



**Integrative Medicine Summit 2021: Clinical Challenges and Solutions**

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# Chronic Bacterial and Viral Diseases: Clinical/Laboratory Diagnosis and Effective Integrative Treatment Strategies

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## **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, 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**

# Practice Gaps: Lyme & TBD's/COVID-19

- Lyme and associated tick-borne diseases (TBD's) are frequently underdiagnosed and misdiagnosed. Lyme is known as the 'great imitator', mimicking CFS/ME, FM, autoimmune illness (e.g., MS, RA), neuropsychiatric disorders (depression, anxiety, OCD, psychosis, ALS) as well as dementia. Many sx overlap COVID-19
- This presentation will discuss the clinical manifestations of Lyme and associated TBD's, provide a validated screening symptom questionnaire to assist with the diagnosis, and discuss differential diagnosis and up-to-date effective integrative protocols for Lyme, associated diseases and COVID

# Overview of COVID-19/Lyme & TBD's

- COVID-19 as well as Lyme disease w/associated co-inf's both have overlapping symptoms: fevers, chills, headaches, chest pain, cough, shortness of breath, fatigue, brain fog, neuropsychiatric symptoms...
- The symptoms of COVID-19 & LD are both are driven by inflammation due to cytokines, where similar cytokines are seen in both illnesses
- The symptoms of long COVID also overlap chronic LD: fatigue, headaches, brain fog, neuropsychiatric, POTS
- Creating a differential diagnosis & treatment plan is therefore necessary

- R.I. Horowitz, P.R. Freeman, Three Novel Prevention, Diagnostic and Treatment Options for COVID-19 Urgently Necessitating Controlled Randomized Trials, Medical Hypotheses (2020) <https://www.sciencedirect.com/science/article/pii/S0306987720308276?via%3Dihub>
- Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020. Article Number: 101063 <https://doi.org/10.1016/j.rmcr.2020.101063>
- Cheryl B. Novak , Verna M. Scheeler, and John N. Aucott. Lyme Disease in the Era of COVID-19: A Delayed Diagnosis and Risk for Complications. Case Report | Open Access. Volume 2021 | Article ID 6699536 | <https://doi.org/10.1155/2021/6699536>

# How Many People Get Lyme Disease in the US?

- A recently released estimate based on insurance records suggests that **each year approximately 476,000 Americans** are diagnosed and treated for Lyme disease. (CDC, Jan 13, 2021)
- This does not account for 5% of the US population that suffers from CFS/ME and Fibromyalgia, which is appx **17 million people; 21 million people also suffer with Autoimmune dx.** There is no reliable test for CFS/FM & symptoms are the same as Lyme disease

Schwartz AM, Kugeler KJ, Nelson CA, et al. Evaluation of commercial insurance claims as an annual data source for Lyme disease diagnoses. *Emerg Infect Dis.* 2021;27(2).

Kugeler KJ, Schwartz AM, Delorey M, et al. Estimating the frequency of Lyme disease diagnoses —United States, 2010-2018. *Emerg Infect Dis.* 2021;27(2).

<https://www.cdc.gov/me-cfs/index.html>

# How Many People in the US have CLD/PTLDS?

Approximately 2 million people in the US may suffer from PTLDS, as of 2020

Horowitz et al published the first potential treatment for Post Treatment LD Syndrome Randomized, controlled trials are necessary

Estimation of cumulative number of post-treatment Lyme disease cases in the US, 2016 and 2020



Allison DeLong<sup>1\*</sup>, Mayla Hsu<sup>2</sup> and Harriet Kotsoris<sup>3</sup>

## Abstract

**Background:** Lyme disease (LD) is an infectious multi-system illness caused by the bacterial genus *Borrelia* and spread by bites of infected ticks. Although most patients are successfully treated by timely antibiotic therapy, it is broadly accepted that a sizeable number of patients experience treatment failure and continue to suffer long-term, debilitating symptoms, including pain, fatigue, cognitive dysfunction and other symptoms. This is known as post-treatment LD (PTLD), for which diagnosis is not standardized and treatment remains controversial. The prevalence and societal burden of PTLD is unknown.

**Methods:** In an effort to help characterize the LD landscape, we estimated the number of PTLD cases in the US in 2016 and 2020 using Monte-Carlo simulation techniques, publically-available demographic datasets, uncertainty in the inputs and realistic assumptions about incidence and treatment failure rates.

**Results:** Depending on the input assumptions, PTLD prevalence estimates for 2016 ranged from 69,011 persons (95% CI 51,796 to 89,312) to 1,523,869 (CI 1,268,634 to 1,809,416). Prevalence in 2020 is predicted to be higher than 2016, and may be as high as 1,944,189 (CI 1,619,988 to 2,304,147) cases.

**Conclusions:** The cumulative prevalence of PLTD in the United States is estimated to be high and continues to increase. These findings will be of interest to epidemiologists and health economists studying disease burden in the US and elsewhere, and justify funding to study PTLD diagnosis and treatment.

Horowitz, R.I.; Freeman, P.R. Efficacy of Double-Dose Dapsone Combination Therapy in the Treatment of Chronic Lyme Disease/Post-Treatment Lyme Disease Syndrome (PTLDS) and Associated Co-infections: A Report of Three Cases and Retro-spective Chart Review. *Antibiotics* 2020, 9, 725. <https://doi.org/10.3390/antibiotics9110725>

# The Financial Implications of a Well-Hidden and Ignored Chronic Lyme Disease Pandemic

- In the USA by 2050, based on present infection rates, **55.7 million people (12% of the population)** may be infected with Lyme disease.
- In Europe by 2050, **134.9 million people (17% of the population)** will have been infected with Lyme disease. Most of these infections will, unfortunately, become chronic.

Davidsson M. The Financial Implications of a Well-Hidden and Ignored Chronic Lyme Disease Pandemic. Healthcare (Basel). 2018;6(1):16. Published 2018 Feb 13. doi:10.3390/healthcare6010016



# Why the Numbers Still Don't Reflect The Truth

- Present diagnostic testing for Lyme disease usually involves one strain of the bacteria, *Borrelia burgdorferi* (B 31)
- There are multiple strains of *Borrelia*, that are not captured on the standard ELISA, C6 ELISA or Western blot
- These strains that cause Lyme disease are called *Borrelia sensu lato* species
- These multiple species can cause illness that will not be picked up on standard testing. IgeneX laboratories Immunblot picks up 8 strains, and improves sensitivity and specificity
- Rudenko N, Golovchenko M, Grubhoffer L, Oliver JH Jr. Updates on *Borrelia burgdorferi sensu lato* complex with respect to public health. *Ticks Tick Borne Dis.* 2011 Sep;2(3):123-8. doi: 10.1016/j.ttbdis.2011.04.002.

# Borrelia burgdorferi sensu lato complex

18 named species

11 species are in Europe:

*B. afzelii*, *B. bavariensis*, *B. garinii*, *B. japonica*, *B. lusitaniae*, *B. sinica*, *B. spielmani*


*B. tanukii*, *B. turdi*, *B. valaisiana*, and *B. Yangtze*

At least 8 species are in the US:

*B. burgdorferi sensu stricto* (s.s.), *B. bissettii*, *B. carolinensis*, *B. mayoni*, *B. americana*,

*B. andersonii*, *B. californiensis*, and *B. kurtenbachii*

Standard two-tiered testing will miss most strains

 NIH Public Access  
Author Manuscript  
*Ticks Tick Borne Dis.* Author manuscript, available in PMC 2012 September 1.

Published in final edited form as:  
*Ticks Tick Borne Dis.* 2011 September ; 2(3): 123–128. doi:10.1016/j.ttbdis.2011.04.002.

**Updates on *Borrelia burgdorferi sensu lato* complex with respect to public health**

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**Summary**

*Borrelia burgdorferi sensu lato* (s.l.) complex is a diverse group of worldwide distributed bacteria that includes 18 named spirochete species and a still not named group proposed as genomospecies 2 (Postic et al., 2007). Descriptions of new species and variants continue to be recognized, so the current number of described species is probably not final. Most of known spirochete species are considered to have a limited distribution. Eleven species from the *B. burgdorferi* s.l. complex were identified in and strictly associated with Eurasia (*B. afzelii*, *B. bavariensis*, *B. garinii*, *B. japonica*, *B. lusitaniae*, *B. sinica*, *B. spielmani*, *B. tanukii*, *B. turdi*, *B. valaisiana*, and *B. yangtze*), while another 5 (*B. americana*, *B. andersonii*, *B. californiensis*, *B. carolinensis*, and *B. kurtenbachii*) were previously believed to be restricted to the USA only (Rudenko et al., 2009b, 2009c; Margos et al., 2010). *B. burgdorferi sensu stricto* (s.s.), *B. bissettii*, and *B. carolinensis* share the distinction of being present in both the Old and the New World. Out of the 18 genospecies, 3 commonly and 4 occasionally infect humans, causing Lyme borreliosis (LB) – a multisystem disease that is often referred to as the ‘great imitator’ due to diversity of its clinical manifestations. Among the genospecies that commonly infect humans are *B. burgdorferi sensu stricto*, *B. bissettii*, and *B.*

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# What Else Might We Be Missing?

Apart from an estimated ½ million new cases of LD each year in the US, 2 million suffering from PTLDS, 17 million with CFS/FM and 21 million with AI illness, there are also **46.5 million cases of pre-clinical dementia**

Lyme disease spirochetes have been found in the brains of Alzheimer's patients. ? What is the true incidence of Lyme ? Is it a factor in causing Alzheimer's disease?

Lyme is the 'Great Imitator' and may be present in much larger portions of the population. **These #'s do not include co-infs!**

Miklossy, J. Alzheimer's disease - a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. *J Neuroinflammation* 8, 90 (2011).  
<https://doi.org/10.1186/1742-2094-8-90>

# Problems with Diagnostic Testing

- Sensitivity & specificity of 2-tiered testing: 56%/99%. Misses 55% of early LD cases
- Intra/Interlaboratory variation
- Misses *B. sensu lato* spp.
- Marangoni J Med Microbiol 2005;
- De Marteno Med Mal Infect 2007
- Coulter, et al., J Clin Microbiol 2005;43:5080-5084
- 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.



