Complicating Factors in Lyme Disease: Multiple Chronic Infectious Disease Syndrome (MCIDS) and the Cell Danger Response

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ASSOCIATION FOR THE ADVANCEMENT OF RESTORATIVE MEDICINE REGIONAL CONFERENCE

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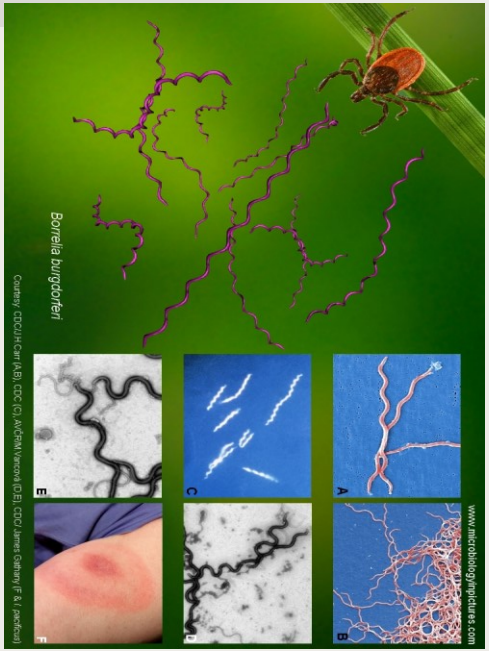
Disclosure Statement

I, Kelly K. McCann, MD, have no financial arrangements or affiliations with any commercial entities whose products, research or services may be discussed in these materials.

Objectives

- Discuss how chronic infections such as Lyme Disease and Co-infections lead to oxidative stress, chronic inflammation, and immune system dysfunction which manifests in physical and mental health symptoms.
- Review the Multiple Systemic Infectious Disease Syndrome (MSIDS) and the use of the questionnaire for suspected Lyme disease.
- Discuss the Cell Danger Response and its impact in chronic infections.
- Comprehensive treatment strategies addressing environmental exposures such as mold and toxicants.
- Utilizing case presentations to highlight teaching points.

