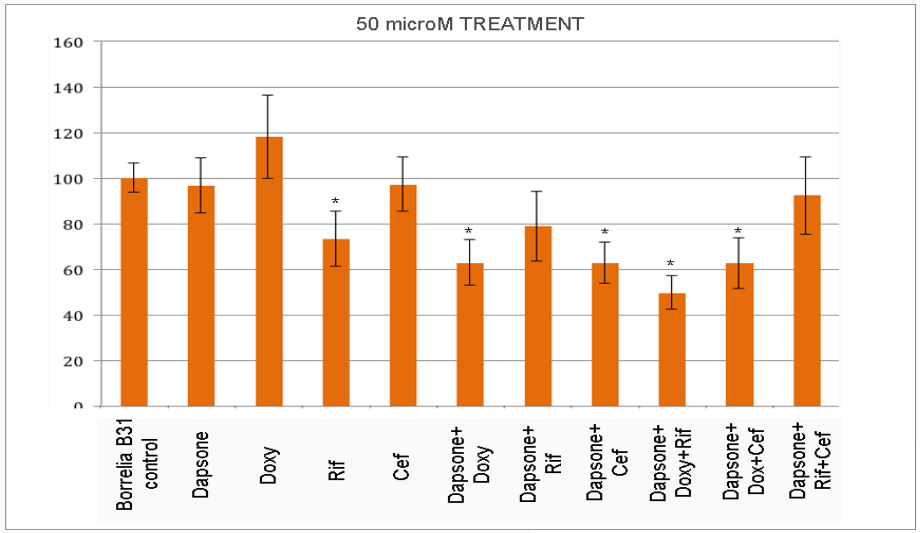
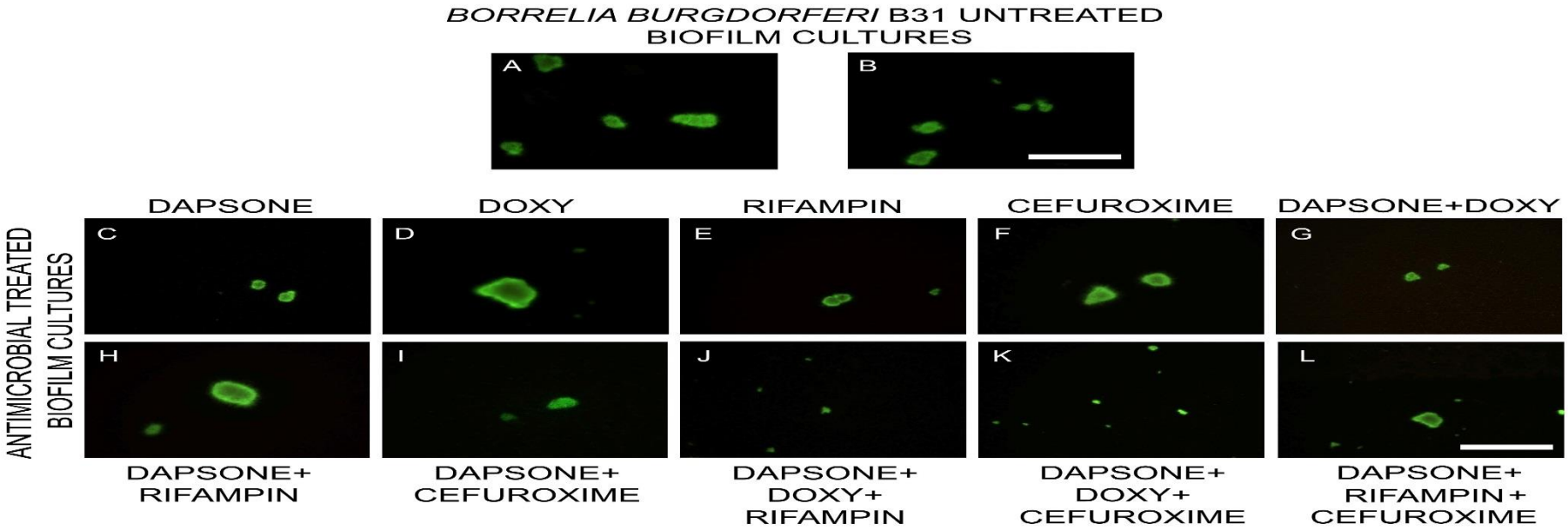






Dapsone: Prevent H.A.R.M.