# Other Problems with Diagnostic Testing

- Failure to detect antibodies secondary to circulating immune complexes: ↓ ability to find antibodies in the spinal fluid of Lyme patients w/ significant CNS dx
- *Borrelia* subverts a B cell response, decreasing antibody production, leading to T cell independence
- 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
- 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;
- Baumgarth et al. *PLoS Pathog* 7(5): e1002066. doi:10.1371/journal.ppat.1002066
- Dorward, et al. *Journal 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

# Lyme Is A Clinical Diagnosis: To Test or Not to Test?

- A recent review by Dessau et al support both the clinical diagnosis and a more rational use of laboratory testing in clinically suspected Lyme dx
  - Testing individuals with non-specific symptoms is not recommended, due to a low + predictive value
  - Consider using the HMQ, a statistically validated screening questionnaire: migratory pain is specific
- 
- Dessau RB, et al. To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis. *Clin Microbiol Infect.* 2017 Sep 5. pii: S1198-743X(17)
  - Horowitz R, Lacout A, Marcy PY, Perronne C, To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis. *Clin Microbiol Infect.* 2017 Oct 10
  - Freeman, P., Horowitz, RI et al. Empirical Validation of the Horowitz MSIDS Questionnaire. *International Journal of General Medicine* 2017;10 249-273

# Are Your Symptoms Due to Lyme Disease? Take the Horowitz Lyme-MSIDS Questionnaire (HMQ)

This is a validated screening tool to determine the probability of having Lyme and associated tick-borne illness (without an EM rash)

Photo credit Bart rash: Marna Erickson, Md,  
EM Rash photos: CDC (EM, RMSF)

- **Empirical Validation of the Horowitz Multiple Systemic Infectious Disease Syndrome Questionnaire for Suspected Lyme Disease.** Maryalice Citera<sup>1</sup>\*, Ph.D., Phyllis R. Freeman<sup>2</sup>¶, Ph.D., Richard I. Horowitz<sup>2</sup>¶, M.D., *International Journal of General Medicine* 2017;10 249-273



# HMQ Validation: 1600 individuals, healthy/LD hx

- 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**
- **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 I 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



# The Horowitz Multiple Systemic Infectious Disease Syndrome Questionnaire (HMQ): 4 sections

- **Section 1: The Symptom Checklist:** 38 symptoms rated from 0 (none) to 3 (extremely frequent)
- **Section 2: The Lyme Incidence scale:** ? Likelihood, & evaluate for migratory pain (hallmark of LD)
- **Section 3: The Healthy Days Scale:** physical and mental health) over the last 30 days
- **Section 4: The Common Lyme Score:** points for most common Lyme symptoms



# HMQ Section 1: 38 Item Questionnaire

## Horowitz/MSIDS 38 Point Symptom Checklist

M \_\_\_\_\_ F \_\_\_\_\_ Age \_\_\_\_\_

This is a questionnaire to determine the probability of your having Lyme disease and other tick borne disorders. Please fill this out to the best of your ability and follow the directions below.

	Frequency			
	never	sometimes	most of the time	all of the time
Unexplained fevers, sweats, chills, or flushing	0	1	2	3
Unexplained weight change.....Loss or Gain	0	1	2	3
Fatigue, tiredness	0	1	2	3
Unexplained hair loss	0	1	2	3
Swollen glands	0	1	2	3
Sore throat	0	1	2	3
Testicular pain / Pelvic Pain	0	1	2	3
Unexplained menstrual irregularity	0	1	2	3
Unexplained breast milk production, breast pain	0	1	2	3
Irritable bladder or bladder dysfunction	0	1	2	3
Sexual dysfunction / loss of libido	0	1	2	3
Upset stomach	0	1	2	3
Change in bowel function (Constipation or Diarrhea)	0	1	2	3
Chest pain or Rib soreness	0	1	2	3
Shortness of Breath / Cough	0	1	2	3
Heart palpitations, pulse skips, heart block	0	1	2	3
History of Heart Murmur or Valve Prolapse	0	1	2	3
Joint pain or Swelling	0	1	2	3
Stiffness of the neck or back	0	1	2	3
Muscle pain or cramps	0	1	2	3
Twitching of the face or other muscles	0	1	2	3
Headaches	0	1	2	3
Neck cracks or Neck Stiffness	0	1	2	3
Tingling, numbness, burning or stabbing sensations	0	1	2	3
Facial Paralysis (Bells Palsy)	0	1	2	3
Eyes/Vision - Double, Blurry	0	1	2	3
Ears/Hearing - Buzzing, Ringing, Ear Pain	0	1	2	3
Increased motion sickness, vertigo	0	1	2	3
Lightheadedness, poor balance, difficulty walking	0	1	2	3
Tremors	0	1	2	3
Confusion, difficulty thinking	0	1	2	3
Difficulty with concentration or reading	0	1	2	3
Forgetfulness, poor short term memory	0	1	2	3
Disorientation; getting lost, going to wrong places	0	1	2	3
Difficulty with speech or writing	0	1	2	3
Mood swings, irritability, depression	0	1	2	3
Disturbed sleep - Too Much, Too Little, Early Awake	0	1	2	3
Exaggerated symptoms or worse hangover from alcohol	0	1	2	3

Please add up your totals from each column, then add up the 4 column totals: \_\_\_\_\_. This is your first score.

# Scoring the HMQ/Differential Diagnosis of Migratory Pain

- A score > 63: high likelihood of exposure to Lyme disease
- Especially if “migratory” pain is present
- Score between 45-62 (probable)
- Score between 25-44 (possible)
- Healthy individuals scored < 24
- Q’s 1 +22 on the HMQ indicate possible co-inf w/ Babesia

## 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

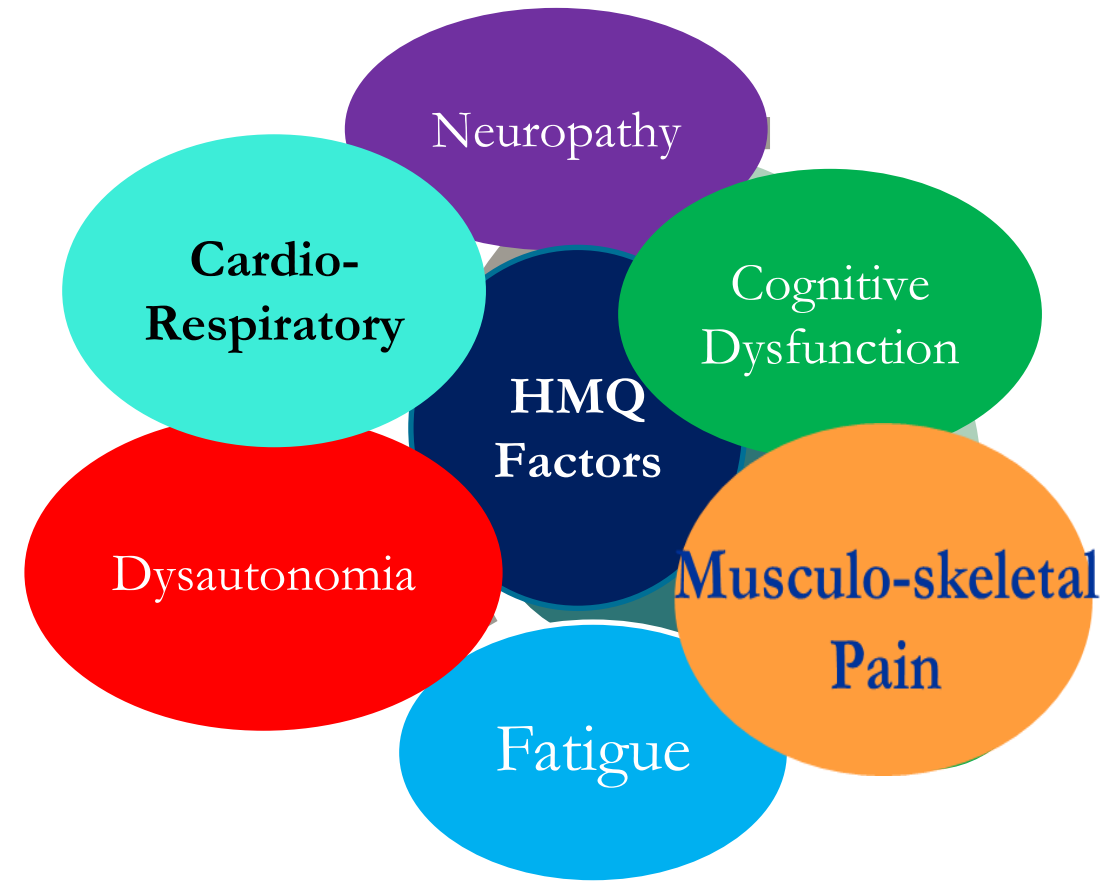
- Acute Rheumatic Fever:  
ASO, anti-DNAase Ab
- Crohn’s Disease/Inflammatory Bowel Disease: colonoscopy, calprotectin (IBD)..
- Gonococcal Arthritis:  
Check for triad: suppurative arthritis, tenosynovitis and dermatitis
- Hepatitis (A, B, C, D, E): check viral Abs’, PCR, RNA
- Reactive Arthritis (Salmonella, Yersinia, Chlamydia species..., HLA B 27+): Reiters triad
- SLE (Lupus): dsDNA, Smith Ag
- Lyme Disease: this is the only disease with migratory nerve pain!