Defining terms

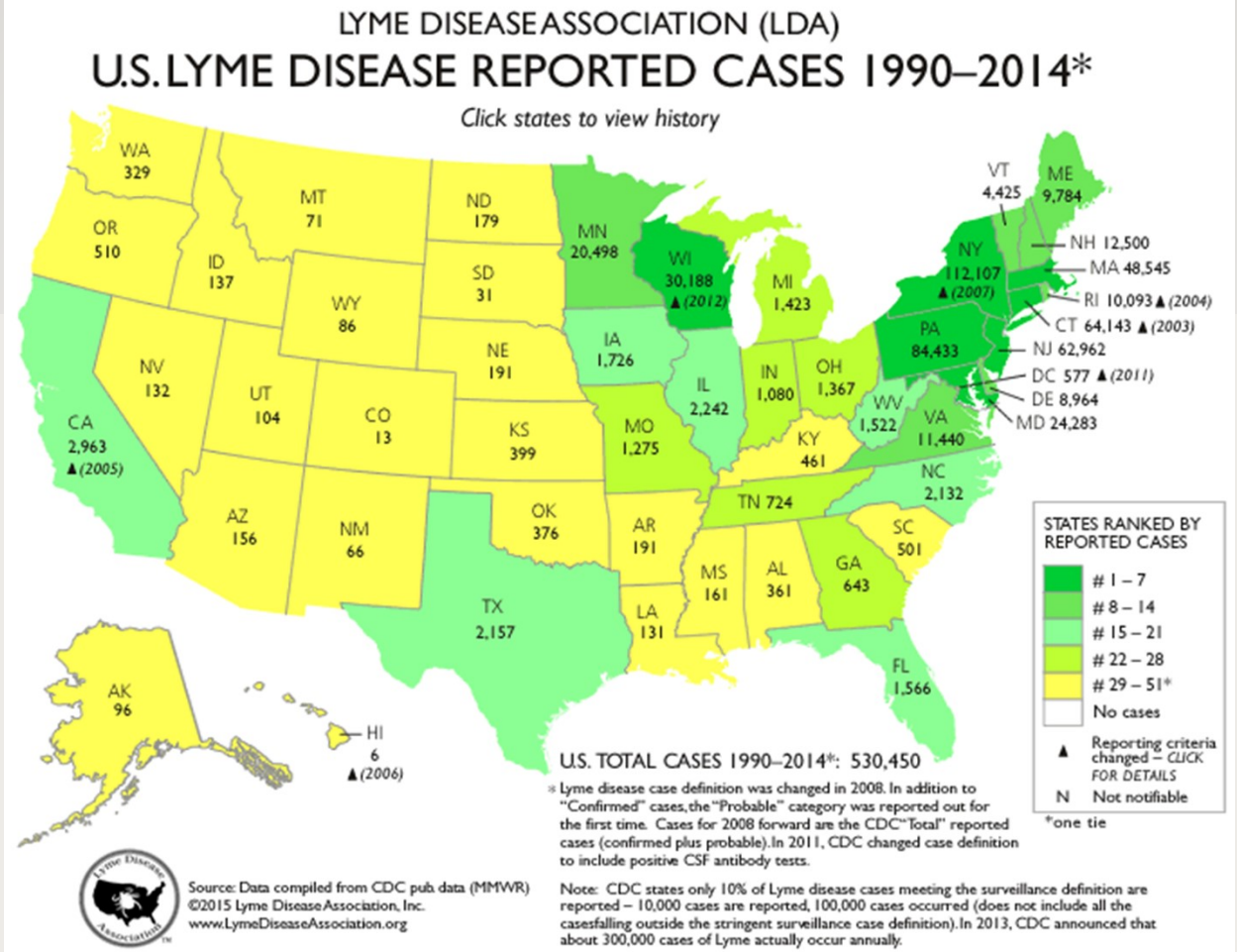


- **Lyme Disease** (interchangeable with Lyme): refers to the infection that includes not only *B. burgdorferi* but many co-infections.
- **Lyme Borreliosis**: Solo infection with *B. burgdorferi*.
- **Persistent Lyme Disease**: A patient with persistent and chronic Lyme disease has Borrelia infection and likely other infections, as well as; immune dysfunction, inflammation, opportunistic infections, deficient biological terrain, metabolic and hormonal imbalances, deconditioning, biotoxin illness or chronic inflammatory response syndrome (CIRS) or environmental toxicant burden, etc. that need to be addressed in order to bring the patient to wellness.

Meet Otzi the Iceman

- The autopsy of Otzi, a 5,300 year old mummy found in the Italian Alps in 2010, revealed the presence of *Borrelia burgdorferi* DNA.
- Earliest known human with Lyme disease.