- **H**erxheimer Reactions: can be severe. Use LDN, glutathione, detoxification support (alkalize, drainage remedies, clay/charcoal?). Use herbs & medication to lower inflammation. ? pulse Dapsone (28 hour ½ life), or start low (25 mg QOD, every other day) and work up to 100 mg/day, or the highest tolerated dose
- **A**nemia: Average: 3 gram drop Hb w/ 65 mg folic acid (Leucovorin 25 mg BID, + Folafy ER (15 mg of L-methylfolate). Watch for overmethylation
- **R**ashes: Dapsone is a sulfa drug. ? H1/H2 blockers (Zyrtec/Zantac 2 x per day)
- **M**ethemoglobinemia: check levels before/during tx

Is it Methemoglobinemia?

Shifting the Paradigm: The MSIDS Model

- **The Problem**: multiple inf's & environmental toxins ↑ A.I. manifestations & inflammation with epigenetic changes, immune dysfunction/immune deficiency
- Inflammation + downstream effects (i.e., HPA axis dysfunction, mitochondrial damage, autonomic neuropathy with POTS/dysautonomia) ↑ symptoms
- **Solution**: **↓ inflammation** (treat inf's, block NFK-B and NO), **↑ detoxification** (↑ Nrf2 pathway, drainage, GSH) **& repair damage: 4 R's**: Replace (hormones), Repair (mitochondria), Rebalance (ANS) and Reinoculate G.I. bact

- Nicolson GL, Nicolson NL, Haier J. Chronic Fatigue Syndrome patients subsequently diagnosed with Lyme Disease Borrelia burgdorferi: evidence for Mycoplasma species co-infections. J Chronic Fatigue Syndr. 2008; 14(4): 5-17.
- Nicolson,G., et al. Lipid Replacement Therapy with a Glycophospholipid Formulation with NADH and CoQ10 Significantly Reduces Fatigue in Intractable Chronic Fatiguing Illnesses and Chronic Lyme Disease Patients. International Journal of Clinical Medicine, 2012, 3, 163-170: Cimmino MA, Trevisan G. Lyme arthritis presenting as adult onset Still's disease. B Clin Exp Rheumatol. May-June 1989;7(3):305-308.

How Can We Improve Patient's Health?

Treat Primary Sources of Inflammation

- Chronic Infections (borrelia, bartonella, + other IC bacteria, parasites like Babesia), biofilm forms/"persisters"
- Environmental toxins and detoxification problems (nutritional deficiencies, inadequate glutathione)
- G.I.: leaky gut/food allergies/dysbiosis
- Sleep disorders

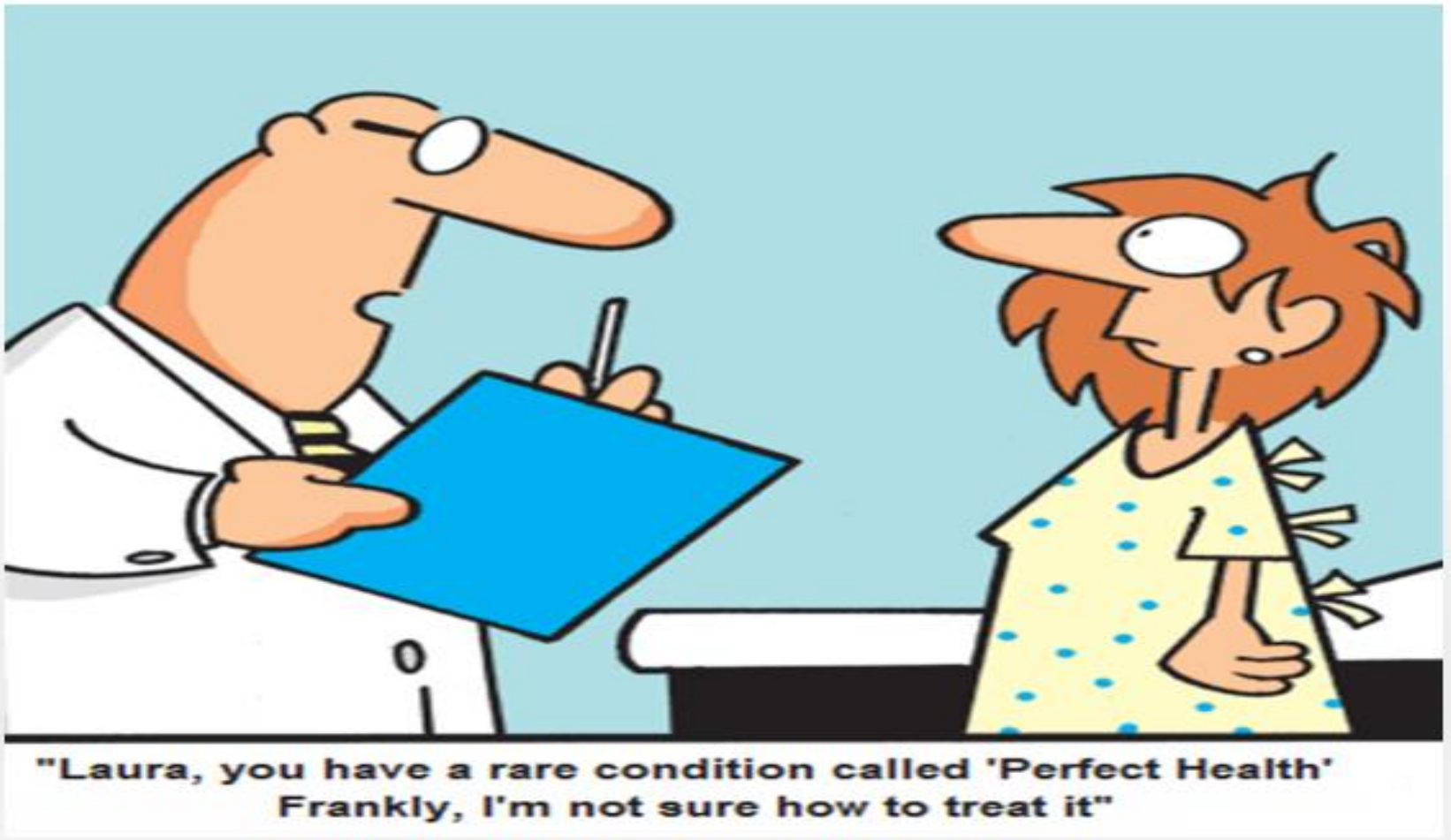
Moldofsky H. Sleep and the immune system. Int J Immunopharmacol 1995;17:649-54

Treat Downstream Effects of Inflammation

- Autoimmune phenomenon with pain (DMARDS, IVIG)
- ↑ production of cytokines (↓NFKB, NO): LDN, ↑NrF2 activation (antioxidants)
- Remove cytokines, neurotoxins (quinolinic acid, NH3..)
- Repair mitochondrial function
- Replace hormones (↓ HPA axis)
- Treat POTS/dysautonomia

Karas B., et al. The Postural Orthostatic Tachycardia Syndrome: A Potentially Treatable Cause of Chronic Fatigue, Exercise Intolerance, and Cognitive Impairment in Adolescents. PACE 2000; 23:344-351

The Future of Medicine: Shift the Paradigm to a Personalized, Precision Multifactorial Model



Thank You: BAL, MRF & Staff HVHAC

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