# Validation of the MSIDS Questionnaire: HMQ

5 factors consistent with LD: fatigue, flu like symptoms, joint stiffness, tingling (neuropathy), concentration problems

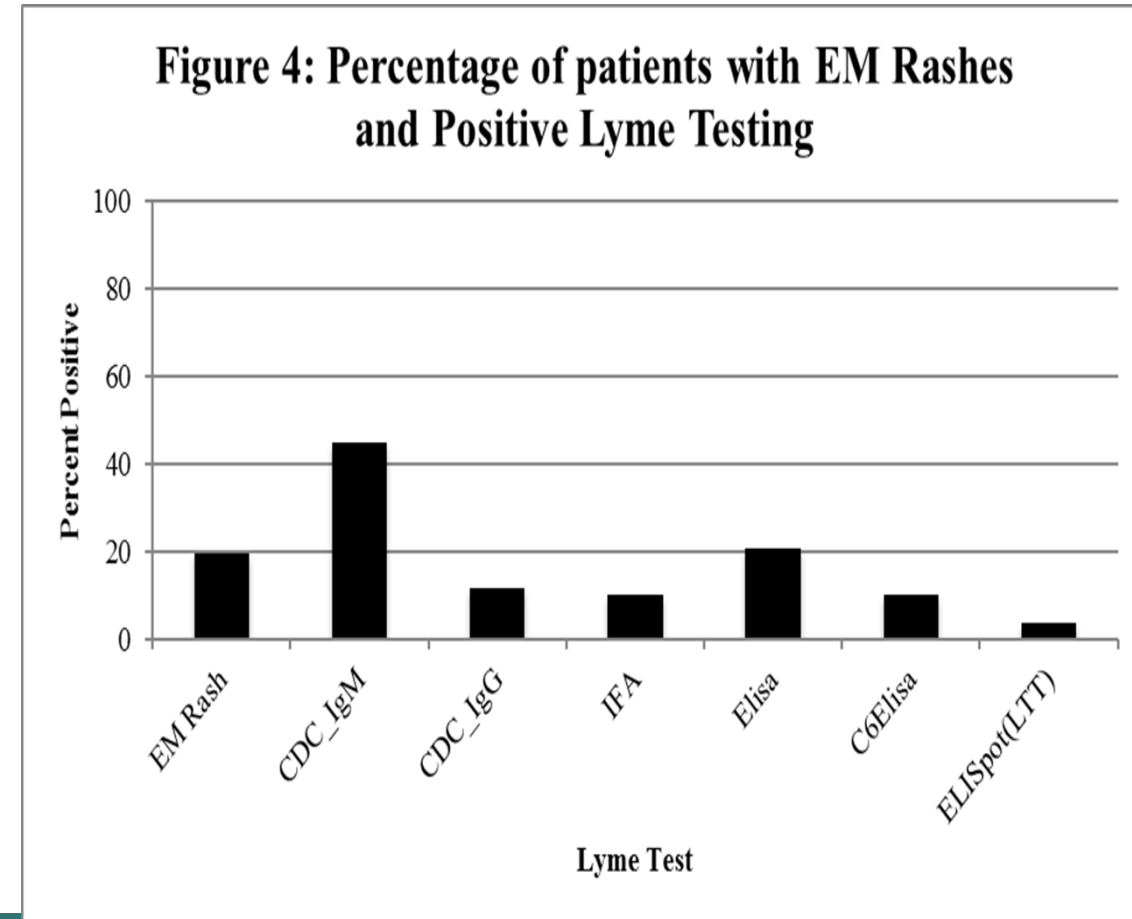
**Migratory joint/muscle/nerve pain was significant!**

Demonstrated convergent and divergent construct validity, as well as predictive validity. **Discriminant analysis showed we could accurately classify the Lyme Status with an 87% accuracy. Superior to 2-tiered testing**



# What About Relying on the Incidence of EM Rashes?

- Percentage of CLD Patients with EM Rashes & + Lyme Testing: 20%
- EM Rash Incidence: 9% - 70-80%
- Variability of clinical presentations
- **Horowitz, R., Freeman P. 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**
- **Stonehouse A, Studdiford JS, Henry CA. An update on the diagnosis and treatment of early Lyme disease: “focusing on the bull’s eye, you may miss the mark.” J Emerg Med. 2010;39(5):e147-151.**
- **Schutzer SE, Berger BW, Krueger JG, Eshoo MW, Ecker DJ, Aucott JN. Atypical Erythema Migrans in Patients with PCR-Positive Lyme Disease. Emerg Infect Dis. 2013;19(5):815-817.**



# Ask If Multiple EM Rashes or ACA Are Present: Implies Dissemination! Treat Until Well!

An EM rash or ACA with one or multiple symptoms:

Neck stiffness with headaches, light and sound sensitivity

Memory and concentration problems, Vertigo, dizziness, difficulty walking: indicates infection in the CNS (Central Nervous System)

Tingling, numbness, burning sensations hands and feet (indicates infection in PNS), or face/scalp (CNS)

Fevers, sweats, chills (? Babesia): see Questions 1+22 HMQ



Marques, A. et al. Early Disseminated Lyme Disease Causing False-Positive Serology for Primary Epstein-Barr Virus Infection: Report of 2 Cases. *Clin Infect Dis*, Volume 65, Issue 2, 15 July 2017, Pages 336-337

Horowitz, RI, Freeman, P. Healthy Fetal Outcomes Using A Novel Treatment For Maternal Lyme Disease And Babesiosis During Consecutive Pregnancies: A Case Study and Literature Review. *Archives of Med Case Reports*. 2020; 2(1): 1-19.

# Diagnostics: Key Points

Panel Approach is best. Do Indirect & Direct tests after establishing a clinical diagnosis (HMQ score). An EM/ACA = LD

**Indirect tests:** IFA, ELISA, C6 ELISA, W. Blot, EIA's , Immunoblot (IgeneX), LTT [Elispot], iSpot, Spirotest

**Direct tests:** PCR, FISH [RNA], culture, Nanotrap, ? Phage

**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

Sedegah M. The Ex Vivo IFN- $\gamma$  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.

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

- 1. Lyme is a **multisystemic illness**. Usually involves multiple body systems
- 2. Symptoms come and go w/ good and bad days, for no apparent reason
- 3. **The pain migrates** around the body (joint/muscle/nerve)
- 4. **Women: symptoms tend to worsen right before, during, and after the menstrual cycle** (low estrogen ↑ symptoms)
- 5. **Symptoms worsen or improve after antibiotic therapy** (Herxheimer reactions)
- 6. You have **positive blood tests** for Lyme and associated TBD's/ + borrelia sp bands

■ 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.

■ 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



# Remember Tick-borne Relapsing Fever (TBRF) + Cross Reactivity of the C6 ELISA & BMD

There are multiple spp. of *Borrelia sensu lato* & soft tick relapsing fever (*B. hermsii*, *B. parkerii*...)

Hard tick RF: *Borrelia miyamotoi* (BMD) is now a common infection in ticks & co-infection. Standard 2-tiered testing will not pick it up

**A + C6 ELISA could imply + BMD**

**Do a RF panel if suspecting LD**

Sudhindra et al., 2016

Molloy et al., 2018

<https://www.hhs.gov/ash/advisory-committees/tickbornedisease/reports/other-tbds-2018-5-9/index.html>

## Cross Reactivity of the C6 ELISA & BMD:

Recent studies have reported cross-reactivity in the Lyme disease C6 ELISA with sera from BMD patients (Sudhindra et al., 2016; Molloy et al., 2018)

Ticks and Tick-borne Diseases 11 (2020) 101-114

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

journal homepage: [www.elsevier.com/locate/tbdis](http://www.elsevier.com/locate/tbdis)

Original article

Identification of immunoreactive linear epitopes of *Borrelia miyamotoi*

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*Borrelia miyamotoi*  
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ABSTRACT

*Borrelia miyamotoi* is an emerging tick-borne spirochete transmitted by ixodid ticks. Current serologic assays for *B. miyamotoi* are impacted by genetic similarities to other *Borrelia* and limited understanding of optimal antigenic targets. In this study, we employed the TB-Serochip, a peptide array platform, to identify new linear targets for serologic detection of *B. miyamotoi*. We examined a wide range of suspected *B. miyamotoi* antigens and identified 352 IgM and 91 IgG reactive peptides, with the majority mapping to variable membrane proteins. These included peptides within conserved fragments of variable membrane proteins that may have greater

# What Else Can Help Establish the Diagnosis?

- Apart from a **high score on the HMQ (> 63)**, **ruling out other causes of migratory pain, & having any borrelia specific bands** on a Western blot or Immunoblot (**23 kda** (Osp C), **31 kda** (Osp A): exception: other viral inf's like EBV can cross react; **34 kda** (Osp B), **39 kda**, **83/93 kda**)
- **Also, any other + tick-borne titers** (HME, HGA, RMSF, Q-fever, tularemia, *B. miyamotoi*, Relapsing fever) **or PCR/FISH** (*Babesia*, *Bartonella*): **↑ probability LD**
- Do an IgM/IgG Immunoblot (IgeneX) and broad tick-borne panel
- 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. Horowitz, R. *How Can I Get Better*. St Martin's Press 2017

# Establishing a Differential Diagnosis: Lyme vs COVID

- COVID-19 as well as Lyme disease w/associated co-inf's both have overlapping symptoms: fevers, chills, headaches, chest pain, cough, shortness of breath, myalgias, arthralgias, fatigue, brain fog, neuropsychiatric symptoms, even diarrhea (**fevers, chills, SOB in the setting of LD: rule out babesiosis**)
- The symptoms of long COVID (PASC) also overlap chronic LD: fatigue, headaches, brain fog, neuropsychiatric symptoms, POTS
- Similarities of symptoms in COVID-19 & LD are due to cytokines ↑ inflammation. **Differences: 88% of COVID patients have anosmia /dysgeusia early in the illness. Lyme causes migratory pain, & Herxheimer reactions w/ antibiotics are also only seen in LD**
- **R.I. Horowitz, P.R. Freeman, Three Novel Prevention, Diagnostic and Treatment Options for COVID-19 Urgently Necessitating Controlled Randomized Trials, Medical Hypotheses (2020)**

# Treatment of Lyme Disease & COVID-19

Finding an effective treatment of CLD/PTLDS has been a ‘medical mystery’ until recently, when Univ researchers discovered biofilm and “persister” forms of LD

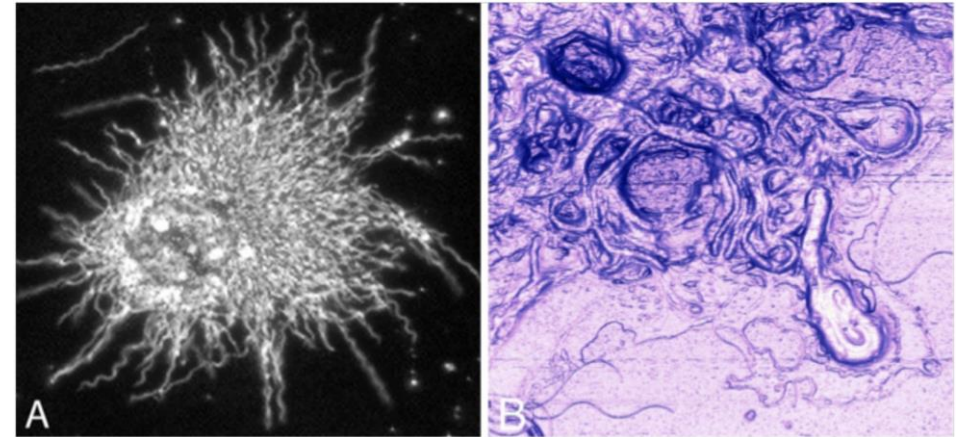
Biofilms are made up of cells & extracellular polymeric substance (EPS), creating a matrix, which provide a physical barrier for antibodies, antibiotics, & shield persisters from the immune system.

Bacteria can genetically exchange material

Horowitz et al discovered that

Dapsone combination therapy (DDS CT)

effectively treats resistant biofilm forms of Bb



- Sapi E, et al. (2012) Characterization of biofilm formation by *Borrelia burgdorferi* In vitro. *PLoS ONE* 7(10): e48277
- Horowitz, R.I., Murali, K., Gaur, G. et al. Effect of dapsone alone and in combination with intracellular antibiotics against the biofilm form of *B. burgdorferi*. *BMC Res Notes* 13, 455 (2020).

# Stationary Phase Persister/Biofilm Forms

## ↑ Inflammation

- Biofilms have been shown to play a role in the persistence of multiple bacterial infections: *C. Diff*, *Salmonella*, *C. albicans* (yeast), staph, *Klebsiella*, *Porphyromona gingivalis*, *Borrelia*
- Rudenko N, Golovchenko M, Kybicova K, Vancova M. **Metamorphoses of Lyme disease spirochetes: phenomenon of *B. burgdorferi* persisters.** *Parasit Vectors.* 2019; 12(1):237.

## 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

Author: **Jie Feng**

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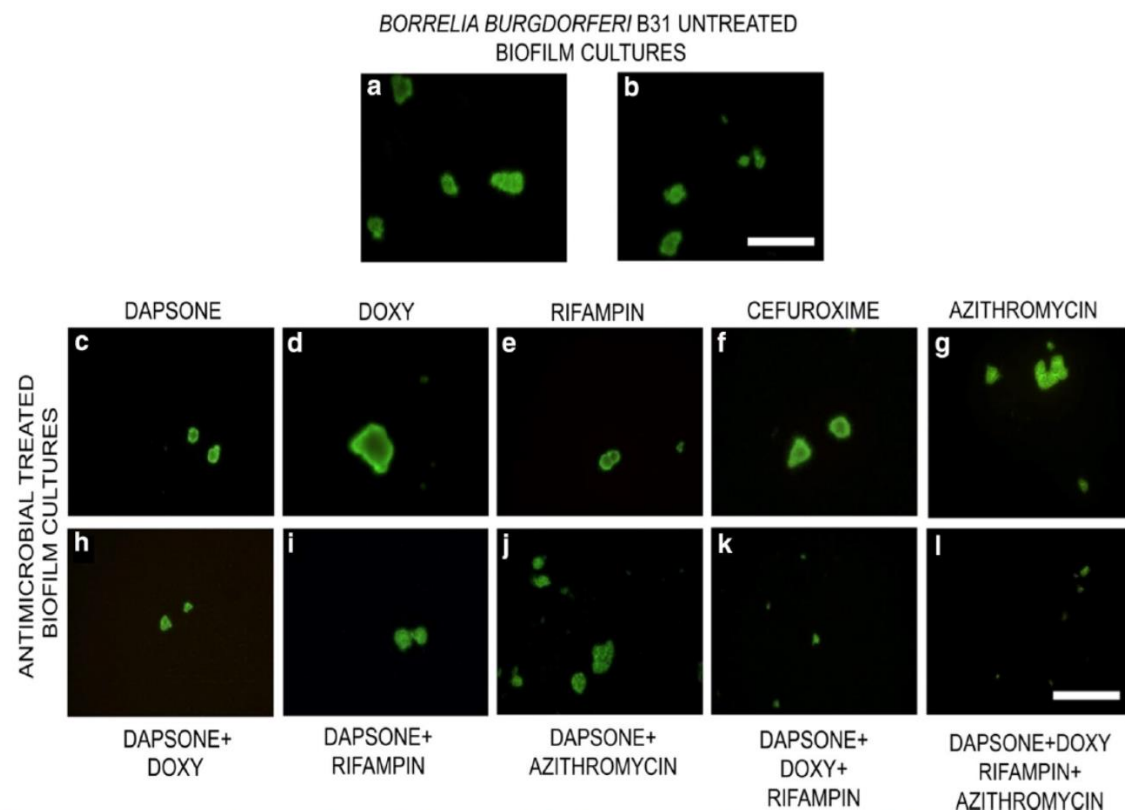
Institution: Department of Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins University

Address: Baltimore, Maryland, 21205, United States

Author: **Rebecca Yee**

Specialty: [Microbiology](#), [Infectious Diseases](#), [Immunology](#)

# Efficacy of Dapsone Alone/In Combination w/IC AB'S



**Fig. 1** Representative Live/Dead images of the attached *B. burgdorferi* biofilms following a 72 h treatment with different antimicrobial agents at 10  $\mu$ M. Biofilms were analyzed by LIVE/DEAD assay as outlined in the Methods and representative images were taken at 100X magnification. Scale bar: 100  $\mu$ m

Horowitz et al. *BMC Res Notes* (2020) 13:455  
<https://doi.org/10.1186/s13104-020-05298-6>

BMC Research Notes

## RESEARCH NOTE

Open Access

### Effect of dapsone alone and in combination with intracellular antibiotics against the biofilm form of *B. burgdorferi*



Richard I. Horowitz<sup>1,2\*</sup>, Krithika Murali<sup>3</sup>, Gauri Gaur<sup>3</sup>, Phyllis R. Freeman<sup>2</sup> and Eva Sapi<sup>3</sup>

#### Abstract

**Objective:** Lyme disease is a tick-borne, multisystemic disease caused by *Borrelia burgdorferi*. Standard treatments for early Lyme disease include short courses of oral antibiotics but relapses often occur after discontinuation of treatment. Several studies have suggested that ongoing symptoms may be due to a highly antibiotic resistant form of *B. burgdorferi* called biofilms. Our recent clinical study reported the successful use of an intracellular mycobacterium persister drug used in treating leprosy, diaminodiphenyl sulfone (dapsone), in combination therapy for the treatment of Lyme disease. In this in vitro study, we evaluated the effectiveness of dapsone individually and in combination with cefuroxime and/or other antibiotics with intracellular activity including doxycycline, rifampin, and azithromycin

**Horowitz, R.I., Murali, K., Gaur, G. et al. Effect of dapsons alone and in combination with intracellular antibiotics against the biofilm form of *B. burgdorferi*. BMC Res Notes 13, 455 (2020).**

- Dapsone, as a single drug and in combination with doxycycline and doxycycline + rifampin as well as doxycycline + rifampin + azithromycin had the most significant effect in reducing the mass and viability as well the protective mucopolysaccharide layers of *B. burgdorferi* biofilm.
- These findings might explain at least in part its clinical efficacy seen in recent DDS CT trials

# DDD CT in Chronic LD/PTLDS: 45-58% Efficacy

- A 7–8-week regimen of DDD CT was found to be safe and effective in our 40 patients
- It was superior to lower-dose dapsons combination therapy (DDS CT), leading to long-term remission in 45% of patients for one year or longer, including patients sick for decades
- In those with a history of an EM rash/PTLDS, DDD CT led to long term remission in 7/12 patients (58%)
- This is the first short term AB protocol effective in CLD/PTLDS. Next step = Multicenter, placebo-controlled RCT. We need to find effective treatment for babesia/bartonella



Case Report

## Efficacy of Double-Dose Dapsone Combination Therapy in the Treatment of Chronic Lyme Disease/Post-Treatment Lyme Disease Syndrome (PTLDS) and Associated Co-infections: A Report of Three Cases and Retrospective Chart Review

Richard I. Horowitz <sup>1,2,\*</sup> and Phyllis R. Freeman <sup>2</sup>

<sup>1</sup> Member, HHS Babesia and Tick-borne Pathogens Subcommittee, Washington, DC 20201, USA

<sup>2</sup> Hudson Valley Healing Arts Center, Hyde Park, NY 12538, USA; research@hvzac.com

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Received: 30 August 2020; Accepted: 21 October 2020; Published: 22 October 2020

**Abstract:** Three patients with multi-year histories of relapsing and remitting Lyme disease and associated co-infections despite extended antibiotic therapy were each given double-dose dapsons combination therapy (DDD CT) for a total of 7–8 weeks. At the completion of therapy, all three patients' major Lyme symptoms remained in remission for a period of 25–30 months. A retrospective chart review of 37 additional patients undergoing DDD CT therapy (40 patients in total) was also performed, which demonstrated tick-borne symptom improvements in 98% of patients, with 45% remaining in remission for 1 year or longer. In conclusion, double-dose dapsons



# Co-infections with Babesia & Bartonella Interfere with Long Term Remission

**Table 1.** Co-infection status and treatment response in 40 patients on DDD CT.

<b>Response to Treatment</b>	<b>Bm 21</b>	<b>Bd 5</b>	<b>Bab FISH + 6</b>	<b>E 5</b>	<b>A 3</b>	<b>Bart AB + 18</b>	<b>VEGF ↑ 6</b>	<b>Bart PCR +/- Biopsy + 2</b>	<b>Bart FISH + 7</b>	<b>1 Co- inf 20</b>	<b>2 Co- inf's 12</b>	<b>3 Co- inf's 5</b>
Remission	12	2	3	2	1	6	2	0	0	8	6	2
Improved 10-20%	3	1	1	2	1	3	2	1	2	3	2	2
Improved 20-30%	2	0	1	0	0	2	2	0	3	5	1	0
Improved >30%	3	1	1	1	0	6	0	1	1	4	3	0
No change	1	1	0	0	1	1	0	0	1	0	0	1

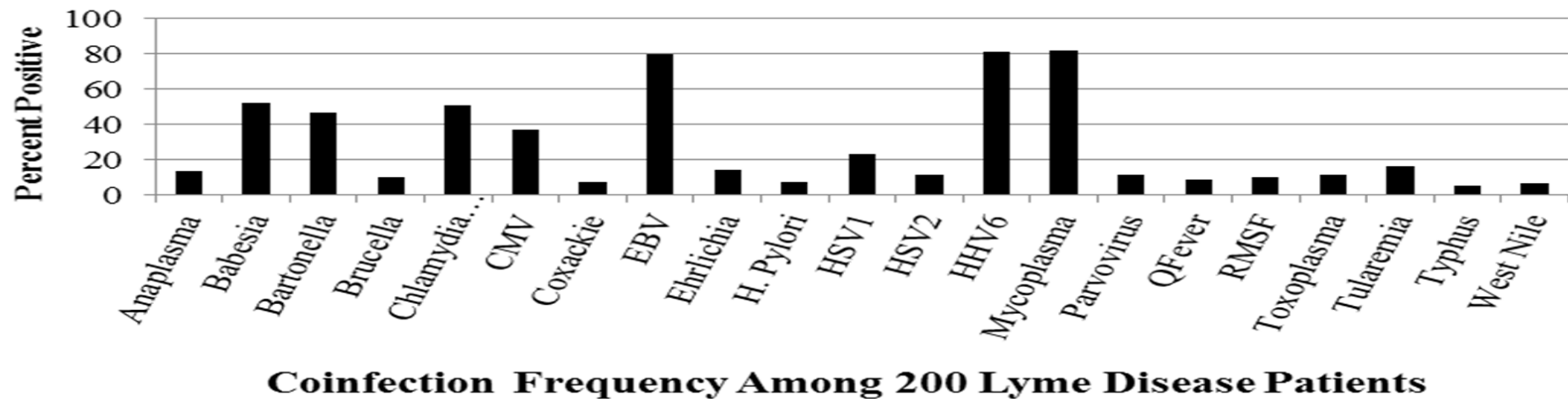
Abbreviations: *Babesia microti* (Bm); *Babesia duncani* (Bd); *Babesia* florescent in situ hybridization (Bab FISH); Ehrlichia (E); Anaplasma (A); *Bartonella* antibody (Bart AB); vascular endothelial growth factor (VEGF); *Bartonella* polymerase chain reaction (Bart PCR); *Bartonella* florescent in situ hybridization (Bart FISH); co-infections (Co-inf).

# Co-infection Status N=200 Dapsonone

## 64% of patients had between 5-8 coinfections

Horowitz, Freeman: Precision Medicine: retrospective chart review and data analysis of 200 patients on dapsonone combination therapy for chronic Lyme disease/post-treatment Lyme disease syndrome: part 1. International Journal of General Medicine 2019;12 101-119

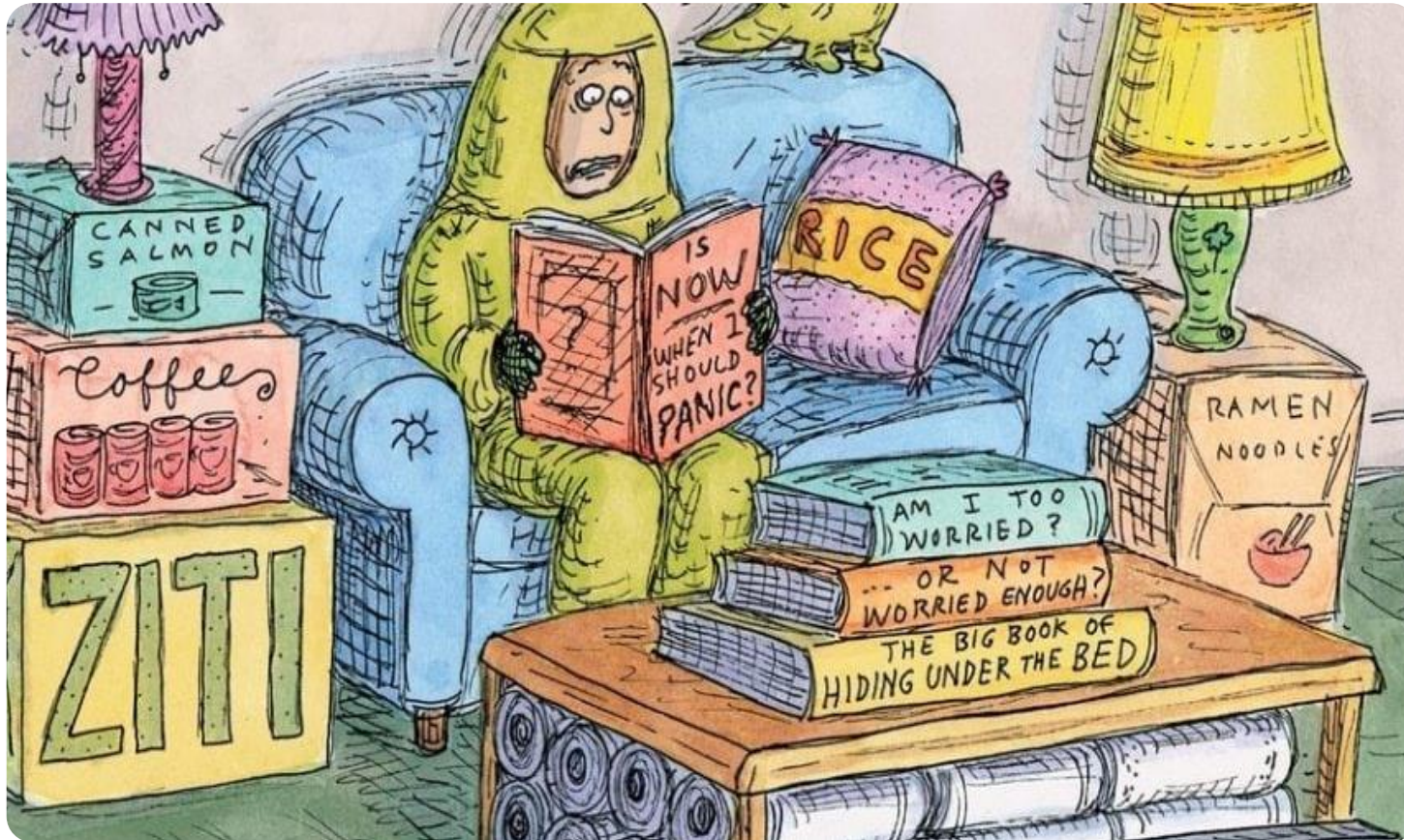
**Figure 4: Coinfections**



# Comprehensive Treatment of Lyme Disease & Associated Co-infections May Therefore Involve:

- **Addressing log phase** (actively growing forms: penicillins, cephalosporins, vancomycin), **round body forms** (Plaq, GSE, Flagyl, Tinidazole), **intracellular forms** (tetracyclines, macrolides, rifampin, rifabutin, PZA, quinolones) & **biofilm/persister forms** (dapsons combination therapy, disulfiram, ? IV azlocillin, daptomycin)
- **Addressing associated co-infections** (esp Babesia & Bartonella spp.)
- **Addressing abnormalities on the 16-point MSIDS model/3 I's**
- 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.

# What About Treatment For COVID-19: Should We Panic?



The answer is NO!

There are effective strategies with medications & nutraceuticals that can support a healthy immune response.

However, we need more studies and RCT's

# Treatment of COVID: Few Effective Medications

- Few drug therapies have been found to be effective in COVID-19 (monoclonal AB's, remdesivir, lopinavir, bamlanivab, dexamethasone, SSRI's, full dose anti-coagulation in non-ICU pts)

Robert L. Gottlieb, MD, PhD, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19. A Randomized Clinical Trial. JAMA. 2021;325(7):632-644.

Ivan Fan-Ngai Hung et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Published Online May 8, 2020. [https://doi.org/10.1016/S0140-6736\(20\)31042-4](https://doi.org/10.1016/S0140-6736(20)31042-4)

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19A Meta-analysis. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. JAMA. Published online September 2, 2020.

Eric J. Lenze, MD, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19A Randomized Clinical Trial. JAMA. Published online November 12, 2020

Nicolas Hoertel, et al. Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: results from an observational study. Molecular Psychiatry. <https://doi.org/10.1038/s41380-021-01021-4>

REMAP-Cap, ACTIV-4, ATTACC clinical trials, NIH: <https://www.nih.gov/news-events/news-releases/full-dose-blood-thinners-decreased-need-life-support-improved-outcome-hospitalized-covid-19-patients>

# Might Addressing ROS & Inflammation Help?

- Activation of NF-kappaB is required for transcription of the genes → ↑ pro-inflammatory mediators associated w/ ARDS.
- NF-κB also plays a key role later in the resolution of inflammation when anti-inflammatory genes are expressed (ARE)
- SARS-CoV-1 N protein interacts with NF-Kappa B in a dose-dependent manner to regulate IL-6 expression. A 2011 study showed that IL-6 induced a dose-dependent decrease in intracellular GSH levels in human cell lines, including lung cells. ↓ GSH has been shown to be associated with an ↑ in IL-6. COVID-19 may stimulate a positive feedback cycle of increased IL-6 and decreased GSH that may explain the cytokine storm that can accompany this infection

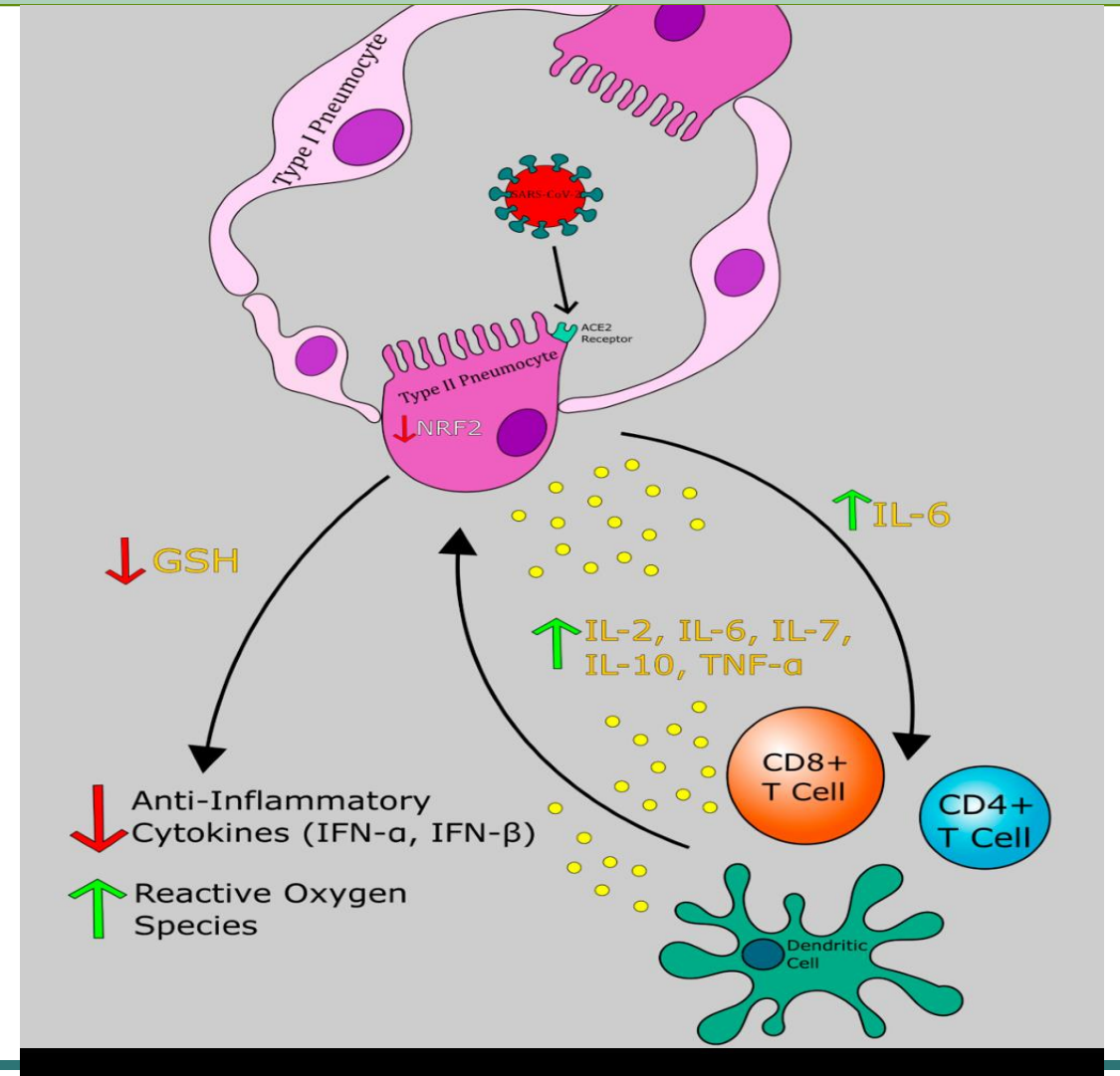
- Gasparini C, Feldmann M. NF-κB as a target for modulating inflammatory responses. *Curr Pharm Des.* 2012;18(35):5735-5745. doi:10.2174/138161212803530763
- Liao, Q.; Ye, L.; Timani, K.; Zeng, Y.; She, Y.; Ye, L.; WU, Z. Activation of NF-kappaB by the Full-length Nucleocapsid Protein of the SARS Coronavirus. *Acta Biochim. Biophys. Sin.* 2005, 37, 607-612.
- Rahman A, Fazal F. Blocking NF-κB. *Proc Am Thorac Soc.* 2011;8(6):497-503. doi:10.1513/pats.201101-009MW

# Treatment of COVID: Oxidative Stress and The Effects of Inflammation Underlie Acute & Chronic Illness

- COVID-19 induced inflammation & “cytokine storm syndrome” with Macrophage Activation Syndrome (MAS) have resulted in extreme morbidity & mortality (esp. w/ co-morbidities)
- Deficiency in RBC, serum and alveolar GSH has been published in the medical literature for ARDS, as well as viral and bacterial pneumonias, resulting from increased levels of free radical/oxidative stress
- Gadek JE, Pacht ER. The Interdependence of Lung Antioxidants and Antiprotease Defense in ARDS. CHEST. 1996;110(6):273S-277S. doi:10.1378/chest.110.6\_Supplement.273S
- Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020;395(10229):1033-1034.
- Gasparini C, Feldmann M. NF- $\kappa$ B as a target for modulating inflammatory responses. Curr Pharm Des. 2012;18(35):5735-5745. doi:10.2174/138161212803530763

# Why Use Glutathione ?

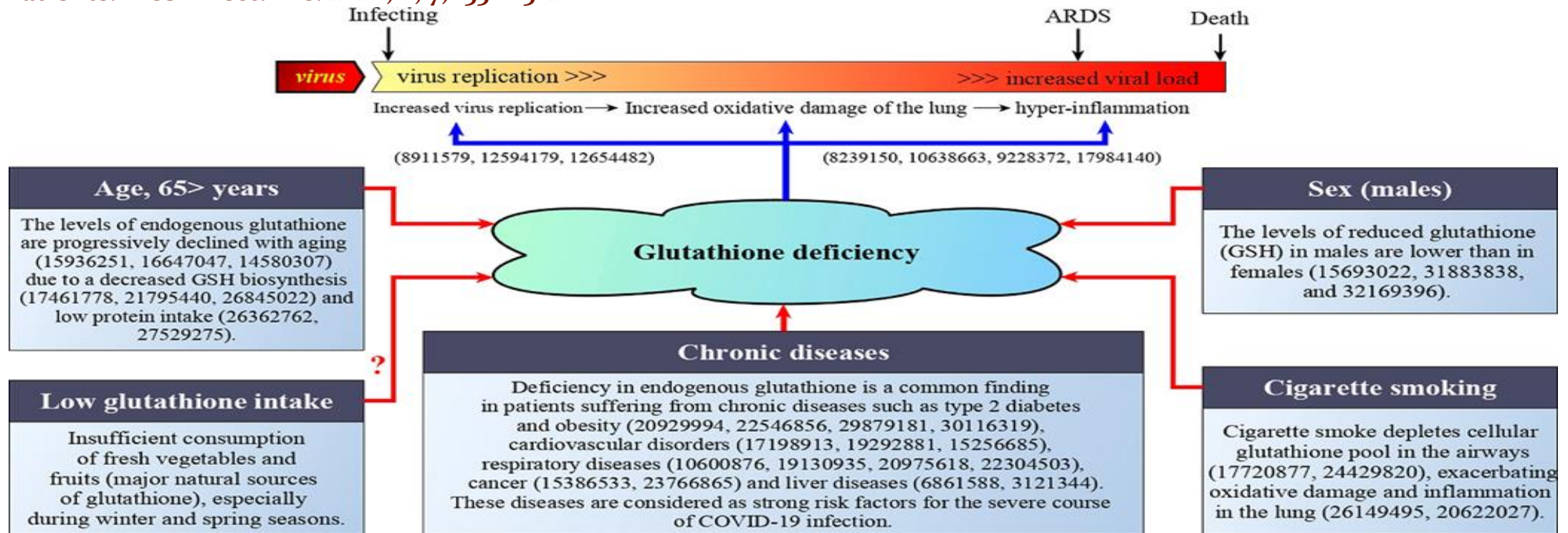
- SARS-CoV-2 can induce cytokine storm and redox imbalance. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor and induces down regulation of nuclear factor erythroid 2-related factor 2 (NRF2), which leads to inhibition of glutathione (GSH) release.
- This results in elevated inflammatory cytokines, elevated reactive oxygen species (ROS), and recruitment of immune cells.
- Antioxidants 2020, 9, 914; doi:10.3390/antiox9100914





# GSH Deficiency: Common Finding in Type 2 DM, Obesity, CV & Respiratory Dis, Cancer: Strong Risk Factors for COVID-19

- Polonikov, A. Endogenous Deficiency of Glutathione as the Most Likely Cause of Serious Manifestations and Death in COVID-19 Patients. *ACS Infect. Dis.* 2020, 6, 7, 1558-1562



# Why Consider Glutathione As Adjunctive Therapy?

- **GSH inhibits viral replication** (influenza, dengue, HIV, hepatitis) through binding w/thiol groups and helping to ↓ **oxidative stress** (prooxidant conditions ↑ viral pathogenesis)
- **Glutathione Fine-Tunes the Innate Immune Response toward Antiviral Pathways** in a Macrophage Cell Line Independently of Its Antioxidant Properties
- **GSH lowers inflammatory cytokines** like IL-6 by blocking NFKappa B. Inflammation ↑ morbidity/mortality in COVID





antioxidants



Review

## Glutathione Supplementation as an Adjunctive Therapy in COVID-19

Vika Guloyan<sup>1</sup>, Buzand Oganessian<sup>1</sup>, Nicole Baghdasaryan<sup>1</sup>, Christopher Yeh<sup>1</sup>, Manpreet Singh<sup>2</sup>, Frederick Guilford<sup>3</sup>, Yu-Sam Ting<sup>1</sup>  and Vishwanath Venketaraman<sup>1,\*</sup> 

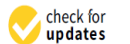
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**Abstract:** Morbidity and mortality of coronavirus disease 2019 (COVID-19) are due in large part to severe cytokine storm and hypercoagulable state brought on by dysregulated host-inflammatory immune response, ultimately leading to multi-organ failure. Exacerbated oxidative stress caused by increased levels of interleukin (IL)-6 and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) along with decreased

# Why Consider Glutathione As Adjunctive Therapy?

- GSH in the lower lining of the upper resp tract is the first line of defense against oxidative stress
- In the epithelial lining fluid, GSH concentrations are 140X higher than in the serum
- Changes in GSH concentration are considered central in the context of inflammatory lung diseases

**Advance Research Journal of Medical and Clinical Science**

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ARJMCS 07 (02), 415-427 (2021) | ISSN (O) 2455-3549

DOI-- <https://doi.org/10.15520/arjmcs.v7i02.247>

**Research Article,**

## **The role of Glutathione as an adjunct therapy in the treatment of patients with COVID-19-Related Acute Respiratory Syndrome**

**Taís Mazzini Setti (TM), MD<sup>1</sup>, Thiago Setti (TS), MD<sup>2</sup>, Lucas Furtado da Fonseca (LF), MD<sup>3</sup>, Stephany Cares Huber, PhD<sup>4</sup>, Gabriel Silva Santos (GS)\*<sup>5</sup>, José Fábio Santos Duarte Lana (JL), MD<sup>6</sup>**

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4. Biomedical Scientist, Universidade Estadual de Campinas (UNICAMP) / The University of Campinas Cidade Universitária Zeferino Vaz Campinas – SP, Brazil

# Could Glutathione Be Used as PrEP? RCT's needed

- Open label, single center study to evaluate safety & efficacy of pre-exposure prophylaxis (PrEP) w/ nebulized GSH (21.3 mg/ml)
- Compared 99 treated HCW's/vs 268 untreated HCW's
- SARS-COVID + in 2/99 (95% CI, 0.3-7.1%) treated HCWs vs 24/268 non-users (95% CI, 5.8-13%,  $p = 0.02$ )
- <https://www.medrxiv.org/content/10.1101/2020.09.25.20199562v1>

medRxiv preprint doi: <https://doi.org/10.1101/2020.09.25.20199562>; this version posted October 6, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a [CC-BY-NC-ND 4.0 International license](https://creativecommons.org/licenses/by-nc-nd/4.0/).

## Pathogenesis-based pre-exposure prophylaxis associated with low risk of SARS-CoV-2 infection in healthcare workers at a designated Covid-19 hospital

Michael V. Dubina, DMSc, Veronika V. Gomonova, MD, Anastasia E. Taraskina, PhD,  
Natalia V. Vasilyeva, DBSc, and Sergey A. Sayganov, DMSc

**Affiliations:** North-Western State Medical University named after I.I. Mechnikov of Ministry of Health of Russian Federation, 41 Kirochnaya str., 191015 St. Petersburg, Russia (V.V.G, A.E.T., N.V.V., and S.A.S.); Russian Academy of Sciences, 14 Leninskiy pr., 119991 Moscow, Russia, and State Research Institute of Highly Pure Biopreparations of Federal Medical Biological Agency of Russia, 7 Pudozhskaya str., 197110 St. Petersburg, Russia (M.V.D.).

**Contact:** Dr. Dubina at the State Research Institute of Highly Pure Biopreparations FMBA Russia, 7 Pudozhskaya str., St. Petersburg 197110, Russia, or at [michael.dubina@gmail.com](mailto:michael.dubina@gmail.com).

**Abstract:** At present, no agents are known to be effective in preventing Covid-19. Based on

# Glutathione Deficiency Can ↑ Symptoms in COVID-19: Successful Treatment of 65 Patients @ HVHAC



Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. *Respiratory Medicine Case Reports*, April 21, 2020. Article Number: 101063

## Efficacy of Glutathione in Relieving Dyspnea Associated w/COVID-19 Pneumonia

Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. *Respiratory Medicine Case Reports*, April 21, 2020

Respiratory Medicine Case Reports 30 (2020) 101063

Contents lists available at [ScienceDirect](#)

 **Respiratory Medicine Case Reports** 

journal homepage: <http://www.elsevier.com/locate/rmcr>

Case report

**Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases**

Richard I. Horowitz<sup>a,b,\*</sup>, Phyllis R. Freeman<sup>b</sup>, James Bruzzese<sup>c</sup>

<sup>a</sup> HHS Biobehavioral and Tickborne Pathogen Subcommittee, Washington, D.C., 20201, USA  
<sup>b</sup> Hudson Valley Healing Arts Center, 4232 Albany Post Road, Hyde Park, NY, 12538, USA  
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**ARTICLE INFO**

**Keywords:**  
COVID-19  
Pneumonia  
ARDS  
N-acetyl-cysteine  
Glutathione  
NF-κB

**ABSTRACT**

**Purpose:** Infection with COVID-19 potentially can result in severe outcomes and death from “cytokine storm syndrome”, resulting in novel coronavirus pneumonia (NCP) with severe dyspnea, acute respiratory distress syndrome (ARDS), fulminant myocarditis and multiorgan dysfunction with or without disseminated intravascular coagulation. No published treatment to date has been shown to adequately control the inflammation and respiratory symptoms associated with COVID-19, apart from oxygen therapy and assisted ventilation. We evaluated the effects of using high dose oral and/or IV glutathione in the treatment of 2 patients with dyspnea secondary to COVID-19 pneumonia.

# Studies on the Efficacy of NAC, GSH & Nutraceuticals in COVID-19: Antiviral, Anti-inflammatory

- **NAC and Glutathione (along with ALA) block NFκB ↓ inflammatory cytokines (similar cytokines in Lyme and COVID) & NAC + GSH are anti-viral (influenza, hepatitis, dengue, HIV): role of thiol groups**
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- Marina Diotallevi et al. Glutathione Fine-Tunes the Innate Immune Response toward Antiviral Pathways in a Macrophage Cell Line Independently of Its Antioxidant Properties. *Front. Immunol.*, 29 September 2017
- Palamara AT et al. Evidence for antiviral activity of glutathione: in vitro inhibition of herpes simplex virus type 1 replication. *Antiviral Res.* 1995 Jun;27(3):237-53.
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# Mechanisms of Action of NAC, GSH: Antiviral Activity via Glutathionylation & Thiol Groups

- Viruses alter the intracellular redox state to pro-oxidant conditions, which is an alteration that contributes to viral pathogenesis. Glutathionylation of cellular proteins during viral infections has been reported since 1997, and these are involved in the cellular response to infection
- Covid-19, and RNA viruses in general, need to progressively lower glutathione levels in cells to replicate. As glutathione becomes depleted, different enzymes (viral and host) get turned on or off. This provides a mechanism for the virus to regulate its life cycle.

- Checconi, P.; Limongi, D.; Baldelli, S.; Ciriolo, M.R.; Nencioni, L.; Palamara, A.T. Role of Glutathionylation in Infection and Inflammation. *Nutrients* 2019, **11**, 1952. <https://doi.org/10.3390/nu11081952>
- Zarka MH and Bridge WJ. 2017. Oral administration of  $\gamma$ -glutamylcysteine increases intracellular glutathione levels above homeostasis in a randomised human trial pilot study. *Redox Biol* **11**, 631-636

# Ivermectin & Nutraceuticals Can Help Support A Healthy Immune/Inflammatory Response:

R.I. Horowitz, P.R. Freeman, Three Novel Prevention, Diagnostic and Treatment Options for COVID-19 Urgently Necessitating Controlled Randomized Trials, Medical Hypotheses (2020)

## Overlap of Inflammation in Lyme & COVID: 2<sup>nd</sup> Study by Horowitz et al, 2020



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Medical Hypotheses

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Three novel prevention, diagnostic, and treatment options for COVID-19 urgently necessitating controlled randomized trials

Richard I. Horowitz<sup>a,b,\*</sup>, Phyllis R. Freeman<sup>b</sup>

<sup>a</sup> HHS Babesia and Tickborne Pathogen Subcommittee, Washington, D.C. 20201, USA

<sup>b</sup> Hudson Valley Healing Arts Center, 4232 Albany Post Road, Hyde Park, NY 12538, USA





# Studies on Ivermectin & COVID-19: 5000-fold Reduction in Viral RNA, Over 26 Studies, 10 RCTs: Positive Effects

- Caly, L. et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Research* Volume 178, June 2020, 104787
- Hill A, Abdulmir A, Ahmed S et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. 2021. doi:10.21203/rs.3.rs-148845/v1
- Fatemeh Heidary et al. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *The Journal of Antibiotics*. 17 May 2020. <https://doi.org/10.1038/s41429-020-0336-z>
- Gupta D, et al. Ivermectin: potential candidate for the treatment of Covid 19. *Braz J Infect Dis*. 2020.
- Ivermectin is effective for COVID-19: meta analysis of 26 studies. *Covid Analysis*, November 26, 2020 (Version 6, December 18, 2020)@CovidAnalysis. <https://ivmmeta.com/?fbclid=IwAR1TJL4ZuXXZResPV-xP8L47aV8CoaMlDjtRrnFrezXhOCskur7QDj8y3AE>
- Martin D. Hellwig et al. A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin. *International Journal of Antimicrobial Agents*. Volume 57, Issue 1, January 2021, 106248
- Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019. The Ivermectin in COVID Nineteen Study. Juliana Cepelowicz Rajter, MD, et al. *CHEST* 2021; 159(1):85-92

# Ivermectin Decreases Ventilator Mortality

- In an observational study from 169 hospitals across Asia, Europe, Africa, North and South America, they evaluated 1970 critically ill hospitalized patients diagnosed with COVID-19 with lung injury requiring mechanical ventilation, between Jan-Mar 2020
- 1,609 survived hospitalization and 361 died (18.3%)
- 52 patients received Ivermectin (150 mcg/Kg) after mechanical ventilation was instituted
- Survival benefit for ivermectin was 18.6% vs 7.7%
- Patel, A. et al. Ivermectin in COVID-19 Related Critical Illness. Univ. of Utah, Salt Lake City, <https://ssrn.com/abstract=3570270>
- Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019. The Ivermectin in COVID Nineteen Study. Juliana Cepelowicz Rajter, MD, et al. CHEST 2021; 159(1):85-92

# Studies on Nrf2 Activation & Suppressing NLRP3 Inflammasome Activation : Curcumin, Sulforaphane Glucosinolate, Melatonin

- Nrf2 inhibits NF-κB activation helping to lower cytokines: Nrf2 activation: curcumin, sulforaphane, resveratrol, EGCG
- Derosa G, et al. Effect of curcumin on circulating interleukin-6 concentrations: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res.* 2016 Sep;111:394-404.
- Sayali Savant et al. Potential Nutraceuticals for COVID-19. *Nutrition and Dietary Supplements* 2021;13 25-51
- McCarty, M.F. et al. Nutraceutical Strategies for Suppressing NLRP3 Inflammasome Activation: Pertinence to the Management of COVID-19 and Beyond. *Nutrients* 2021, 13, 47. <https://doi.org/10.3390/nu13010047>
- Kerch, G. Tissue Integrity and COVID-19. *Encyclopedia* 2021, 1, 206-219. <https://doi.org/10.3390/encyclopedia1010020>

# Glucoraphanin (Broccoli seed extract): Antiviral & Anti-inflammatory Effects via Nrf2 Activation

In double blind studies, sulforaphane has anti-viral effects, & induces granzyme B production in NK cells decreasing viral RNA levels

Sulforaphane is the most potent Nrf2 activator: + effect in minutes in 3 COVID-19 pts



Bousquet et al. *World Allergy Organization Journal* (2021) 14:100498  
<http://doi.org/10.1016/j.waojou.2020.100498>



WORLD ALLERGY ORGANIZATION JOURNAL

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RESEARCH ARTICLE

## Effect of Broccoli Sprouts and Live Attenuated Influenza Virus on Peripheral Blood Natural Killer Cells: A Randomized, Double-Blind Study

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## Efficacy of broccoli and glucoraphanin in COVID-19: From hypothesis to proof-of-concept with three experimental clinical cases

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### ABSTRACT

COVID-19 is described in a clinical case involving a patient who proposed the hypothesis that Nuclear factor (erythroid-derived 2)-like 2 (Nrf2)-interacting nutrients may help to prevent severe COVID-19 symptoms. Capsules of broccoli seeds containing glucoraphanin were being taken before the onset of SARS-CoV-2 infection and were continued daily for over a month after the first

# Decreasing Inflammasome Activation: Role of Melatonin

- Apart from blocking NFκB and stimulating Nrf2, a third pathway that may be affecting COVID patients is inflammasome activation
- Inflammasomes are part of our innate immune system that sense pathogens & danger associated molecular patterns (DAMPs). The activation of inflammasomes → ↑ proinflammatory cytokines IL-1β & IL-18
- High level activation of the NLRP3 inflammasome is essential for inducing cytokine storms & lung injury
- Melatonin Inhibits NLRP3 Inflammasomes



- **Critical role for the NLRP3 inflammasome during acute lung injury** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4061751/>
- **Melatonin Alleviates Acute Lung Injury Through Inhibiting the NLRP3 Inflammasome - PubMed** <https://pubmed.ncbi.nlm.nih.gov/26888116-melatonin-alleviates-acute-lung-injury-through-inhibiting-the-nlrp3-inflammasome/>

# Other Potentially Beneficial Therapies: Zinc

- Zinc plays a central role in the immune system & mediates nonspecific immunity, affecting neutrophils & NK cells
- Zinc-deficiency  $\uparrow$  susceptibility to pathogens. After zinc supplementation  $\rightarrow$   $\downarrow$  incidence of infections,  $\downarrow$  TNF- $\alpha$  & oxidative stress markers
- Provides protection against TNF- $\alpha$ -induced nuclear factor- $\kappa$  $\beta$  activation in mononuclear cells
- Macrophages are adversely affected by zinc deficiency, which can dysregulate intracellular killing and cytokine production

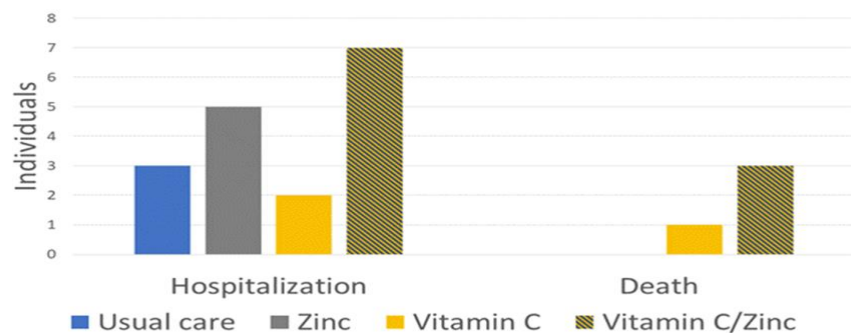
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# Potential Role of Vitamin C in COVID-19?

Vitamin C can ↓ the duration of mechanical ventilation in critically ill patients but zinc & Vit C alone were insufficient in COVID-19 to change time to clinical recovery

Hemilä H. Vitamin C and Community-acquired Pneumonia. *Am J Respir Crit Care Med.* 2011;184(5):621-622.

Thomas S. et al. *JAMA Netw Open.* 2021;4:e210260.



Medscape

↓ Levels of Vitamin C, thiols, and ↓ levels of reduced GSH were found in ICU pts with ↑ oxidative stress, ↑ Cu, low Zn



antioxidants



Article

## Oxidative Stress Status in COVID-19 Patients Hospitalized in Intensive Care Unit for Severe Pneumonia. A Pilot Study

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Citation: Pincemail J, Cavalier E, Charlier C, Cheramy-Bien JP, Brevers E, Courtois A, Fadeur M, Meziane S, Le Goff C, Misset B, Albert A, Defraigne JO, Rousseau AF. Oxidative Stress Status in COVID-19 Patients Hospitalized in Intensive Care Unit for Severe Pneumonia. A Pilot Study. *Antioxidants* 2021; 10(12):2026. doi:10.3390/antiox10122026

# Potential Role for Beta glucan as Immune Support?

- Risk factors for COVID in MAS/sHLH include cytopenias, ↓ NK cells, ↑ LDH, ↑ hs-CRP, ↑ ferritin, coagulopathy
- Medicinal mushroom blends (MMB) have immune-activating, anti-inflammatory & regenerative effects & may ↑ NK cells needed to fight infection

- Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet*. 2020;395(10229):1033-1034.
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ORIGINAL RESEARCH

## Differential Immune Activating, Anti-Inflammatory, and Regenerative Properties of the Aqueous, Ethanol, and Solid Fractions of a Medicinal Mushroom Blend

This article was published in the following Dove Press journal:  
*Journal of Inflammation Research*

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**Purpose:** To compare three fractions of a medicinal mushroom blend (MMB), MyCommunity, on immune-activation, inflammation-regulation, and induction of biomarkers involved in regenerative functions.

**Methods:** A seventeen-species MMB was sequentially extracted: first, saline solution at ambient temperature, followed by re-extraction of the solids in ethanol, and finally resuspension of the homogenized ethanol-insoluble solids in cell-culture media. Fractions were tested on peripheral blood mononuclear cells from three healthy donors. Immunostaining, flow-cytometry, and Luminex protein-arrays measured immune-cell activation and cytokine response. Dose-responses for induction of the CD69 early activation marker and individual cytokine and growth-factor responses for each donor were evaluated. The CD69 and the

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# Conclusion: Future Avenues of Research in COVID

COVID-19 can cause cytokine storm syndrome & Macrophage Activation Syndrome (MAS) in susceptible individuals' w/thrombosis

Inflammation, inflammasomes, ↓ Nrf2 & ↑ NFK-B activation all increase chemokines, cytokines

Infl. cytokines & GSH depletion have been associated with ARDS and injury to internal organs

Using targeted antivirals like ivermectin along with anti-oxidant therapies (NAC, ALA, GSH, curcumin, sulforaphane, melatonin, Zn, Vit C...) & immune support may be useful.

Published case studies and clinical experience w/65 COVID patients show GSH rapidly helps dyspnea and underlying symptomatology (fatigue, myalgias, headaches...)

Randomized, controlled trials need to be done to evaluate the hypotheses. UCI study pending ([www.cangetbetter.com](http://www.cangetbetter.com))

Horowitz, R.I., Freeman P, Bruzzese, J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respiratory Medicine Case Reports, April 21, 2020. R.I. Horowitz, P.R. Freeman, Three Novel Prevention, Diagnostic and Treatment Options for COVID-19 Urgently Necessitating Controlled Randomized Trials, Medical Hypotheses (2020)

# Conclusion: Future Avenues of Research in Lyme

- Antibody testing for both COVID & Lyme may have false negatives (viral variants, multiple species of *Borrelia sensu lato*). Use the HMQ, a validated screening questionnaire, to evaluate risk. Migratory pain and intermittent symptoms c+g w/borrelia specific bands help establish the diagnosis
- Both Lyme & COVID may cause acute & chronic symptoms that resemble each other due to the 3 I's (infection, immune dysfunction, inflammation) resulting in CLD/PTLDS and long COVID (PASC) with POTS
- 'Persisters' and biofilm forms of Bb have been shown to play an important role in driving inflammation, and DDD CT is the first short term AB protocol shown to be effective in CLD/PTLDS. RCT's are needed to prove efficacy
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- Horowitz, R.I., Murali, K., Gaur, G. et al. Effect of dapson alone and in combination with intracellular antibiotics against the bio-film form of *B. burgdorferi*. *BMC Res Notes* 13, 455 (2020). Horowitz, R.I.; Freeman, P.R. Efficacy of Double-Dose Dapsone Combination Therapy in the Treatment of Chronic Lyme Disease/Post-Treatment Lyme Disease Syndrome (PTLDS) and Associated Co-infections: A Report of Three Cases and Retro-spective Chart Review. *Antibiotics* 2020, 9, 725.

Thank You for Your Attention



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