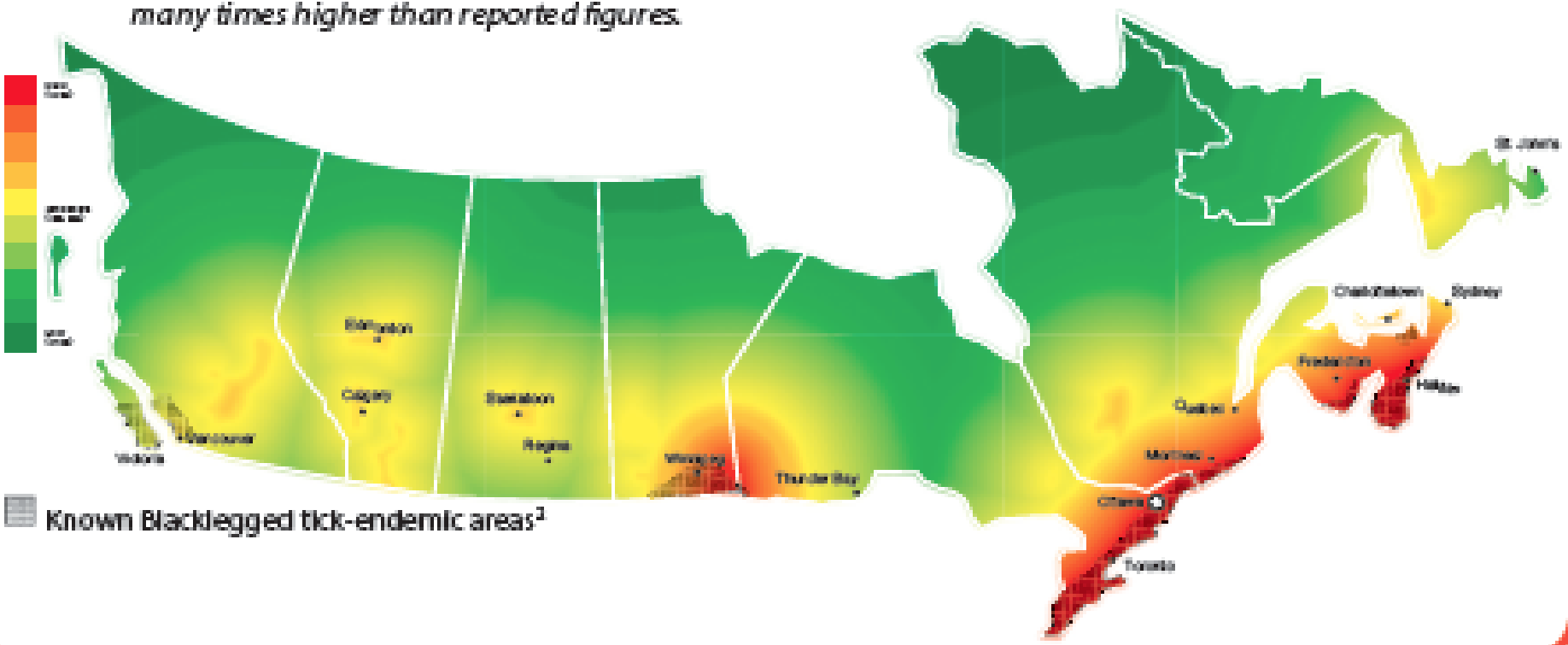
Hall, SS. Iceman Autopsy: Unfrozen. National Geographic. 2011 Nov.

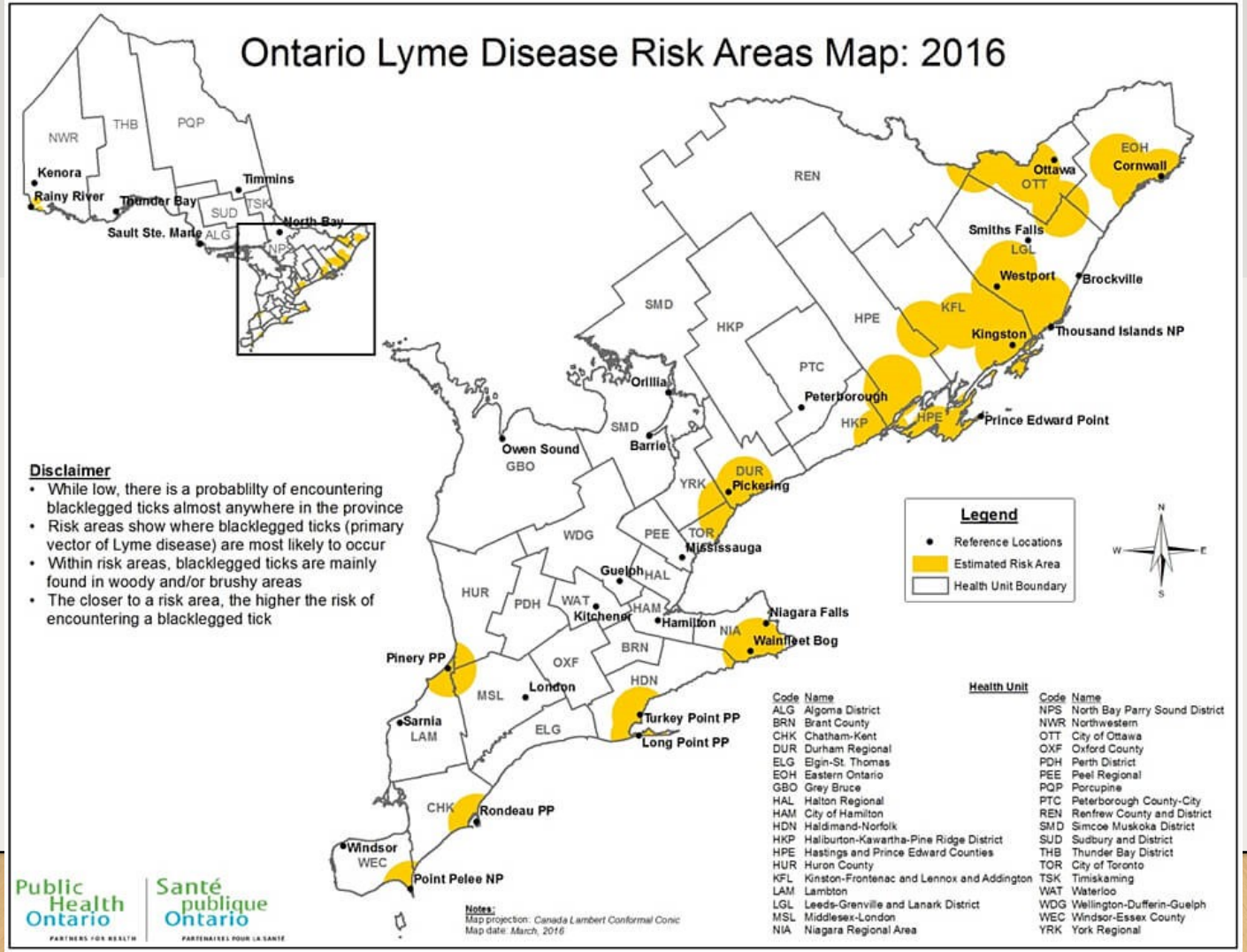

LYME DISEASE ASSOCIATION (LDA)
U.S. LYME DISEASE REPORTED CASES 1990–2014*
Click states to view history
WA 329
OR 510
CA 2,963 ▲(2005)
ID 137
NV 132
MT 71
WY 86
UT 104
AZ 156
CO 13
NM 66
ND 179
SD 31
NE 191
KS 399
OK 376
TX 2,157
MN 20,498
IA 1,726
MO 1,275
AR 191
LA 131
WI 30,188 ▲(2012)
IL 2,242
MS 161
MI 1,423
IN 1,080
KY 461
TN 724
AL 361
OH 1,367
WV 1,522
GA 643
FL 1,566
SC 501
NC 2,132
VA 11,440
PA 84,433
NY 112,107 ▲(2007)
MD 24,283
DE 8,964
NJ 62,962
CT 64,143 ▲(2003)
RI 10,093 ▲(2004)
MA 48,545
VT 4,425
NH 12,500
ME 9,784
AK 96
HI 6 ▲(2006)
U.S. TOTAL CASES 1990–2014*: 530,450
STATES RANKED BY REPORTED CASES
1 – 7
8 – 14
15 – 21
22 – 28
29 – 51*
No cases
▲ Reporting criteria changed – CLICK FOR DETAILS
N Not notifiable
*one tie
* Lyme disease case definition was changed in 2008. In addition to "Confirmed" cases, the "Probable" category was reported out for the first time. Cases for 2008 forward are the CDC "Total" reported cases (confirmed plus probable). In 2011, CDC changed case definition to include positive CSF antibody tests.
Source: Data compiled from CDC pub data (MMWR)
©2015 Lyme Disease Association, Inc.
www.LymeDiseaseAssociation.org
Note: CDC states only 10% of Lyme disease cases meeting the surveillance definition are reported – 10,000 cases are reported, 100,000 cases occurred (does not include all the cases falling outside the stringent surveillance case definition). In 2013, CDC announced that about 300,000 cases of Lyme actually occur annually.

Incidence of reported positive cases of Lyme disease in dogs[1]

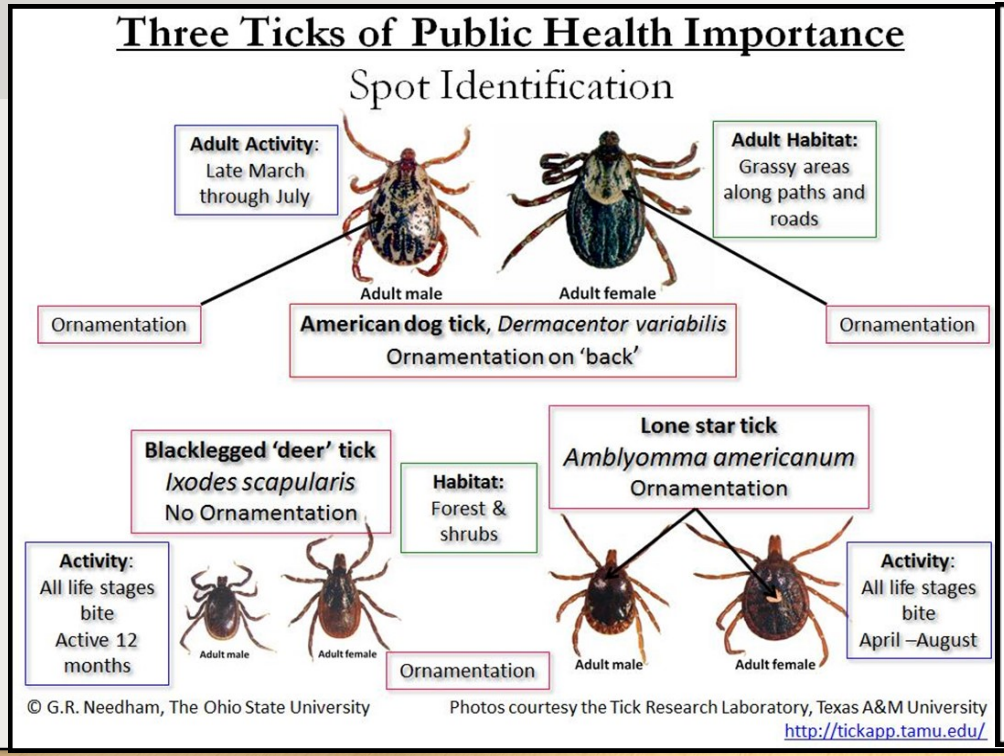
(2007 to Present)

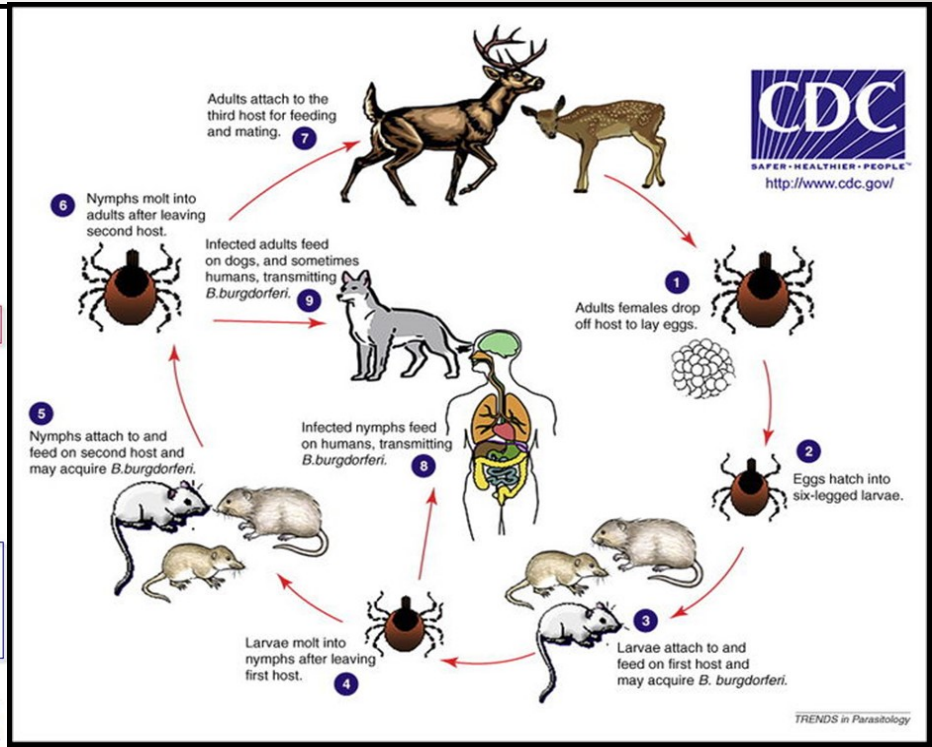
**Actual number of dogs infected by ticks is likely many times higher than reported figures.*




Ontario Lyme Disease Risk Areas Map: 2016
NWR
THB
PQP
Kenora
Rainy River
Thunder Bay
Timmins
SUD
TSK
Sault Ste. Marie
ALG
North Bay
NPS
REN
EOH
Cornwall
Ottawa
OTT
Smiths Falls
LGL
Westport
Brockville
KFL
HPE
Kingston
Thousand Islands NP
SMD
HKP
PTC
Orillia
Peterborough
Prince Edward Point
Owen Sound
GBO
Barrie
YRK
DUR
Pickering
WDG
PEE
TOR
Mississauga
Guelph
HAL
HUR
PDH
WAT
Kitchener
HAM
Hamilton
Niagara Falls
NIA
Wainfleet Bog
BRN
Pinery PP
OXF
HDN
London
MSL
Turkey Point PP
Sarnia
LAM
ELG
Long Point PP
CHK
Rondeau PP
Windsor
WEC
Point Pelee NP
Disclaimer
While low, there is a probablilty of encountering blacklegged ticks almost anywhere in the province
Risk areas show where blacklegged ticks (primary vector of Lyme disease) are most likely to occur
Within risk areas, blacklegged ticks are mainly found in woody and/or brushy areas
The closer to a risk area, the higher the risk of encountering a blacklegged tick
Legend
Reference Locations
Estimated Risk Area
Health Unit Boundary
N
W
E
S
Health Unit
Code Name
ALG Algoma District
BRN Brant County
CHK Chatham-Kent
DUR Durham Regional
ELG Elgin-St. Thomas
EOH Eastern Ontario
GBO Grey Bruce
HAL Halton Regional
HAM City of Hamilton
HDN Haldimand-Norfolk
HKP Haliburton-Kawartha-Pine Ridge District
HPE Hastings and Prince Edward Counties
HUR Huron County
KFL Kinston-Frontenac and Lennox and Addington
LAM Lambton
LGL Leeds-Grenville and Lanark District
MSL Middlesex-London
NIA Niagara Regional Area
Code Name
NPS North Bay Parry Sound District
NWR Northwestern
OTT City of Ottawa
OXF Oxford County
PDH Perth District
PEE Peel Regional
PQP Porcupine
PTC Peterborough County-City
REN Renfrew County and District
SMD Simcoe Muskoka District
SUD Sudbury and District
THB Thunder Bay District
TOR City of Toronto
TSK Timiskaming
WAT Waterloo
WDG Wellington-Dufferin-Guelph
WEC Windsor-Essex County
YRK York Regional
Notes:
Map projection: Canada Lambert Conformal Conic
Map date: March, 2016
Public Health Ontario
PARTNERS FOR HEALTH
Santé publique Ontario
PARTENAIRES POUR LA SANTÉ

Relevant Lyme disease ticks and their life cycle





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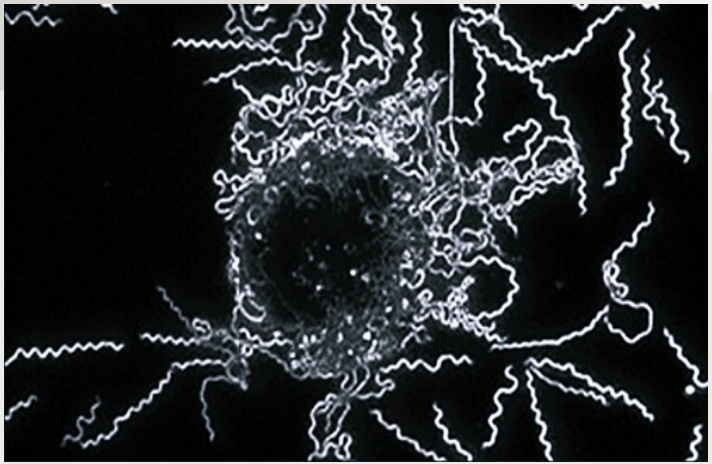
It’s not just about the tick…

- Case reports of illness after mosquito bites and bird mite bites.
- *Borrelia burgdorferi* found in mosquitos, horse flies, and deer flies in endemic areas, but researchers claim those insects are unable to transmit infections to humans.
- Studies in Czech republic prove evidence of Borrelia in mites from wild rodents and in chigger mites from wild birds.
- Evidence to support sexual transmission of Lyme disease.
- Numerous case reports support evidence for congenital transmission of Lyme disease.
- Possible transmission via breast milk.

AGJ Infect Dis. 1986. Aug;154(2):355-8.
J Clin Microbiol. 1988 Aug; 26(8):1482-86.
Exp Appl Acarol. 2008 Apr; 44(4): 307-14.
Expert Rev Anti Infect Ther. 2015;13(11):1303-6.
Vector Borne Zoonotic Dis. 2005 Fall;5(3):277-32.
Ann Intern Med 1985; 103:67-8.
Rheum Dis Clin North Am. 1989 Nov; 15(4):657-77.
Diagn Microbiol Infect Dis 1995 Mar; 21(3):121-8.

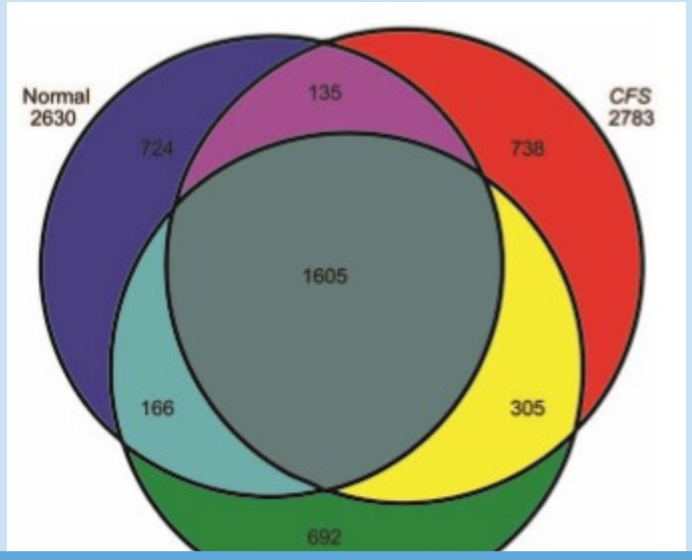
Chronic Lyme vs. Post Treatment Lyme Disease Syndrome



1. Inflammatory
   host response to antigenic debris
2. Autoimmune
3. Residual damage to tissues during infection
4. Co-infection
5. Secondary opportunistic infections
6. **Lyme Persisters**
   not killed by current Lyme antibiotics

Let's use the term…Persistent Lyme

Maloney. Controversies in Persistent (Chronic) Lyme Disease. Art Sci Infusion Nursing. 2016 Nov; 39(6): 369 375.
Marques. