Effective Diagnosis & Treatment of the Chronically Ill Lyme Patient

Environmental Health Symposium

Scottsdale, AZ

April 3rd 2020

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Disclaimer/Conflicts of Interest

- **Conflicts of Interest:**
- 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

Healing: Compassionate Empathetic Attuned Presence: Matt Liotta PhD

Decety, J. Why empathy has a beneficial impact on others in medicine: unifying theories. Front Behav Neurosci, 2014;8:457

Why Do We Get Sick?

- **1. Environment**: Numbers of cases are increasing in part because of changes in predators for small mammals like the white footed mouse (↓ foxes), and building homes in parcels near wooded areas
- **2. Effects of Climate change:** ticks are emerging 3 weeks earlier, & new species are appearing
- **3. Ticks**: types of ticks with different infections are spreading across states and countries due to migratory birds (ex: Lone Star tick, Asian Bush tick)

- Levi T, et al. 2015 Accelerated phenology of blacklegged ticks under climate warming. Phil. Trans. R. Soc. B 370: 20130556; Scott JD. et al. Prevalence of the Lyme Disease Spirochete, Borrelia burgdorferi, in Blacklegged Ticks, Ixodes scapularis at Hamilton-Wentworth, Ontario. I Int J Med Sci. 2016 Apr 10;13(5):316-24.; Longhorned Tick in CT, WCSU, Sept 2018

Why Do We Get Sick?

- **4. Infections**: ↑ numbers of species of borrelia and co-inf's are being found in ticks (bacteria, parasites,viruses)
- **5. Modes of Tick-borne Transmission are Increasing**: B. miyamotoi is the first species with transovarial transmission (6-73%) + larval transmission→ ↑ human infection
- **6. Modes of Human Transmission are Increasing**: Blood transfusion (↑ #'s, types of inf's), solid organ transplantation, maternal/fetal transmission (for borrelia and co-infections), sexual transmission?

- *Krause,P. et al. Borrelia miyamotoi: The Newest Infection Brought to Us by Deer Ticks. Ann Intern Med. 2015;163(2):141-142;*

Tick-borne Diseases & Pregnancy:

Lyme, RF, Babesia, Anaplasma, Ehrlichia, RMSF, Bartonella

Horowitz, R., Freeman P. Healthy Fetal Outcomes using a Novel Treatment for Maternal Lyme Disease and Babesiosis During Consecutive Pregnancies: A Case Study and Literature Review. Arch Med Case Rep. 2020; 2(1): 1-19.

SCIENTIFIC ARCHIVES.COM

https://www.scientificarchives.com/journal/archives-of-medical-case-reports

Archives of Medical Case Reports | Case Report

Healthy Fetal Outcomes using a Novel Treatment for Maternal Lyme Disease and Babesiosis During Consecutive Pregnancies: A Case Study and Literature Review

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Received date: December 05, 2019, **Accepted date:** January 02, 2020

Why Do We Get Sick?

- **7. Diagnostics**: tests lack adequate sensitivity for early and late infection. Leads to improper diagnoses (CFS/ME, FM, A.I. dx & Neuropsychiatric disease w/dementia)
- **8. Persistence**: Borrelia can persist despite seemingly "adequate" antibiotics. "Persisters" have also been reported with Babesia, & multiple IC bacteria: Bartonella, Mycoplasma, Tularemia & Brucella→ chronic disease
- **9. 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
- Abraham A, et al. Establishment of a continuous in vitro culture of Babesia duncani in human erythrocytes reveals unusually high tolerance to recommended therapies. J Biol Chem. 2018 Dec 28;293(52):19974-19981.

The 3 I's in Chronic Disease: Infection, Inflammation, Immune Dysfunction

- **The common denominator underlying various etiologies on the MSIDS map: multiple sources of inflammation (infections, environmental toxins): ↑ inflammation→ A.I. reactions, damages cells**
- **These agents create inflammation through various pathways (NFK-B, NO): ↑ IL-1, IL-6, TNF-α, IL-17. This creates free radicals and oxidative stress which damages cell membranes, mitochondria, nerve cells**

- Anaya JM, et al (2016) The Autoimmune Ecology. Front. Immunol. 7:139.
- Borgermans, L., Relevance of Chronic Lyme Disease to Family Medicine as a Complex Multidimensional Chronic Disease Construct: A Systematic Review Intl Jnl Fam Med, Volume 2014 (2014)
- Nicolson G., et al. Neurodegenerative and Fatiguing Illnesses, Infections and Mitochondrial Dysfunction: Use of Natural Supplements to Improve Mitochondrial Function. Functional Foods in Health and Disease 2014; 4(1):23-65

The 3 I's in Chronic Disease

- Some infectious agents also produce neurotoxins (Quinolinic Acid..) and other toxic by-products
- Autoimmunity may also result from antibodies produced against these agents that cross react with our own tissue antigens (molecular mimicry) + TLR-2 activation by bacteria ↑ TNF-alpha, IL-17
- **The same biological effects are seen in multiple disease processes**: Lyme Disease, CFS/M.E., FM, E.I., ASD, Alzheimer's Disease and AI disorders (SLE, RA, MS),

- Allen HB, et al (2015) Autoimmune Diseases of the Innate and Adaptive Immune System including Atopic Dermatitis, Psoriasis, Chronic Arthritis, Lyme Disease, and Alzheimer's Disease. Immunochem Immunopathol 1: 112;
- Alaedini, A., et al. "Antibodies against OspA epitopes of Borrelia burgdorferi cross- react with neural tissue." J Neuroimmunol 159 (2005): 192–95

Infections & Toxins ↑ Inflammation & Underlie ↑ in Chronic Diseases

Horowitz, R., Arch Med Case Rep 2019, Vol 1, Issue 1

SCIENTIFIC ARCHIVES.COM

https://www.scientificarchives.com/journal/archives-of-medical-case-reports

Archives of Medical Case Reports | Short Communication

The Global Rise of Chronic Diseases: Why Broaden the Paradigm to Include Tick-borne Illness and Environmental Toxin Exposure?

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Received date: November 22, 2019, **Accepted date:** December 03, 2019

The Global Rise in Chronic Disease

- The incidence of chronic diseases is rapidly increasing worldwide.
- In 2001, chronic diseases contributed to approximately 46% of the global burden of disease and 60% of the total reported deaths
- By 2020, that number expected to increase to 57%, when chronic diseases will account for almost 75% of all deaths worldwide

- Murray CJL, Lopez AD, Organization WH, Bank W, Health HS of P. The Global Burden of Disease : A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020 : Summary. World Health Organization;

The Global Rise in Lyme & TBD's

- There has also been a global spread of Lyme & TBD's: The CDC reported a 300% increase in the number of US counties affected by LD w/ record numbers of new cases of tick-borne diseases between 2015-18
- During this time, 7 new inf's were reported: ***Borrelia mayonii***, ***Borrelia miyamotoi***, ***Ehrlichia ewingii***, ***Ehrlichia muris eauclairensis***, ***Heartland virus***, ***Rickettsia parkeri***, and ***Rickettsia species 364D***

- Kugeler KJ, Farley GM, Forrester JD, Mead PS. Geographic Distribution and Expansion of Human Lyme Disease, United States. Emerging Infect Dis. 2015;21(8):1455-1457
- How many people get Lyme disease? | Lyme Disease | CDC. https://www.cdc.gov/lyme/stats/humancases.html. Published February 13, 2018.
- CDC. Prevention is key in fight against Lyme and other tickborne diseases. Centers for Disease Control and Prevention. https://www.cdc.gov/ticks/. Published April 22, 2019.

The Global Rise of Environmental Toxins

- The CDC's 2003 initial 6.5-million-dollar study evaluated more than 116 different environmental toxins and found a significant % of Americans affected
- An updated report measured 212 toxins: blood and urinary levels of heavy metals (mercury, arsenic and lead), 30 different solvents, acrylamides, bisphenol A, phthalates, chlorinated and organophosphate pesticides and aromatic hydrocarbons

- Stephenson J. CDC Report on Environmental Toxins. JAMA. 2003;289(10):1230-1233.
- Crinnion WJ. The CDC fourth national report on human exposure to environmental chemicals: what it tells us about our toxic burden and how it assist environmental medicine physicians. Altern Med Rev. 2010;15(2):101-109.

Data Mining of MSIDS Variables: Environmental Toxins

- **Heavy Metals: 84.5% had one or more heavy metals using a 6-hour urine DMSA challenge**
- 159 (79.5%) had ↑ lead levels (73 were ↑, 59 were very high)
- 136 (68%) had ↑ mercury levels (77 were ↑, 59 were very high)
- 30 (15%) had ↑ cadmium levels (26 were ↑, and 4 were very ↑)
- 25 (12.5%) had ↑ aluminum levels (N=25 were elevated)
- 5 (2.5%) had ↑ arsenic levels (3 were elevated, and 2 were very elevated)

- Clarkson, T. W.; Magos, L. The toxicology of mercury and its chemical compounds. Crit. Rev. Toxicol. 2006, 36, 609–662
- Horowitz, R.I.; Freeman, P.R. 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. Healthcare 2018, 6, 129.

Data Mining of MSIDS Variables: Exposure To Mold Toxins > 70%

- **Mold: 30/42 (71.4%) had 1 or more ↑ mold levels**
- 13/25 (52%) had elevated aflatoxins: RealTime Labs, urine mycotoxin
- 18/26 (69%) had elevated ochratoxins: RealTime Labs urine test
- 20/26 (76.9%) had elevated trichothecenes: RealTime Labs urine test
- 17/17 (100%) had elevated gliotoxins: RealTime Labs urine test
- **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 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.
- Horowitz, R.I.; Freeman, P.R. 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. Healthcare 2018, 6, 129.

Interactions Between ↑ TBD's & Environmental toxins: ↑ Inflammation

- Both infections & toxins may ↑ an inflammatory response in the body & evidence suggests a close link between inflammation and chronic health conditions:
- Diabetes, Metabolic syndrome,Cardiovascular disease
- Cancer
- Rheumatoid arthritis, inflammatory bowel disease
- Asthma and COPD

- Signore A. About inflammation and infection. EJNMMI Res. 2013;3:8.
- Thompson PA, Khatami M, Baglole CJ, et al. Environmental immune disruptors, inflammation and cancer risk. Carcinogenesis. 2015;36(Suppl 1):S232-S253.
- Zhong J, Shi G. Editorial: Regulation of Inflammation in Chronic Disease. Front Immunol. 2019;10.

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

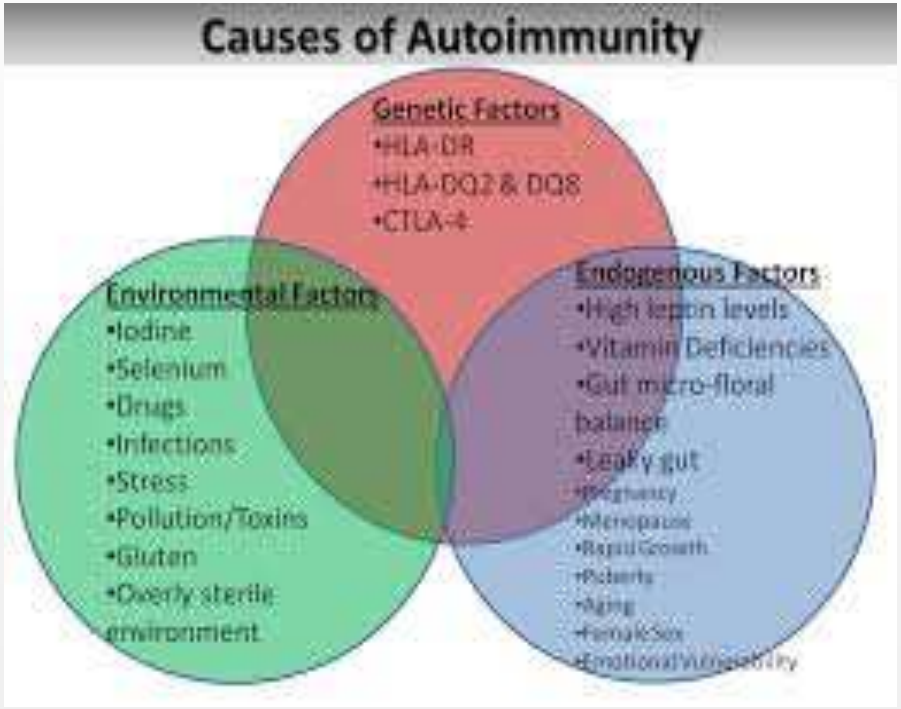
Horowitz, R.I. et al. Precision Medicine: The Role of the MSIDS Model in Defining, Diagnosing, and Treating Chronic Lyme Disease/PTLDS and Other Chronic Illness: Part 2. Healthcare 2018, 6, 129.

- **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.

Overlapping Causes of Autoimmunity Are On the MSIDS Map

- Genetic Factors: HLA
- Endogenous Factors:
- Vitamin D deficiency
- Microbiome imbalance
- Leaky Gut
- Hormonal factors
- Environmental Factors:
- Infections (Borrelia, Bartonella..)
- Pollution/Toxins: Hg, BPA, asbestos, small particle pollution→ A.I. rxn



- Cooper, GS et al. Occupational risk factors for the development of systemic lupus erythematosus. (2004) J Rheumatol 31: 1928–1933
- Pfau J, et al "Autoimmunity and asbestos exposure" Autoimmune Dis 2014
- Can Prevotella copri Be a Causative Pathobiont in Rheumatoid Arthritis? Donghyun Kim, et al. ARTHRITIS & RHEUM, Vol. 68, No. 11, November 2016, pp 2565–2567
- Mangin et al. Inflammation and Vit D, The Infection Connection. Inflamm. Res. (2014) 63:803–819

7 Point Action Plan for Lyme-MSIDS:

Horowitz, R. How Can I Get Better? St Martin's Press 2017

- Rule One: Symptoms Drive Diagnosis and Treatment
- Rule Two: Lower Inflammation. ? Persister drug tx
- Rule Three: Detoxify, Detoxify, Detoxify
- Rule Four: Repair the Damage
- Rule Five: Provide Internal Balance:
  Cytokines, Hormones, Microbiome
- Rule Six: Master the Big Three:
  Sleep, Food, and Exercise
- Rule Seven: Heal Your Emotional Wounds

Initial History & Physical

- **Initial visit**: fill out the Horowitz MSIDS questionnaire (HMQ) to determine the probability of Lyme and associated tick-borne disease
- **Do a complete History and Physical** with CC's, PMH & current symptoms, defining severity & frequency
- **Social history, Family history**
- **Environmental history** (? Mold ? Chem exposure)
- **Review of Systems & Physical examination**
- **Differential Diagnosis and Testing**

- Empirical Validation of the Horowitz Multiple Systemic Infectious Disease Syndrome Questionnaire for Suspected Lyme Disease. Maryalice Citera1¶*, Ph.D., Phyllis R. Freeman2¶, Ph.D., Richard I. Horowitz2¶, M.D., International Journal of General Medicine 2017:10 249–273

Six Signs That Your Aches and Pains May be Due to Lyme Disease

- 1. **You have more than one symptom**: Lyme disease is a multisystemic illness. Classic constellation of symptoms: fatigue, pain, insomnia, cognitive problems, depression..
- 2. **Symptoms c + g with good & bad days**
- 3. **Your pain migrates around your body** (migratory joint, muscle & nerve pains that come and go and migrate are classic for Lyme!)

- Rebman A., et al. The Clinical, Symptom, and Quality-of-Life Characterization of a Well-Defined Group of Patients with Posttreatment Lyme Disease Syndrome. Front. Med. 4:224. 14 Dec 2017

Six Signs that Your Aches and Pains may be due to Lyme Disease

- 4. **Women: symptoms tend to worsen right before, during, and after the menstrual cycle** (hormonal changes affect symptoms)
- 5. **Symptoms worsen or improve after antibiotic therapy** (for Lyme or an unrelated infection like a urinary tract infection). Worsening of symptoms: ? Herxheimer reaction (JH reaction), killing off of spirochetes with inflammatory cytokine release: TNF-alpha, IL-1, IL-6, 8

- Kaplanski G, Granel B, Vaz T, Durand JM (July 1998). "Jarisch–Herxheimer reaction complicating the treatment of chronic Q fever endocarditis: elevated TNFalpha and IL-6 serum levels". J. Infect. 37 (1): 83–4.

Six Signs that Your Aches and Pains may be due to Lyme Disease

- 6. You have positive blood tests for Lyme and associated tick-borne diseases
- The tests are not reliable (ELISA, Western blot)
- Different strains of Borrelia: →*Borrelia burgdorferi ss, B. mayonii. B. bisettii* (USA, Europe, North Africa), *Borrelia afzelii* (Europe, Asia) *Borrelia garinii* (Europe, Asia, North Africa), *Borrelia valaisiana*, *Borrelia lusitaniae* (Portugal, Italy, North Africa): vasculitis, *Borrelia spielmanii* (Holland, Germany, Hungary, Slovenia)
- 5 bands on the Western Blot are specific for Bb:
- 23 (Osp C), 31 (Osp A), 34 (Osp B), 39, 83-93
- Ma et al: Serodiagnosis of Lyme Borreliosis by Western Immunoblot. Jnl of Clin Microbiology, Feb. 1992, p. 370-376; Horowitz, R.I., Freeman PR. International Journal of General Medicine 2019:12 101–119

Empirical Validation of the Horowitz MSIDS Questionnaire for Suspected Lyme Disease

Citera M, Freeman PR, Horowitz RI. International Journal of General Medicine 2017:10 249–273. http://www.ncbi.nlm.nih.gov/pubmed/28919803

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

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

Validation of the MSIDS Questionnaire

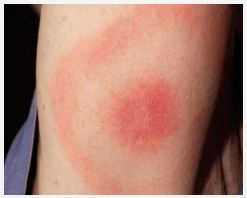
Citera, Freeman, Horowitz, RI. International Journal of General Medicine 2017:10 1–25

- **Purpose of this study**: evaluate the HMQ designed by Dr. Richard Horowitz as an initial screening tool for Lyme and other tick-borne co-infections. Is it reliable and valid?
- **Data were collected from two independent samples:** **1600** patients from medical practices specializing in treating Lyme and healthy individuals recruited through email and social media to complete an online survey

The Horowitz Multiple Systemic Infectious Disease Syndrome Questionnaire (HMQ)

Section 1: The Symptom Checklist: 38 symptoms rated from 0 (none) to 3 (extremely frequent)

Section 2: The Lyme Incidence scale: items related to the likelihood of having Lyme, & migratory symptoms



Section 3: The Healthy Days Scale: contains 2 items about the individual's overall health (physical and mental health) over the last 30 days

Section 4: The Common Lyme Score: awards points for the most common Lyme symptoms

- A score > 63: high likelihood of exposure
- Especially if "migratory" pain is present

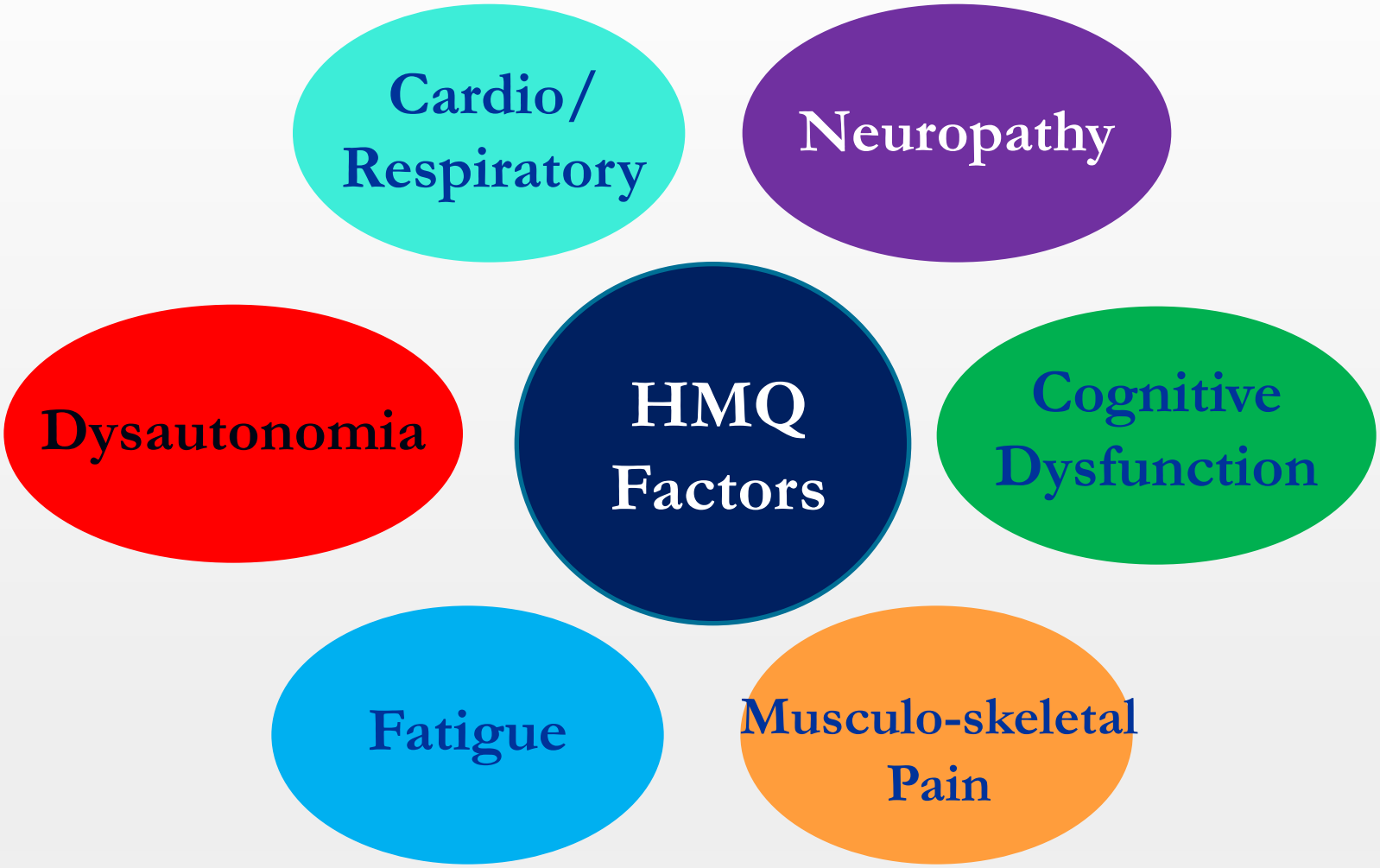
Differential Diagnosis Migratory Pain

Horowitz et al: International Journal of General Medicine 2017:10 1–25
See: Table 11 MSIDS differential diagnosis of migratory pain

- Acute Rheumatic Fever: ASO, anti-DNAase Ab
- Crohn's Disease/Inflammatory Bowel Disease: colonoscopy, calprotectin (IBD)..
- Gonococcal Arthritis:

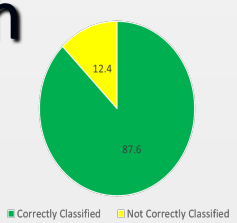
Check for triad: suppurative arthritis, tenosynovitis and dermatitis

- Hepatitis (A, B, C, D, E): check viral Abs', PCR, RNA
- Reactive Arthritis (Salmonella, Yersinia, Chlamydia species…, HLA B 27+): Reiters triad
- SLE (Lupus): dsDNA, Smith Ag
- Lyme Disease: **this is the only disease with migratory nerve pain!**


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

Validation of the MSIDS Questionnaire

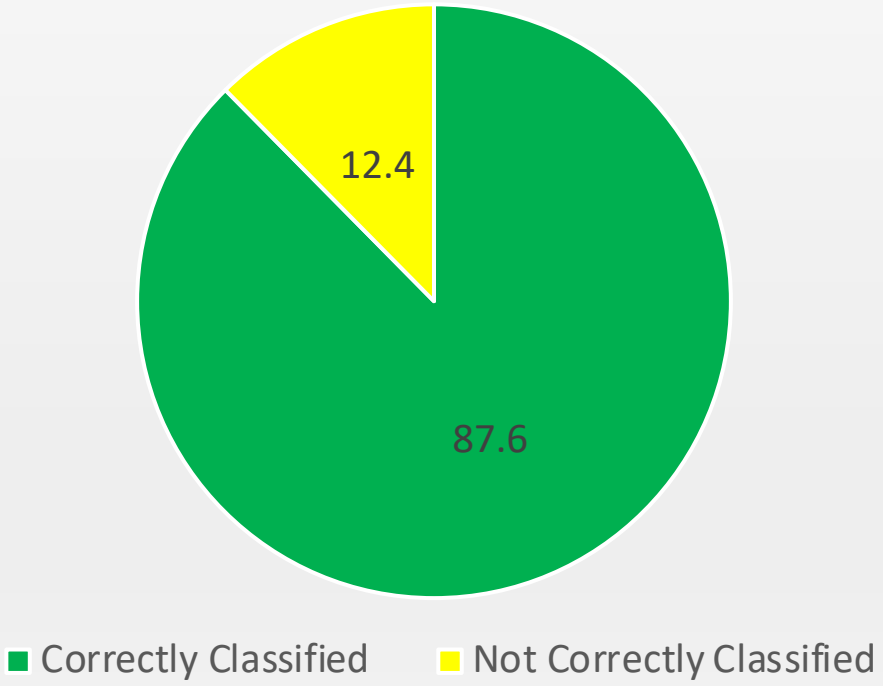
- **5 factors consistent with LD**: fatigue, flu like symptoms, joint stiffness, tingling, concentration problems (1600 individuals, 3 medical practices)
- Migratory joint/muscle/nerve pain was significant!
- Demonstrated convergent and divergent construct validity, as well as predictive validity. Discriminant analysis showed we could accurately classify the Lyme Status: 87% accuracy
- Conclusion: A score > 63 on the HMQ confers a high probability of LD; Between 45-62 (probable), 25-44 (possible). Healthy individuals scored below 24



- Q's 1 +22 on the HMQ indicate possible co-inf w/ Babesia

- Empirical Validation of the Horowitz Multiple Systemic Infectious Disease Syndrome Questionnaire for Suspected Lyme Disease. Maryalice Citera, Ph.D., Phyllis R. Freeman, Ph.D., Richard I. Horowitz, M.D., International Journal of General Medicine 2017:10 249–273

Discriminant analysis also showed we could accurately classify the Lyme Status of individuals using their HMQ scores: Overall accuracy was 87.6%



To Test or Not to Test? That is the Question…

Horowitz, R.I. et al. Clin Microbiol & Infection, 10 October 2017

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis

Dessau *et al.* [1], in their analysis of testing for Lyme borreliosis, address important testing issues for borreliosis testing, but several problems with establishing a diagnosis remain. Formal serology in patients presenting with presumptive Lyme disease symptoms is not sufficient to definitively rule out Lyme disease for the following reasons.

First, positive serology can be delayed in early Lyme or remain negative in late Lyme disease [2]. This may be explained by inherent limitations of the tests (lack of 100% sensitivity), where a proper comparative study between an established Lyme disease population and a negative control group is mandatory.

Second, many serotypic variants of *Borrelia* species exist which may vary on a regional scale, and which differ regarding their clinical manifestations (*Borrelia garinii* and neuroborreliosis, for example). Some of those species could not be detected by commercial serology test kits [3].

Third, false-negative serologic results could be attributed to antibiotic therapy, the sequestration of *Borrelia* antibodies in immune complexes and/or location within the intracellular compartment, with inactive cystic forms of *Borrelia* [4].

Finally, the European Centre for Disease Prevention and Control reported a sensitivity of the enzyme immunoassay/immunoblot of 0.77 (95% confidence interval, 0.67–0.85) in the diagnosis of neuroborreliosis, and warned that the results should be interpreted with

References

[1] Dessau RB, van Dam AP, Fingerle V, Gray J, Hovius JW, Hunfeld K-P, et al. To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis: a position paper of ESGBOR, the ESCMID study group for Lyme borreliosis. Clin Microbiol Infect. 2018;24:118–24.
[2] Alby K, Capraro GA. Alternatives to serologic testing for diagnosis of Lyme disease. Clin Lab Med 2015;35:815–25.
[3] Cook MJ, Puri BK. Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. Int J Gen Med 2016;9:427–40.
[4] Schutzer SE, Coyle PK, Belman AL, Golightly MG, Drulle J. Sequestration of antibody to *Borrelia burgdorferi* in immune complexes in seronegative Lyme disease. Lancet 1990;335:312–5.
[5] Leeflang MM, Ang CW, Berkhout J, Bijlmer HA, Van Bortel W, Brandenburg AH, et al. The diagnostic accuracy of serological tests for Lyme borreliosis in Europe: a systematic review and meta-analysis. BMC Infect Dis 2016 Mar 25;16:140.
[6] Bil-Lula I, Matuszek P, Pfeiffer T, Woźniak M. Lyme borreliosis—the utility of improved real-time PCR assay in the detection of *Borrelia burgdorferi* infections. Adv Clin Exp Med 2015;24:663–70.

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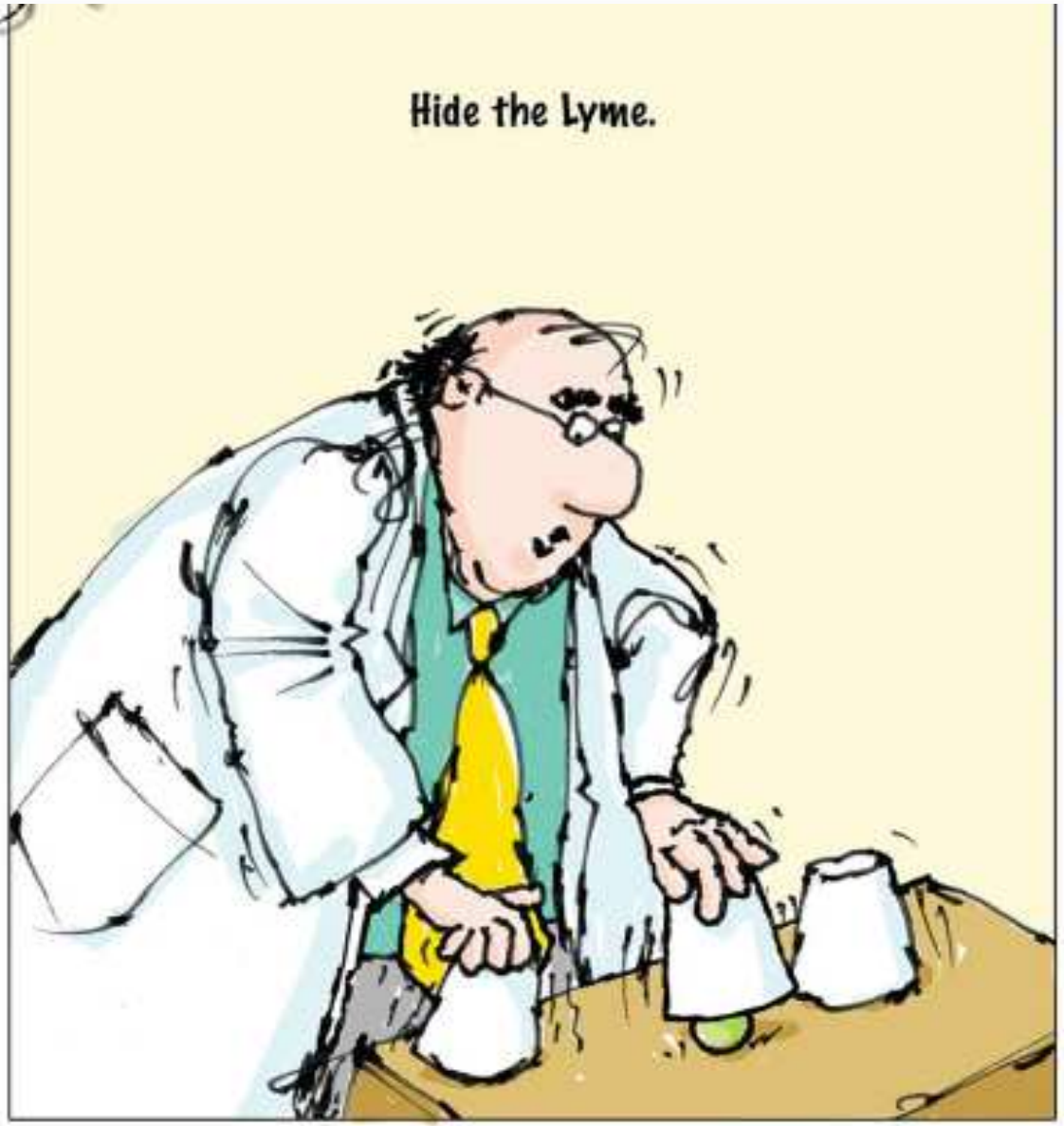
Problems with Diagnostic Testing



Testing for Lyme Disease

- The mean sensitivity for all tests and for all samples was 59.5% and 53.7% when the two-tier methodology was used (Puri, Cook)
- The two-tier test generated over 500 times more false-negative results than two-stage HIV testing
  - Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. Cook, MJ, Puri, BK. Int J Gen Med. 2016 Nov 18;9:427-440
  - Application of Bayesian decision-making to laboratory testing for Lyme disease and comparison with testing for HIV. Cook, MJ, Puri, BK. Int J Gen Med 2017:10 113-123
- Serology changes over time:
  - Variable manifestations, diverse seroreactivity and post-treatment persistence in non-human primates exposed to Borrelia burgdorferi by tick feeding. Embers, M. et al. PLoS ONE 12(12): e0189071. https://doi.org/10.1371/journal.pone.0189071

Problems with Diagnostic Testing

- **1)Intra & Inter-laboratory Variation**

  Marangoni J Med Microbiol 2005: 3 different commercial Elisa tests showed discrepant results. Sensitivity for the same sera 36,8% to 70.5%

  De Marteno Med Mal Infect 2007: Compared 14 Elisa test kits for the diagnosis of neuro Lyme. Sensitivity varied from 20.9% -97.7%

- **2) Different species of Borrelia:**

  Rudenko FEMS Microbiol Letter 2009 ; Lopes de Carvalho Clin Rheumatol 2008

- **3) Problems w/ 2 -Tiered Testing in Early Lyme: CDC two tiered testing missed up to 55% of positive Lyme cases**

  I Coulter,et al.,*J Clin Microbiol* 2005;43:5080-5084. CDC correspondance with NYS DOH

- **4) Sensitivity/Specificity of Commercial Two-Tier Testing for Lyme Disease=56%/99%**

  Stricker and Johnson BMJ 2007; 335:1008; The mean sensitivity for all tests and for all samples was 59.5% and 53.7% when the two-tier methodology was used (Puri, Cook)

What Are Other Problems w/ Testing? Immune Complexes/Immune Evasion

- **5. Failure to detect Antibodies:** Circulating immune complexes, ↓ ability to find AB's in the spinal fluid of Lyme patients w/ significant CNS dx.

  Coyle, et al. Detection of Bb antigens in CSF. Neurology 1993;43:1093-1097; Schutzer SE et al. Sequestration of antibody to Borrelia burgdorferi in immune complexes in seronegative Lyme disease. Lancet. 1990 Feb 10;335(8685):312-5;

- **6. Borrelia subverts a B cell response** (which produces antibodies), leading to T cell independence: Baumgarth et al. PLoS Pathog 7(5): e1002066. doi:10.1371/journal.ppat.1002066

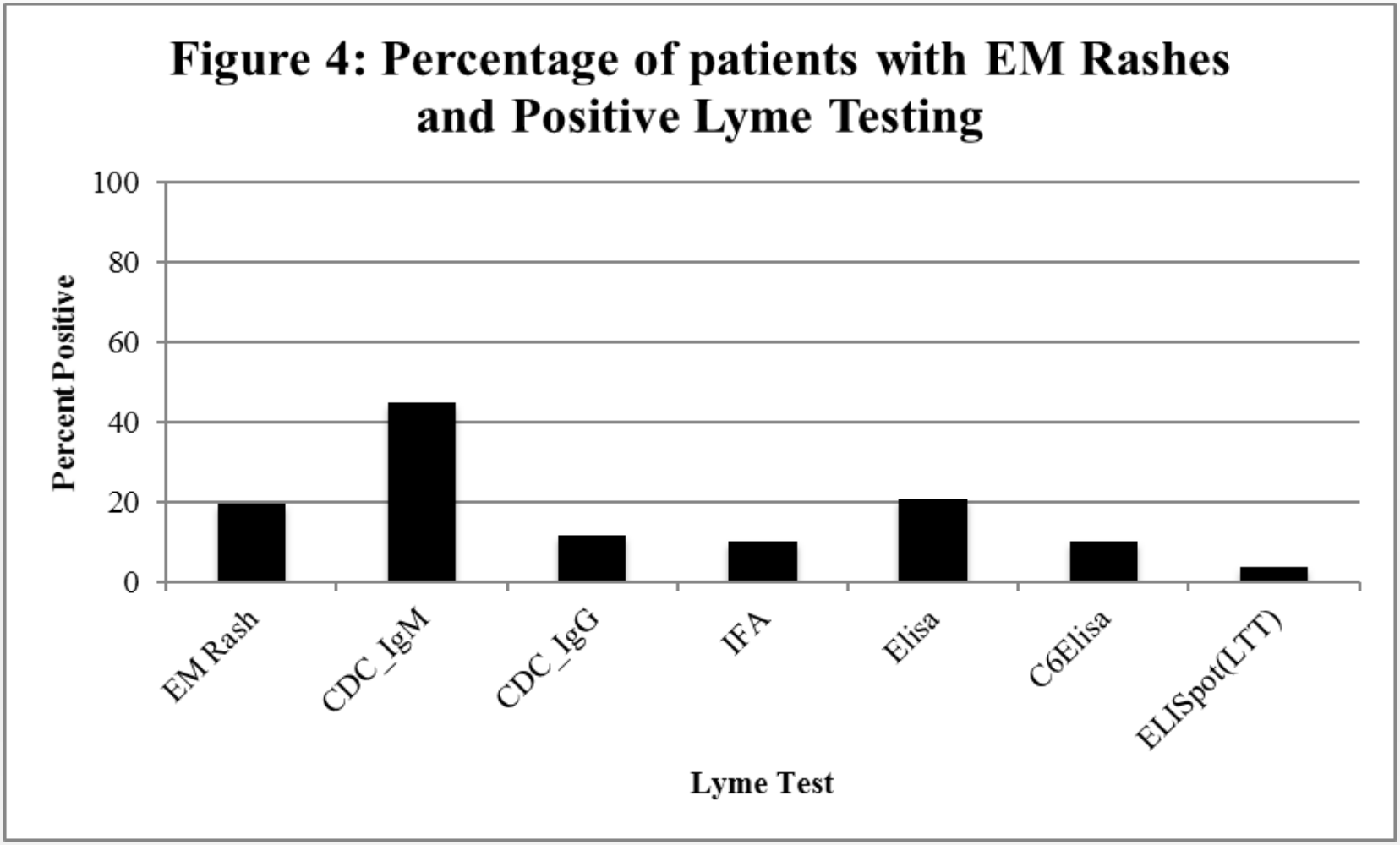
- **7. Bb Has the Ability to Evade The Immune System:** Long replication time, changes outer surface proteins, cloaking→Bb surrounds itself w/ the body's lymphocytic proteins, ↓ immune recognition: Dorward, et al. Jounal of Clin Microbiol 1991;29:1162-70; Berndtson, Review of evidence for immune evasion and persistent infection in Lyme disease. International Journal of General Medicine 2013:6 291–306

Problems with LD Two-Tiered Testing

- I Schutzer SE, Coyle PK, Belman AL, Golightly MG, Drulle J. Sequestration of antibody to Borrelia burgdorferi in immune complexes in seronegative Lyme disease. Lancet. 1990 Feb 10;335(8685):312-5;
- Marangoni, A. et al. Comparative evaluation of three different ELISA methods for the diagnosis of early culture-confirmed LD in Italy. J. Med. Microbiol. 54, 361-367 (2005);
- Ang, C.W.,et al. T. Large differences between test strategies for the detection of anti-Borrelia antibodies are revealed by comparing eight ELISAs and five immunoblots. Eur. J. Clin. Microbiol. Infect. Dis. 30, 1027-1032 (2011).
- Cook MJ, Puri BK. Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. Int J Gen Med. 2016 Nov 18;9:427-440. eCollection 2016.
- Cook MJ, Puri BK. Application of Bayesian decision-making to laboratory testing for Lyme disease and comparison with testing for HIV. Int Jnl of Gen. Medicine 2017:10 113–123
- Embers 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.
- Horowitz, R.I., Freeman PR. 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. International Journal of General Medicine 2019:12 101–119

Percentage of Patients with EM Rashes & Positive Lyme Testing

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



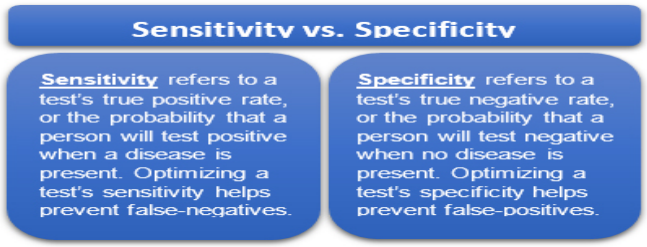
Diagnostics: Key Points

- Panel Approach is best. Do Indirect & Direct tests after establishing a clinical diagnosis (HMQ score)
- Indirect tests: IFA, ELISA, C6 ELISA, W. Blot, EIA's Immunoblot (IgeneX),LTT [Elispot], iSpot, Spirotest
- Direct tests: PCR, FISH [RNA], culture, Nanotrap
- Key: Look for borrelia specific bands on the W. Blot: **23** kda (Osp C), **31** (Osp A), **34** (Osp B), **39**, **83-93** kda. 1-2 borrelia specific bands in the right clinical setting helps make the diagnosis: 'Lyme Bingo'

- Sedegah M. The Ex Vivo IFN-γ Enzyme-Linked Immunospot (ELISpot) Assay Methods Mol Biol. 2015;1325:197-205; Sapi E, et al. Improved Culture Conditions for the Growth and Detection of Borrelia from Human Serum. Int J Med Sci 2013; 10(4):362-376.

Panel Approach: Indirect Tests for Lyme Disease

ELISA Test	WESTERN Blot/Immunoblot Test	IFA (Immunofluorescence Assay)	LTT (ELISPOT) & SPIRO Test	C6 ELISA
Detects IgM and/or IgG antibodies	Detects IgM & IgG antibodies W blot (IgeneX): 297. B31 Immunoblot: B sensu lato spp.	Detects IgM, IgG & IgA antibodies	Spirotest is being evaluated at Columbia; based on work at Johns Hopkins	**Sensitivity – 88%**
Most commonly used screening test for primary diagnosis, despite significant limitations	Generally more sensitive & specific than ELISA	Antibodies are detected 2-3 weeks after infection	Soloski MJ, Crowder LA, Lahey LJ, Wagner CA, Robinson WH, et al. (2014). PLoS ONE 9(4): e93243.http://doi.org/10.1371/journal.pone.0093243	**Standard ELISA Sensitivity - 52%**
Many ins providers require these tests to be ordered first Unreliable as screening test	Lab may be able to report if findings are consistent with early, late, persistent and/or recurrent disease	May remain elevated for a long time in some patients	Sensitivity – 84% Specificity -- 94% (Lehman PV et al.: Unique Strengths of ELISPOT for T Cell Diagnostics. In: Kalyuzhny AE. Handbook of ELISPOT: Methods and Protocols, Methods in Molecular Biology, Vol. 792. 2nd Ed: Springer; 2012: 3-23)	**Performance of United States Serologic Assays in the Diagnosis of Lyme Borreliosis Acquired in Europe** Clinical Infectious Diseases (2013) 57 (3): 333-340 John A. Branda, Franc Strle, Klemen Strle, Nikhil Sikand, Mary Jane Ferraro, Allen C. Steere
Misses 35% of culture proven Lyme Disease	**20-30% of acute culture-proven Lyme disease remain seronegative on western blot sampling**		LTT already being used in clinical practice	
52% of patients with chronic Lyme disease are negative by ELISA but positive by Western blot	Including highly specific bands 31 and 34, which are not generally reported by commercial labs			



Direct Tests for Lyme Disease

Lyme PCR	LDA/Lyme Dot Blot Assay	CULTURE Test & NANOTRAP Test
Detects the genomic & plasmid DNA of the Lyme bacteria	Detects antigens of Lyme bacteria in urine samples & cerebral spinal fluid/CSF	
Can be performed on whole blood, serum, urine, breast milk, skin & CSF	Can be useful when initial Lyme panel tests on blood samples are negative (including PCR) but symptoms for Lyme disease are present	NANOTRAP is urine antigen test
Increased specificity to ID unusual strains of B. burgdorferi	Cross reactions may occur with other non-Lyme antigens so use caution	Application of Nanotrap technology for high sensitivity measurement of urinary outer surface protein A carboxyl-terminus domain in early stage Lyme borreliosis. Magni et al. J Transl Med (2015) 13:346. DOI 10.1186/s12967-015-0701-z
Test can often be negative due to the bacteria's ability to "hide" behind biofilms		
Standard PCR generally not sensitive enough due to the low numbers of bacteria present	.	Sapi E, et al. Improved Culture Conditions for the Growth and Detection of Borrelia from Human Serum. Int J Med Sci 2013; 10(4):362-376
Multiple sample types (blood & serum) improve sensitivity of test		

Newer Markers of Early & Late Human Lyme Disease Activity: Chemokines

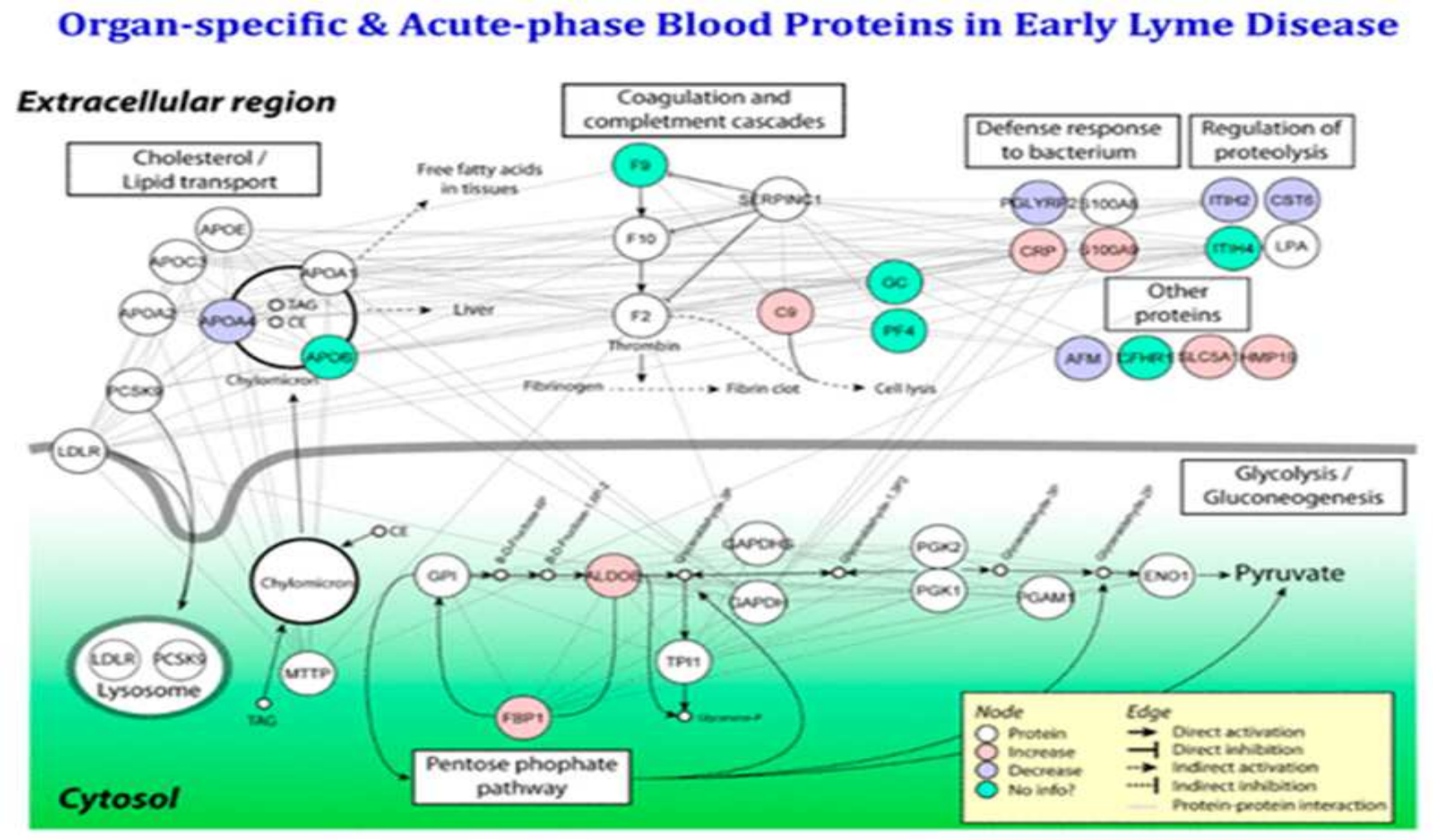
- Chemokine signatures are associated with the early stages of infection: (CXCL9, CXCL10, CCL19)
- Acute phase proteins (CRP and serum amyloid A) are also seen in early disease
- CXCL13 is a biomarker of acute neurological Lyme
- CCL19 has also been identified in late Lyme

- I Soloski MJ, Crowder LA, Lahey LJ, Wagner CA, Robinson WH, et al. (2014). PLoS ONE 9(4): e93243.http://doi.org/10.1371/journal.pone.0093243
- Aucott JN, et al. 2016. CCL19 as a chemokine risk factor for posttreatment Lyme disease syndrome: a prospective clinical cohort study. Clin Vaccine Immunol 23:757–766.
- Karrasch, M. et al. Neuroborreliosis and acute encephalopathy: The use of CXCL13 as a biomarker in CNS manifestations of Lyme borreliosis. Ticks and Tick-borne Diseases11 December 2017

Acute Phase Blood Proteins in Early LD

In erythema migrans, 6 proteins ↑: APOA4, C9, CRP, CST6, PGLYRP2, & S100A9

Zhou, Y, et. al., J. Proteome Res. 2020, 19, 1, 346-359



Understanding Laboratory Testing TBD's

Overview:

1. Lyme Disease is a CLINICAL DIAGNOSIS. The laboratory only helps to support that clinical diagnosis.

2. An EM rash is definitive evidence of Lyme Disease, and DOES NOT require laboratory confirmation to make the diagnosis

3. Patients are often seronegative if tested too early, or if antibiotics have been used early in the course of the disease, which may abrogate the immune response

Laboratory Testing in TBD's

4. The 2 tiered protocol of an Lyme ELISA followed by a Western Blot misses approximately 1/2 of the patients: Consider C6 ELISA, IFA…+ Immunoblot

5. The utility of the Western Blot is based on understanding specific bands which reflect exposure to Bb: 23, 31, 34, 39, 83-93

6. PCR testing is an important diagnostic tool for seronegative patients, but many require multiple sets over time. Other tests may be helpful to confirm the diagnosis (LTT (Elispot), Nanotrap, Lyme Dot Blot, culture, RNA testing..)

Casselli T, et al. MicroRNA and mRNA Transcriptome Profiling in Primary Human Astrocytes Infected with Borrelia burgdorferi. PLoS One. 2017 Jan 30;12(1):e0170961

Understanding Laboratory Testing in TBD's

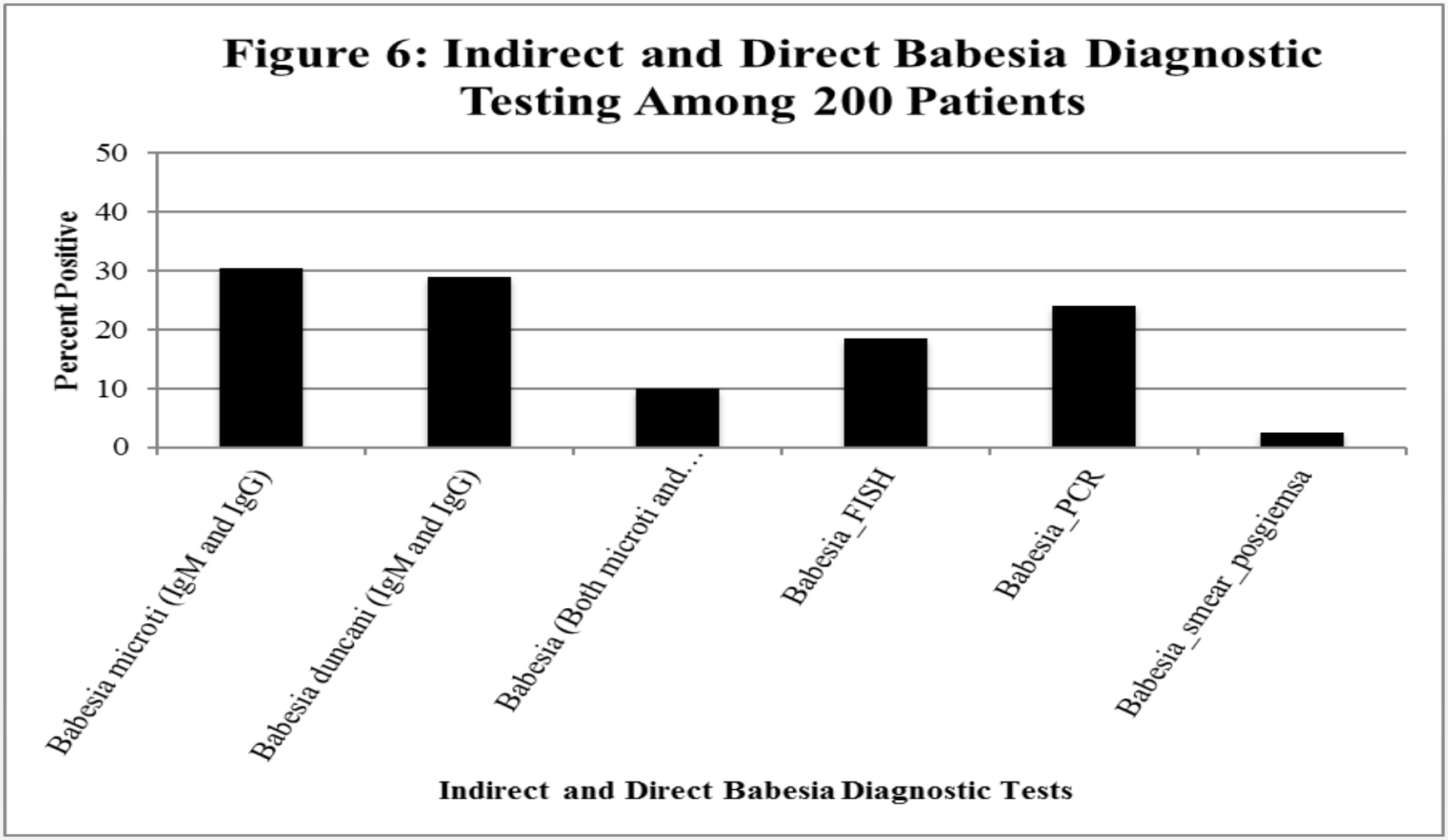
7. 10-20% of the Borrelia presently in ticks in the Northeastern United States are genetically related to ***Borrelia miyamotoi***, the agent of relapsing fever (RF) in Japan. These organisms will not test positive by ELISA, Western Blot, or PCR assays for Lyme Disease. **? Cause of Lyme-like syndromes**

8. Other tick-borne diseases such as Babesia and Bartonella are similarly unable to be reliably diagnosed using standard screening procedures.

- Aliota MT, et al. The prevalence of zoonotic tick-borne pathogens in Ixodes scapularis collected in the Hudson Valley, New York State. Vector-Borne Zoonot. Dis. 2014; 14:245–250.
- Horowitz, R., Freeman P. International Journal of General Medicine 2019:12 101–119

Babesia Testing: Antibody, PCR, FISH, Giemsa Stain

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



Problems with Testing for Co-inf's

- **Babesia:** Akoolo, L., et al. A novel quantitative PCR detects Babesia infection in patients not identified by currently available non-nucleic acid amplification tests. BMC Microbiology. 201717:16
- **Multiple Borrelia species**: Krause PJ, Carroll M, Fedorova N, Brancato J, Dumouchel C, et al. (2018) Human Borrelia miyamotoi infection in California: Serodiagnosis is complicated by multiple endemic Borrelia species. PLOS ONE 13(2): e0191725.
- **Bartonella**: Edward B. Breitschwerdt , et al. Bartonella Species in Blood of Immunocompetent Persons with Animal and Arthropod Contact. Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 6, June 2007; Bartonella Henselae: Limitations of Serological Testing: Evaluation of Elisa and Polymerase Chain Reaction Testing In a Cohort of Lyme Disease Patients and Implications for Treatment. Horowitz R.I., M.D. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.
- **Tularemia**: Horowitz RI, Freeman PR (2016) Are Mycobacterium Drugs Effective for Treatment Resistant Lyme Disease, Tick-Borne Co-Infections, and Autoimmune Disease? JSM Arthritis 1(2): 1008
- **Mycoplasma**: Eskow E, Adelson ME, Rao RV, Mordechai E. Evidence for disseminated Mycoplasma fermentans in New Jersey residents with antecedent tick attachment and subsequent musculoskeletal symptoms. J Clin Rheumatol. 2003; 9: 77-87.

Check For Common Co-infections: Laboratory, Symptom Complexes

- **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 & tick borne viral infections (POWV). Some of these can be fatal
- **Chronic Babesia and Bartonella: Big Problem!**

- 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;
- Horowitz, R.I.; Freeman, P.R. 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. Healthcare 2018, 6, 129.

Step 1: Prioritize Likely Abnormalities on the 16 point MSIDS Map Based on an H and P

- **History**: HMQ score > 63? (c/w Lyme), Migratory pain? (Lyme, other Borrelia spp.), questions 1/22 + (sweats) ? (Babesia). Perform differential diagnostic work-up based on history. Focus on key questions: ? Multiple tick-bites (↑ risk co-inf's) ? Pain bottom feet (? Bart), ? New onset seizure d/o (Bart, POWV), ? Dizziness standing (POTS)
- **Physical**: ? Rashes (EM), striae (Bartonella), granulomas (Bartonella), other rashes (BMD, STARI, RMSF..), large LN's (? Bart), Bells palsy (? Lyme), evidence of PNP (? Lyme, Bartonella, heavy metals, DM, hypothyroidism, CTS…), √ sitting/standing BP/pulse (POTS), dermatographism(MCAD)

Step 1: Prioritize the Most Important Abnormalities on the 16 point MSIDS Map

- **Other Important History**: Change in symptoms, what makes it better or worse?
- ? Feel better or worse with antibiotics or herbs (Lyme, co-inf's, Herxheimer reactions)
- ? Feel better or worse with detoxification, i.e., GSH, CSM, charcoal/clay (Detoxification issues)
- ? Feel better or worse with methylation (Detox issues)
- ? Change in symptoms based on hormonal cycles (women with Lyme disease tend to flare around the menses)
- ? Change in diet w/ ↑ carbs, w/ mid am +/or aft fatigue that is sudden, profound (hypoglycemia, Candida)

Step 2: Create A Differential Diagnosis For Every Symptom

- Every symptom should have several differential diagnoses
- See pages 50-64 "How Can I Get Better?" for a list of extensive differentials to be considered. Often more than 1 etiology is affecting symptoms in the Lyme-MSIDS pt
- Ex: Neuropathy symptoms: seen in up to 94% of all Lyme patients. Differential includes: Borreliosis, Bartonella, Autoimmune disorders (MS), carpal and cubital tunnel syndrome, or any nerve entrapment (thoracic outlet), DM, hypothyroidism, heavy metals (Hg, Pb, As), other environmental toxins (TCE, mold), vitamin deficiencies (B vit's, B12, folate, MMA, HC), immune deficiency (CVID), mitochondrial dys(f), hx CVA, pregnancy, hyperventilation..

Establish a Differential Diagnosis: Table 2.1: Symptoms and Associated Medical Conditions on the MSIDS Map

Symptoms	Possible Medical Conditions	Laboratory Testing to Consider
Unexplained fevers, sweats, chills, or flushing	• Lyme disease (chronic and other bacterial, viral, parasitic, and fungal infections) • Babesiosis • Malaria •Brucellosis • Hyperthyroidism • Hormonal failure (early menopause) • Tuberculosis* • Non- Hodgkin's lymphoma* • Panic disorders • Autoimmune disorders • Inflammation	• CBC with a white cell count • CMP with liver functions • Giemsa stain and malarial smears • Babesia IFA • Babesia WA- 1/duncani titers • Babesia FISH and PCR • Thyroid function tests (TFT's) • Sex hormone levels • Chest X-ray/PPD • ANA, RF • Erythrocyte sedimentation rate (ESR),C-reactive protein (CRP) • Cytokine panel

Step 3: Address Inflammation To Heal

- 1. Block NFKappa-B and Activate Nrf2 with antioxidants (curcurmin, green tea, resveratrol) and phytochemicals (sulforaphane..)
- 2. Block Activation of Glial cells in the brain: LDN: Blocks NFKappa-B and TLR4 signaling (decreasing glial cell activation) and shifts immune responses from TH2 to TH1
- 3. Do an Anti-inflammatory diet: ↑ omega 3, ↓ omega 6 FA (Medit diet)→ ↓ arachidonic acid, avoid allergic/sensitive foods, reduce simple sugars, red meat, eggs, dairy, gluten, ? histamine
- 4. Replace minerals (zinc, copper, magnesium)
- 5. Get proper sleep and exercise (insomnia:↑ IL-6)

Address Inflammation To Heal

- 6. **Treat the Infections** causing inflammation, immune dysfunction (The 3 I's): antibiotics and natural therapies
- 7. **Detoxification**: Remove chemicals and inflammatory cytokines causing inflammation
- 8. **Balance** the hormones, cytokines, & the microbiome
- 9. **Heal the Damage to the Body**: Repair the mitochondrial damage from free radicals and oxidative stress (may improve energy; neuro/card)
- 10. **Heal the Damage to the Mind/Emotions**: role of meditation, love and compassion
- Annie Hopper, Dynamic Limbic Neural Retraining (DNRS)

MSIDS Map: Treatment

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, Mycoplasma species

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

International Journal of General Medicine

Dovepress

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]

[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.

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

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

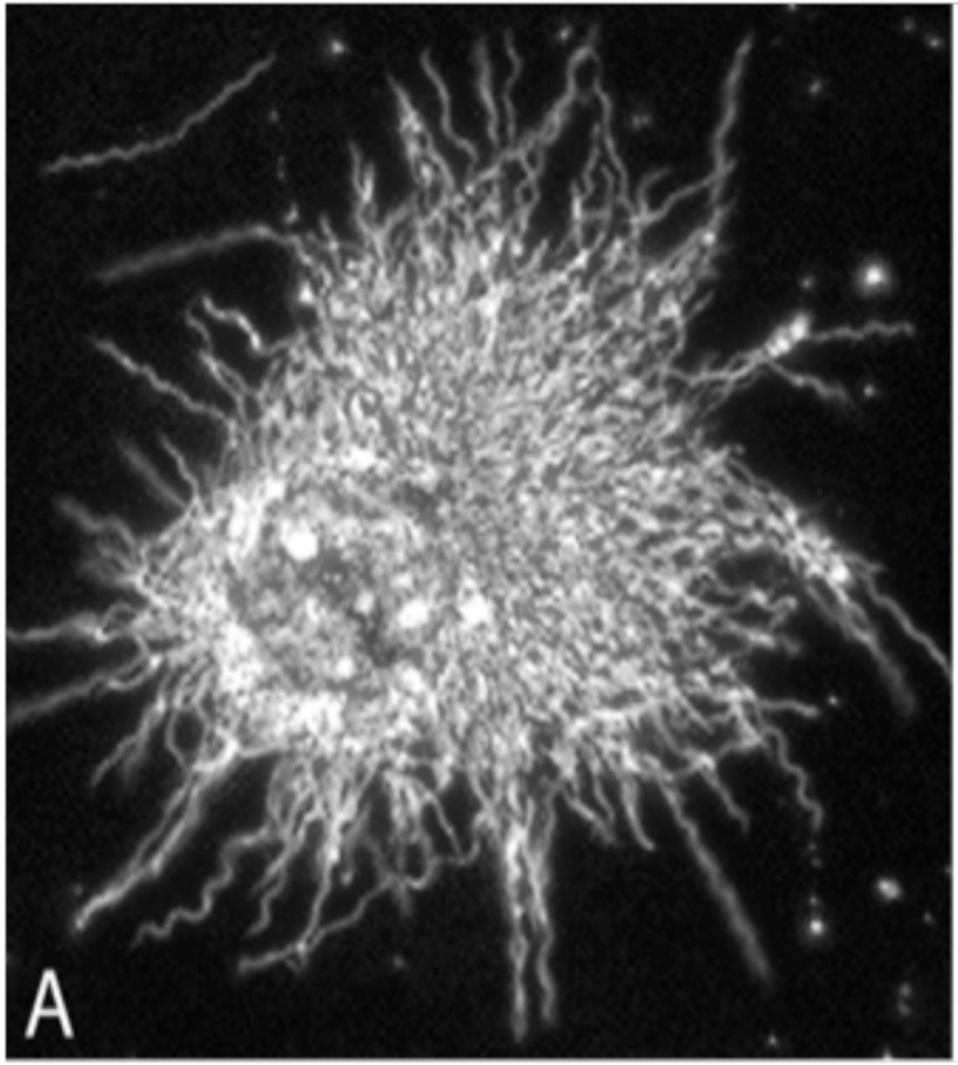
- **Borrelia burgdorferi: 14.5%** of patients were PCR + despite "adequate" antibiotic therapy for months or years prior to DDS CT (N=29, 14.5%).
- **Babesia spp.: + PCR/FISH** despite M+Z, C+Q
- **Bartonella henselae: + PCR, + FISH**
- Other: **tularemia** (4x ↑titers), **Brucella** (+ agglut)
- **M.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

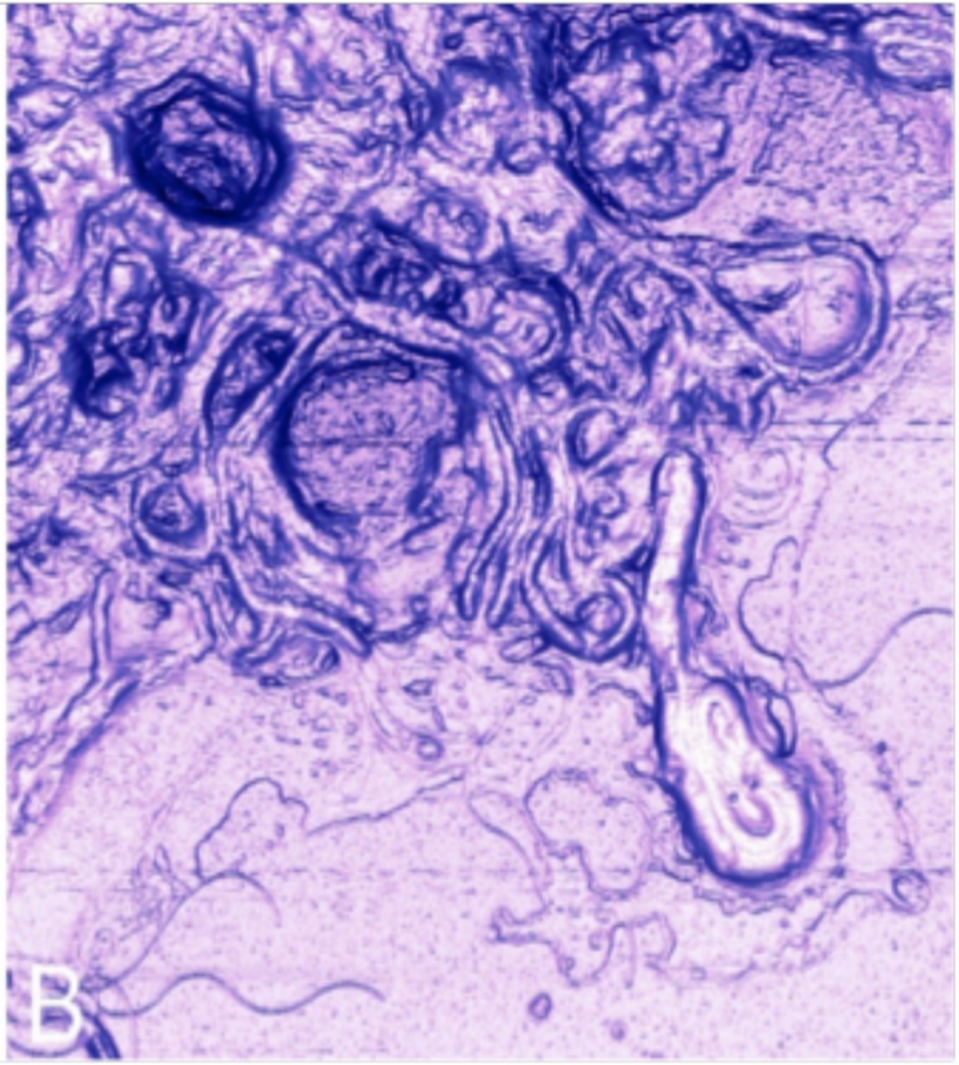
- Lemieux, J. E. et al. A global map of genetic diversity in Babesia microti reveals strong population structure and identifies variants associated with clinical relapse. Nat. Microbiol. 2016, 1, 16079

Borrelia Biofilms: Protect the Bacteria

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.





Stationary Phase Persister/Biofilm Microcolonies Cause ↑ Disease

B. burgdorferi in the tick could develop variant forms that may represent different forms of persisters (Cabello)

DISCOVERY MEDICINE

Article Published in the Author Account of
Jie Feng

Stationary Phase Persister/Biofilm Microcolony of Borrelia burgdorferi Causes More Severe Disease in a Mouse Model of Lyme Arthritis: Implications for Understanding Persistence, Post-Treatment Lyme Disease Syndrome (PTLDS), and Treatment Failure

Published on March 28, 2019

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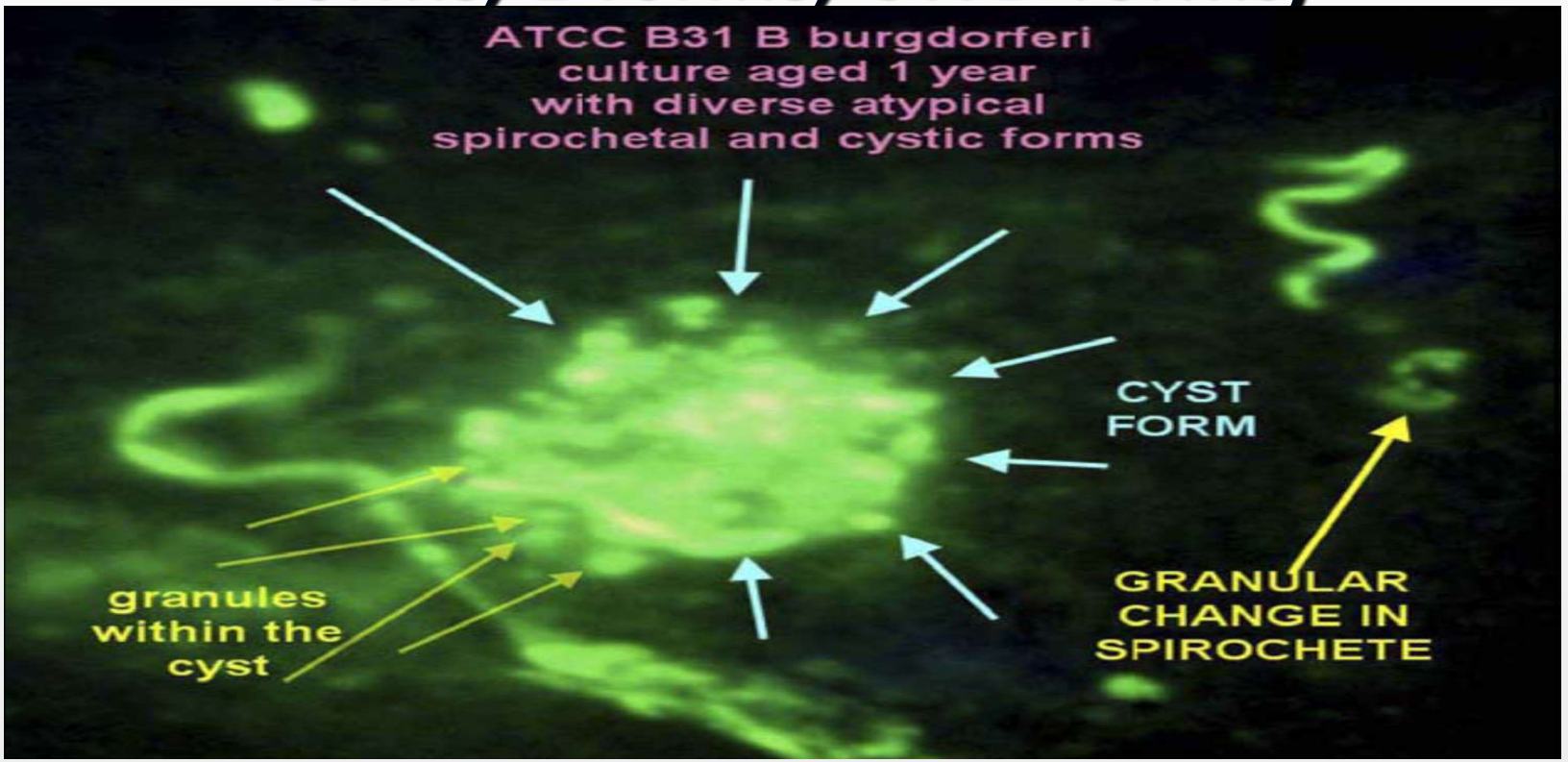
Specialty: Microbiology, Infectious Diseases, Immunology

Treatment failures due to Persistence of Lyme Borreliosis: Cystic Forms (round bodies, S-forms, L-forms, CWD forms)



I Preac-Mursic, V et al, Formation and Cultivation of Borrelia burgdorferi Spheroplast-L-form Variants, Infection 24 (1996);No 3:218-26

Brorson,O et al, Transformation of cystic forms of Borrelia burgdorferi to normal, mobile spirochetes, Infection 25 (1997); No 4:240-45.

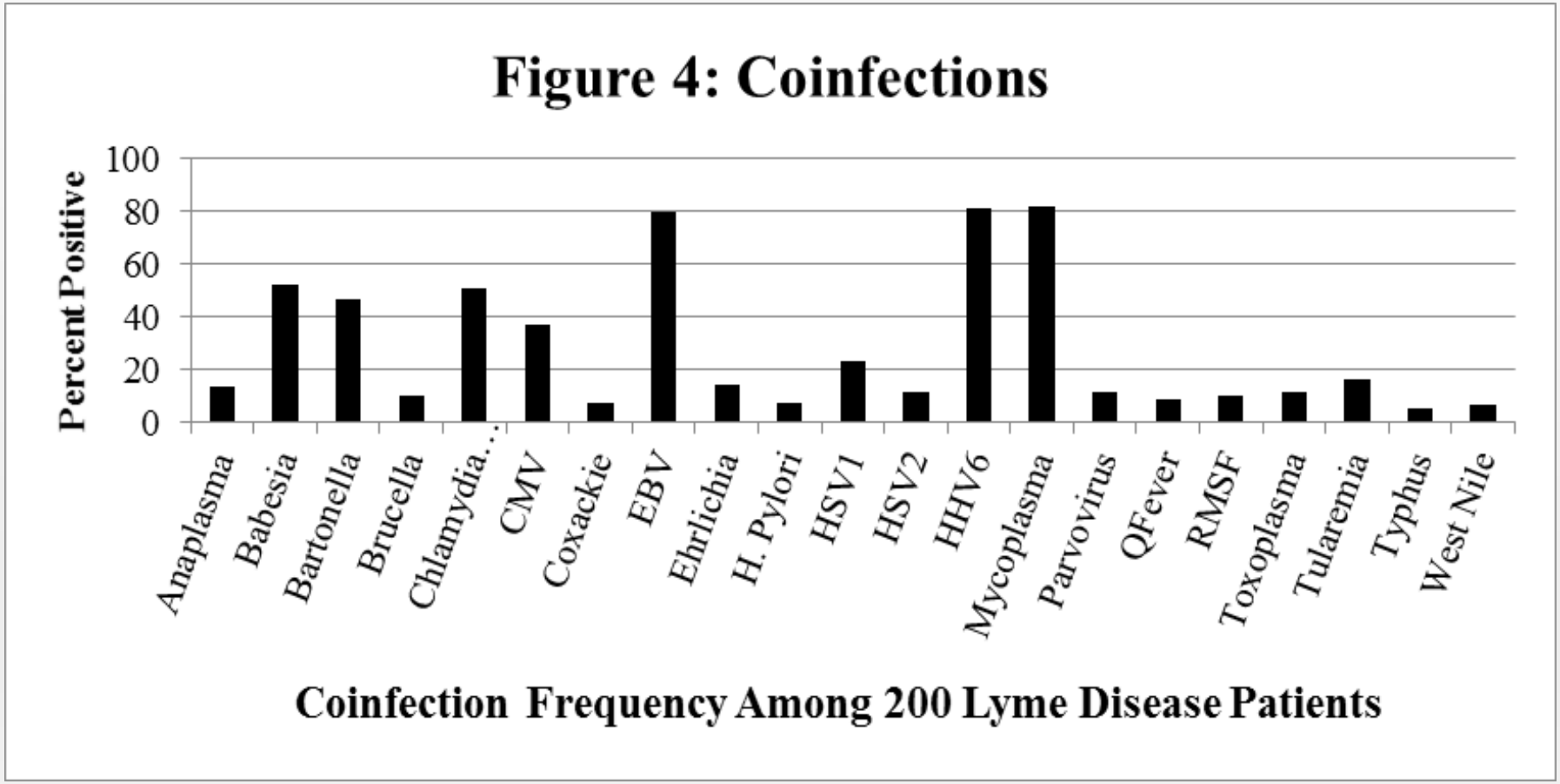
Comprehensive Treatment for Persistent Lyme May Need To Address:

- **Log Phase/Actively dividing forms**: Penicillin's: (Amoxicillin, Augmentin, IM Bicillin), Cephalosporins: Ceftin [cefuroxime axetil], Omnicef [cefdinir], IV Rocephin [ceftriaxone], IV Teflaro [5th generation], IV Vancomycin..
- **Round body/cystic forms (L-forms, S-forms, CWD forms)**: Plaquenil (hydroxychloquine), GSE (grapefruit seed extract), Flagyl (metronidazole), Tindamax (tinidazole)
- **Intracellular forms**: tetracyclines (doxy, mino), macrolides (azithromycin, clarithromycin), rifampin, rifabutin, quinolones (cipro, Levaquin, moxifloxacin)
- **Stationary Phase Persisters/biofilm forms**: DDS (dapsone), PZA, ? Disulfuram + Stevia, Oreg. oil, Biocidin, Lauricidin, Serrap.

Co-infection Status N=200 Dapsone

64% of patients had between 5-8 coinfections: Address them!

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



What is the Common Denominator?

Multiple (Intracellular) Infections + toxins + nutritional deficiencies, leaky gut, food all's +↓ sleep→ 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, persisting despite standard therapies

- 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.

IV. Multiple Chronic Infections

- Bacteria: goal is to treat multiple IC pathogens at once, and address different forms of borrelia during the treatment course, personalizing treatment
- Cell wall forms: penicillins, cephalosporins (Ceftin 500 BID)
- Round body/cystic forms: Plaquenil 200 BID, GSE 2 PO BID (Pure Encap's), occ Flagyl/Tindamax (body wt), Alinia
- Intracellular location: tetracyclines, macrolides, quinolones, rifampin, rifampicin, sulfa (dapsone), PZA. Extracell: Gent
- Biofilm/persister forms: dapsone, PZA, + add on treatment for Bartonella persisters (? methylene blue, clotrimazole, berberine, Macrobid) + add on treatment for Babesia

- Leigner, K. Disulfiram in the Treatment of LD & Babesiosis: Report of Experience in Three Cases, Antibiotics, 30 May 2019

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]*

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 (stationary phase) 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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Submitted: 15 June 2016

Accepted: 14 July 2016

Published: 16 July 2016

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

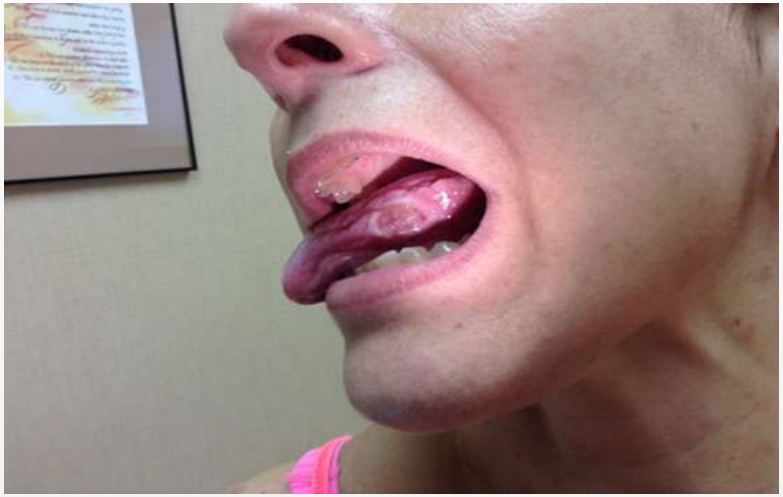
INTRODUCTION

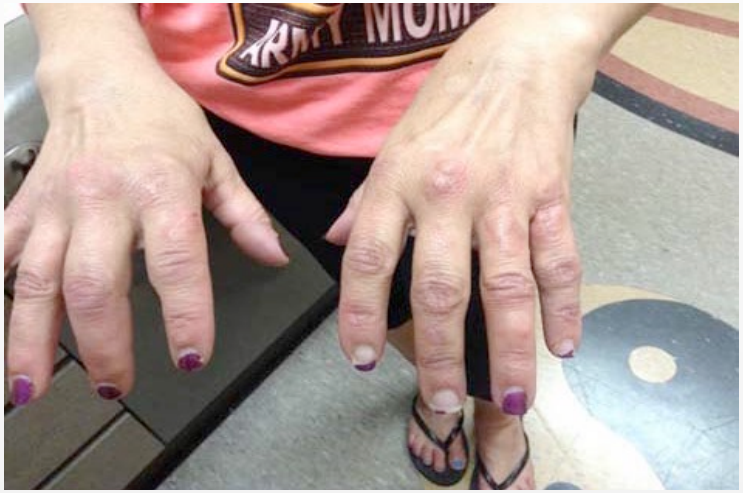
Autoimmune diseases like rheumatoid arthritis and lupus are rising in incidence in the United States and environmental factors are being implicated [1-3]. Tick-borne diseases, such as Lyme disease are also increasing in number as per recent Centers for Disease Control (CDC) studies [4,5], and have been 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.

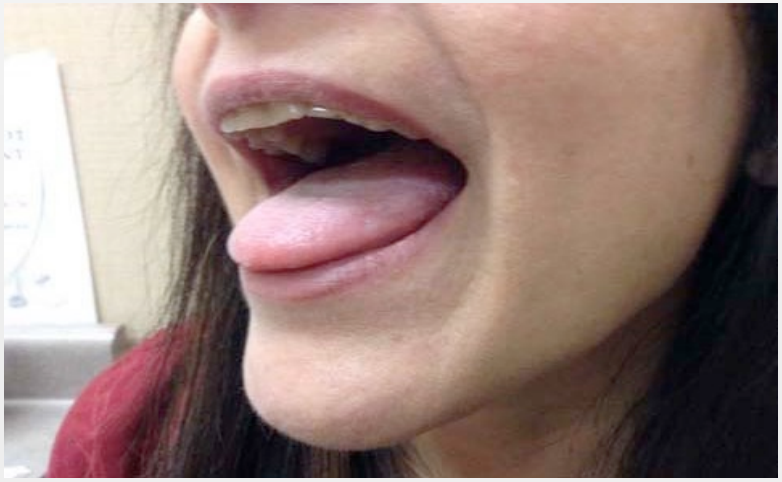
The National Science Foundation has identified Lyme disease as one of several emerging pandemic disease outbreaks that threaten global public health and world economies [8]. The CDC reported a significant increase in the number of Lyme cases in

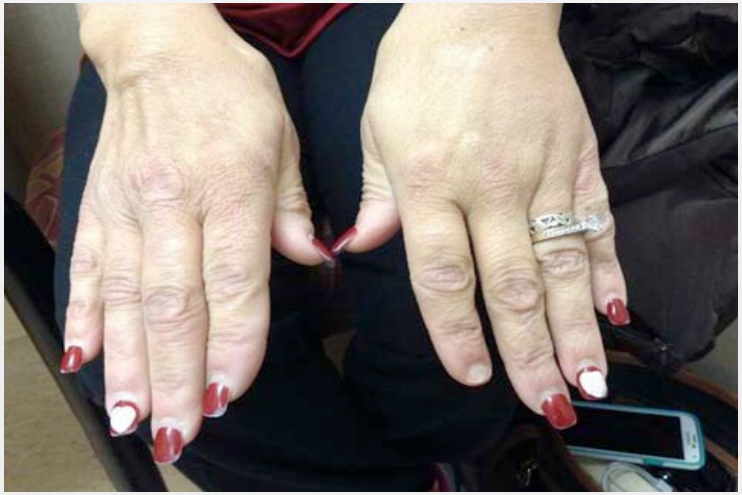
PZA in Lyme, Bartonella, Behcet's Dx:

Horowitz & Freeman JSM Arthritis, July 2016









- Evidence of persistent Bartonella, Tularemia, HHV6

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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Received date: March 04, 2016; **Accepted date:** April 02, 2016; **Published date:** April 06, 2016

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: $t(164)=8.36$, $p < .001$

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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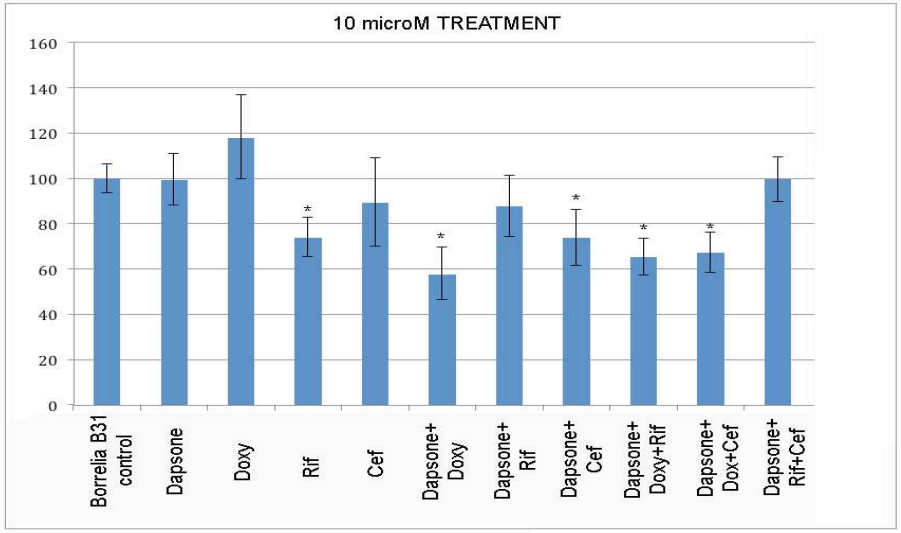

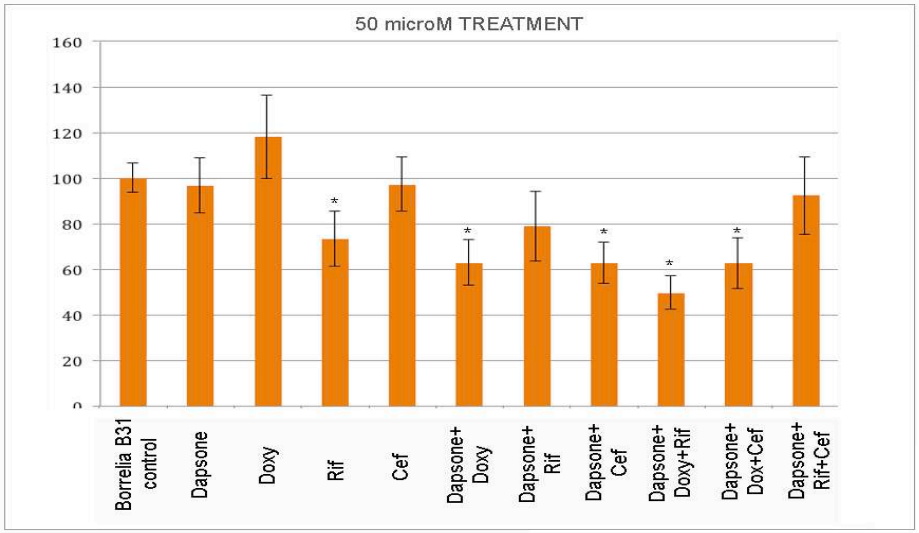

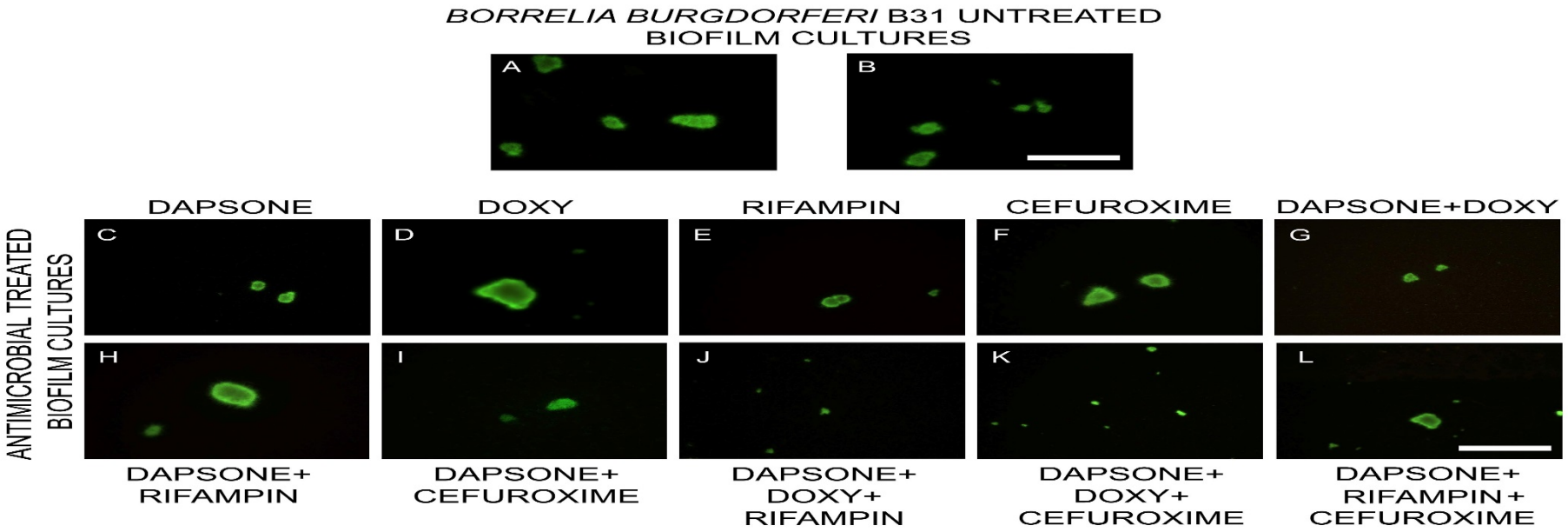

Disulfiram For Resistant Lyme and Babesiosis?

antibiotics

MDPI

Article

Disulfiram (Tetraethylthiuram Disulfide) in the Treatment of Lyme Disease and Babesiosis: Report of Experience in Three Cases

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Received: 28 March 2019; Accepted: 25 May 2019; Published: 30 May 2019

check for updates

Abstract: Three patients, each of whom had required intensive open-ended antimicrobial therapy for control of the symptoms of chronic relapsing neurological Lyme disease and relapsing babesiosis, were able to discontinue treatment and remain clinically well for periods of observation of 6–23 months following the completion of a finite course of treatment solely with disulfiram. One patient relapsed at six months and is being re-treated with disulfiram.

Keywords: Chronic Lyme disease; neuroborreliosis; Post-treatment Lyme disease syndrome (PTLDS); relapsing babesiosis; persistent infection; antibiotic treatment failure; disulfiram

antibiotics

MDPI

Article

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

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Received: 9 April 2019; Accepted: 25 April 2019; Published: 29 April 2019

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

New Bartonella "Persister" Drugs

- Bartonella has been shown to have stationary persister forms, like borrelia. Methylene blue, Gent, daptomycin & clotrimazole were among the most active agents.? Berberine
- 7 azole drugs including had high activity vs stationary phase Bh. Best: clotrimazole (also anti-malarial prop's)
- Daptomycin: 21% residual viability (IV, expensive, SE's)
- Methylene blue: 25% residual viability (used with dapsone)
- Gent (not IC)/?Nitrofurantoin: MIC values of 0.31–0.63 µg/mL
- Rifampin was the most effective against growing Bh (doxy/zithro/quinolones also useful for growing forms)

- Li, T. et al. Identification of FDA-Approved Drugs with Activity against Stationary Phase Bartonella henselae. Antibiotics 2019, 8(2), 50;

Possible Combination Therapy Bartonella

Active/Log phase Bartonella

- Rifampin # 1 active
- Doxycycline (? Mino)
- Azithromycin
- Quinolones (Cipro, Levaquin, Avelox..)
- Clotrimazole (anti-fungal)
- Berberine (anti-fungal)
- Consider combination tx for IC/active (? PZA)

Stationary phase Bartonella

- Methylene blue (anti-malarial, anti-fungal, helps w/DDS CT)
- Clotrimazole (also anti-malarial prop's)
- Gentamycin (IV/IM, no IC penetration)
- Macrobid (nitrofurantoin)
- ? Combine above for stationary phase Bh

Dapsone Combination Therapy

- DDS CT: Plaquenil 200 BID, doxycycline (100-200 mg) BID, rifampin 300 mg BID (empty stomach, or rifabutin 150 mg BID with a full stomach), dapsone (from 25 mg QOD, to 25 mg QD, to 50/25 QOD, to 50 mg/d, max usual dose 100 mg/day), Nystatin 500,000 U tabs, 2 BID, Leucovorin 25 mg BID, Folafy-ER (L-methylfolate) 15 mg QD or BID (increase doses of folic acid based on anemia), triple probiotics *(Ultraflora DF BID, Theralac BID, saccharomyces boulardii BID) with 3 biofilm agents, including oregano oil cap's BID, Stevia (NutramediX) 15 drops BID, Biocidin 2 sprays BID (work up doses of biofilm agents according to Herxing). Future: Double dose dapsone study secondary to success
- Works well long term if no active co-infections (Bab, Bart)

Monitoring on Dapsone Combination Therapy

- Initial G6PD levels must be normal. Rule out and treat any underlying anemia (Fe deficiency, B12..) before treatment with DDS CT
- Monitor CBC, CMP, methemoglobin levels: frequency depends on the dose of dapsone (q wk, w/ ↑ doses)
- Make sure women report any unusually heavy periods/clots where the risk of anemia rises. Stop dapsone if any heavy bleeding, and ↑ folic acid (? > 100 mg/day)
- Stop dapsone if methemoglobin levels ↑> 8-10% despite methylene blue 50 BID and 1000 mg liposomal GSH BID, NAC 600 BID, ALA 600 mg BID, esp. if symptomatic. Lower DDS dose to previously tolerated, helpful dose

Add on Babesia/Bartonella Therapy to DDS CT if Symptoms/Inf's Persist

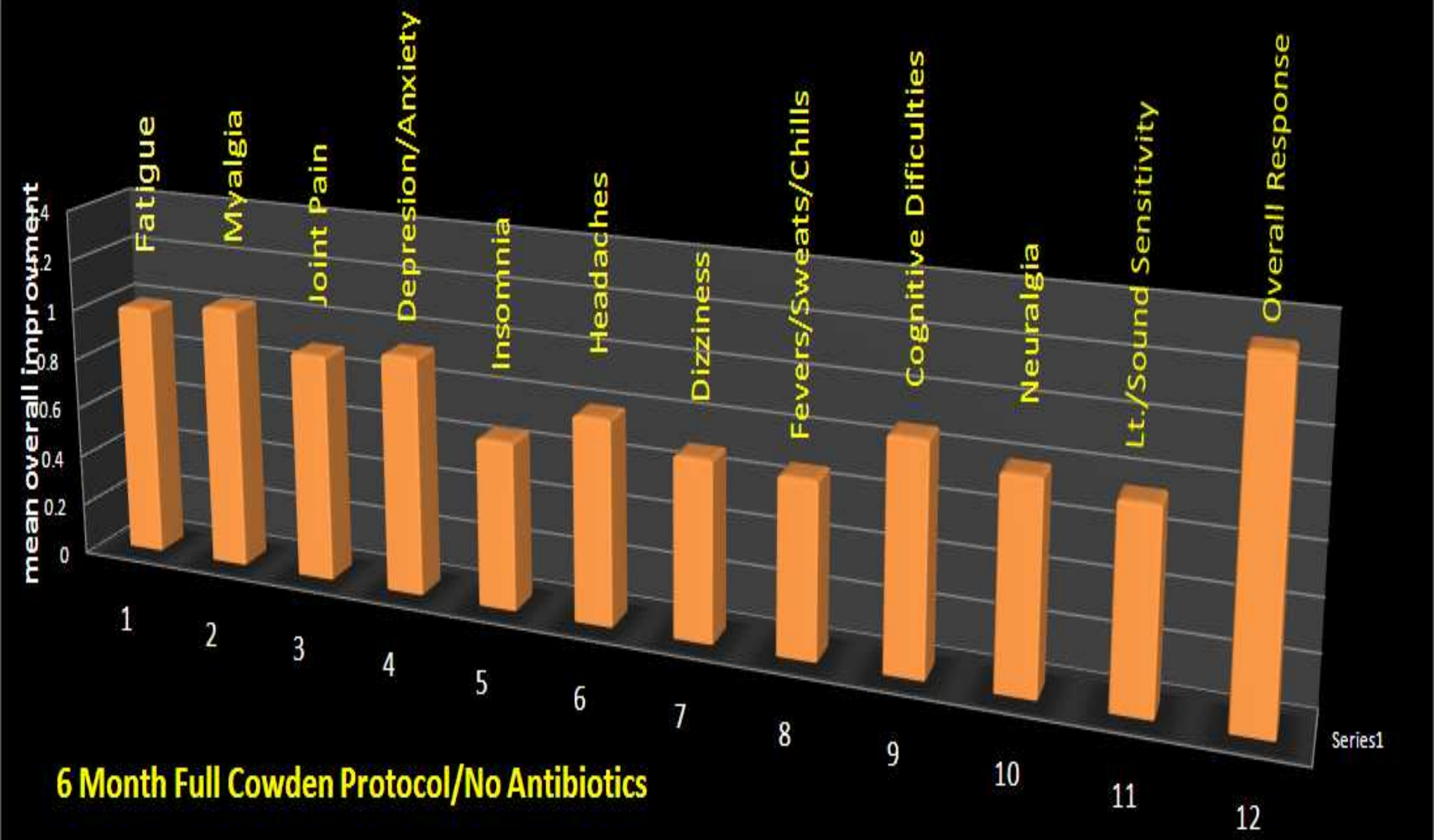
- **Add for Bartonella:** Zithro (can be pulsed i.e. Zithro BID, Mon-Thurs) + PZA (body weight), methylene blue 150 BID? (aver), clotrimazole QID, Macrobid. Avoid mixing QT drugs Follow Bart titers, PCR, FISH, VEGF w tx
- **Add for Babesia:** Clinda + macrolide (or quinine), +/- Mepron (1-2 tsp BID) or malarone (2 BID) + artemisinin (? Liposomal), cryptolepis (1 tsp BID to TID), CSA…Consider 3 day rotations of Coartem 4 BID. ? Disulfiram for resistant Babesia. ? Tafequonine. Follow sx, titers, PCR, FISH…

- Mordue, D.G., & Wormser, G.P. (2019). Could the Drug Tafenoquine Revolutionize Treatment of Babesia microti Infection? The Journal of Infectious Diseases, 220(3), 442-447.

Add Herbal/Integrative Therapies: Solo, Combination Treatments

- **Buhner protocol** (Samento, Andrographis, J K..)
- **Zhang protocol** (TCM→Coptis, HH, Allicin, Circ P)
- **Homeopathy:** Ledum, syphilitic, malarial nosodes..
- **Byron White protocol** (A-L, A-Bab, A-Bart)
- **Cowden protocol** (Samento, Banderol, Cumunda..)
- **Beyond Balance** (MC Bab 2, Bab 1, BB-1..)
- **Others**: Biocidin, Lauricidin, Liposomal Vitamin C, Rife, Coil machines, Bionic 880, heat therapy, stem cells, Acupuncture, oxidative stress tx (ozone)…

- Silver Enhances Antibiotic Activity Against Gram-Negative Bacteria. Jose Ruben Morones-Ramirez et al. Sci Transl Med 5, 190ra81 (2013);



	1	2	3	4	5	6	7	8	9	10	11	12
Series1	1	1.04	0.9	0.94	0.66	0.8	0.7	0.68	0.88	0.8	0.76	1.32

Commonly Seen Obstacles to Healing

- **The most difficult to treat, sensitive patients usually have certain things in common:**
- 1. MCAD is often present, triggered by infections like Lyme (PIMCAD) and/or environmental toxins like mold
- 2. Patients often have GI issues: disruption of the microbiome, +/- SIBO, gluten sensitivity, leaky gut, parasites, +/- enzyme deficiencies…
- 3. Often they suffer from MCS and detoxification problems

Multiple Chemical Sensitivity (MCS)

- **Avoidance of chemicals:** #1, + **Measure body burden** of mold, metals, VOC's, pesticides..(DD, PacTox..)
- **Air and water purifiers**, + fresh, clean food…? **EMF free**
- **Evaluate detoxification pathways** (Genova, Great Plains..)
- **Support detoxification**: **Skin** (FIR saunas), **GI** (fiber, flax, binders [clay/charcoal], pre/probiotics, saccharomyces..), **liver** (phase I and II support: NAC, ALA, DIM, sulforaphane glucosinolate [Oncoplex ES] , GSH, methylation, MedCaps DPO…), **kidney** (> 2 L fluid/day) **+ remove mold, metals..**
- **Mental detox**: Annie Hopper's Dynamic Limbic Retraining
- ? Low dose Keppra (250 mg +) HS

- Kakisaka, Y. et al. Levetiracetam improves symptoms of multiple chemical sensitivity: Case report. J Med Invest. 2017;64(3.4):296-298.

Commonly Seen Obstacles to Healing

- 4. Multiple chronic infections are often present:
- Bacteria we have seen persist: Borrelia spp and Bartonella spp. are on the top of the list, with Mycoplasma spp., tularemia, & brucella right behind. We have only seen a rare case of a chronic rickettsial infection (Q-fever)
- Parasites we have seen persist: Babesia spp. persist despite most rotations of anti-malarial medications/herbs
- Viruses we have seen persist: HHV6 reactivation was seen in our practice, w/ 4x ↑ titers and + PCR's. EBV PCR+ was occ. found. Also, chronic candidiasis possible…

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

Commonly Seen Obstacles to Healing

- 5. There is immune deficiency: over 20% of our practice had immunoglobulin deficiencies & subclass deficiencies
- 6. There is immune overactivation: autoimmune markers and inflammatory markers were elevated in up to 70% of our sickest patients
- 7. There are disrupted sleep patterns: including DSPS, circadian rhythm disorders and insomnia/hypersomn
- 8. There is a history of emotional trauma, with PTSD & unresolved issues of abuse

- Horowitz, R.I.; Freeman, P.R. 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. *Healthcare* **2018**, *6*, 129.

Commonly Seen Obstacles to Healing

- 9. There is resistant POTS/dysautonomia with severe autonomic dysfunction
- 10. There is mitochondrial dysfunction w/the cell danger response (CDR). Difficult to find a safe environment without continuous exposure to toxins
- 11. Whatever underlying medical problems are present (including endotoxemia from dental/GI sources), they are not well controlled, & contribute to the burden of illness, w/ genetic predispositions

- Horowitz, R.I.; Freeman, P.R. 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. *Healthcare* **2018**, *6*, 129.

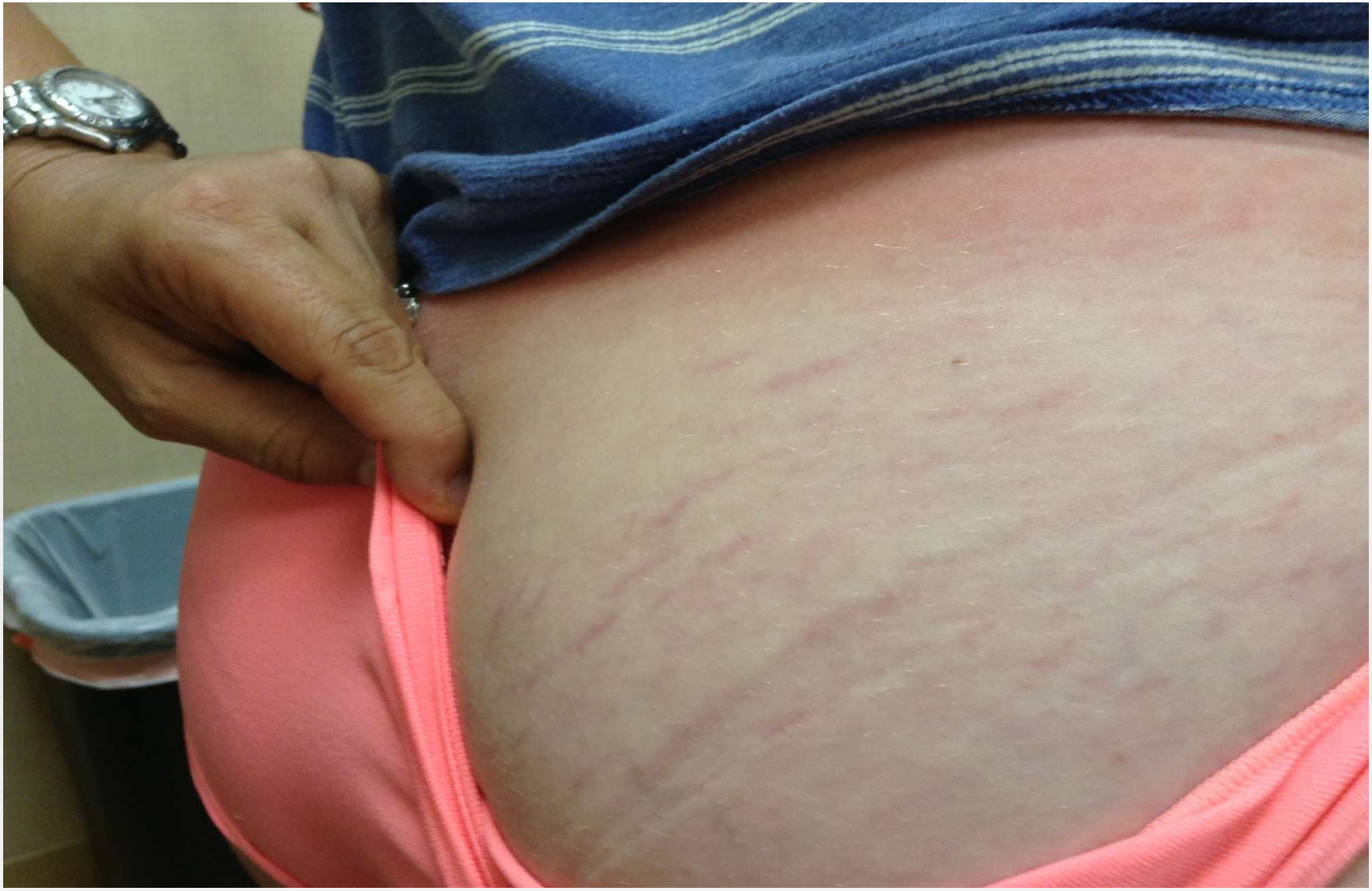
Case 1: Seizures, Syncope, Drenching Sweats & Weight Loss

- **PMH:** 15 year old female, PMH significant for a one year history of extreme fatigue, severe migratory joint pain, requiring high doses of morphine sulfate (which didn't control the pain), drenching sweats, uncontrolled seizures (on Depakoate, but failed other seizure medication), frequent episodes of passing out (syncope) and pre-syncope. Patient is wheelchair bound and unable to walk.
- Unable to eat, bathe or go to the bathroom on her own, and Lost significant amounts of weight, poor appetite. Saw over 8 physicians (GP, Neurology, Infectious Disease) with no diagnosis.

Case 1: Seizures, Syncope, Drenching Sweats & Weight Loss

- Flies up to see me in a wheelchair from southern US
- Physical exam: Sitting BP 90/60, pulse 82 and regular. Standing BP drops to ? 70's/ 50's after several minutes (difficult to hear either the systolic or diastolic pressure) with a pulse rate rising to 124 BPM. Feels like she is going to pass out
- PE is otherwise unremarkable except for tender joints to palpation (no redness or swelling) & patient has "stretch marks" which appeared in the last year. Never gained weight (she lost significant amounts of weight and was never obese).

Bartonella rashes



Case 1: Seizures, Syncope, Drenching Sweats & Weight Loss

- Treatment: Based on migratory pain (Lyme), drenching night sweats (probable Babesia), stretch marks (probable Bartonella), and low BP standing with a greater than 30 BPM increase in heart rate with pre-syncope (POTS/Dysautonomia), she was placed on doxycycline 200 mg 2 X per day, rifampin 300 mg 2 X per day, Plaquenil 200 mg 2 X per day, Malarone 100/250 mg, two 2 X per day with Artemesia SOD 3 X per day, Nystatin tablets 500,000 units, 2 twice a day, as well as Florinef 0.1 mg with a high salt diet and a minimum of 2-3 liters of fluid per day

Case 1: Seizures, Syncope, Drenching Sweats & Weight Loss

- **Laboratory:** returned positive for Lyme specific bands on the Western Blot, + Babesia WA-1/duncani titers
- **Clinical Course**: Patient returned one month later. Was walking out of her wheelchair, seizure free (Depakote was tapered), off her narcotics and pain free. Is now able to eat on her own and go to the bathroom on her own. No further episodes of syncope. Went to a Broadway play in NYC and is now "going out to parties with her friends"
- **Take home message**: The clinical history and physical exam made the diagnosis, independent of laboratory results!

Case 2: MSIDS 'Gal' w 16/16 Abnormalities, Relapsing off AB's

- 60 yo W/F w/ PMH significant for: Lyme (+ IgM W Blot), + PCR Borrelia burgdorferi in the blood despite years of antibiotic and herbal rotations on and off
- Also: Babesia, Bartonella, Mycoplasma fermentans PCR +, Adrenal dysfunction (phase II), hypothyroidism, hypoglycemia/metabolic syndrome, menopause with low estrogen, prog, food allergies with leaky gut, inflammation with MCAD (+histamine, tryptase, chromogranin A), detoxification problems (ION test), PTSD (Family trauma), sleep apnea, and mitochondrial dysfunction. Apart from that, she was fine.

Case 2: MSIDS 'Gal' w 16/16 Abnormalities, Relapsing off AB's

- **Labs**: + ANA, elevated CRP, elevated HbA1c (5.7), hyperlipidemia, low free T3 with high normal TSH, phase 2 adrenal dysfunction on DHEA/cortisol test, Babesia microti titer 1:160, Bartonella henselae titer 1:64 +, Mycoplasma fermentans PCR + , Alcat food panel with > 30 food allergies, elevated histamine, elevated chromogranin A, elevated tryptase (MCAS), urine heavy metals + for Pb, As, Hg, Cd, mold exposure (black mold found under bedroom/bathroom) with + Stachybotrys titer, low serum glutathione, RBC magnesium, iodine, zinc

Case 2: MSIDS 'Gal' w 16/16 Abnormalities, Relapsing off AB's

- Treatments over the years: every abnormality on the MSIDS map was treated, and usually each time she felt somewhat better. Percentage of normal kept ↑
- Rotated through multiple cell wall/cystic/IC regimens (Ceftin, Plaquenil, Zithromax) or double IC regimens (Mino+Zithro, Mino+Cipro, Mino+rifampin). Each time felt better on a new regimen, relapsed within weeks off
- Herbal regimens would occasionally help to stay in longer remissions (Zhang, TCM: Coptis/circP/HH) or Samento/Banderol/Parsley/Burbur

Case 2: MSIDS 'Gal' w 16/16 Abnormalities, Relapsing off AB's

- **Finally tried dapsone combination therapy**: doxycycline, rifampin, dapsone + Plaquenil/GSE/Nystatin: got help with ↑ doses of dapsone, after getting through Herxheimer reactions lasting days (Good Herxes)
- **Detox support helped Herxes**: + response to Alka Seltzer Gold and 2 g liposomal glutathione, increased salt and fluids, liver support (NAC, ALA, GSH, broccoli extracts: [DIM, sulforaphane glucosinolate], methylation support, with drainage remedies
- **FIR saunas** + **coffee enemas** occ. helpful. Husbands expresso wasn't enough.

Case 2: MSIDS 'Gal' w 16/16 Abnormalities, Relapsing off AB's

- Felt good after 6 months of DDS CT, with 50 mg of dapsone. Stopped treatment.
- Bb PCR + → restarted treatment with higher dose dapsone combination therapy (100 mg/d). Felt good after 6 months. Stopped treatment.
- Relapsed several months later. Did double dose dapsone therapy (100 mg BID) with same doses of doxy, rifampin, and biofilm agents (Stevia, Biocidin, oregano oil). Worked up dose of DDS over 3 weeks (25, 50, 100 mg) and then did 4 weeks of 200 mg/d of dapsone

Case 2: MSIDS 'Gal' w 16/16 Abnormalities, Relapsing off AB's

- **Anemia**: Hemoglobin dropped from 12.9 to 8.9 over 5 weeks. Slow decline didn't cause symptoms except some DOE walking outside on hills. Remained on Leucovorin 25 mg two in am, one in pm (75 mg), with L-methylfolate 15 mg BID (30 mg)= 105 mg of folic acid
- **Methemoglobin levels held at 3.9%** with NAC, ALA and 1000 mg liposomal glutathione BID. Methylene blue unnecessary (but usually is helpful at min. 50 mg BID)
- After a several day Herx at 200 mg/d of DDS, the patient felt fine (and even well) for the rest of the month

Case 2: MSIDS 'Gal' w 16/16 Abnormalities, Relapsing off AB's

- **Anemia**: resolved over 4-6 weeks off DDS, keeping high dose folic acid on board X 1 month (Leucovorin 25 mg BID + L-methylfolate 15 mg/d or BID). Repeat Hb 13.6
- No kidney or liver abnormalities. GI was fine, remaining on Ultraflora DF, Theralac & saccharomyces b. BID
- Has stayed in remission now for almost 2 years, on no herbs to treat TBD's. Remains on immune, G.I., hormonal and detox support. Exercises at least 30 min/day
- POTS has required ongoing low doses of Florinef and Midodrine. Annie Hoppers limbic retraining is now helping to decrease doses of medications, ↓ symptoms of MCAD

Summary: Healing the Difficult to Treat Pt

- **Lyme, other TBD's and co-infections** result in inflammation/immune dysfunction. Treat the 3 "I"s
- **Evaluate all 16 differential diagnostic categories on the MSIDS map** and prioritize those that most need to be addressed early on in the illness
- **Infections and toxins create inflammation** through various pathways (NFK-B, NO, histamine, MCAS..) contributing to fatigue, pain, and neuropsychiatric symptoms
- In the difficult to treat, resistant patient: focus on evaluating and treating (if present): chronic inf's, MCS, toxins + detoxification issues, GI abN's, MCAS, vagal nerve dysfunction w/POTS, resistant sleep disorders, immune dysfunction/PTSD/genetic abn's/mitochondrial dys(f)+ CDR
- Limbic and vagal retraining is important in this population!

“Wisdom is the marriage of knowledge and experience bound by compassion.”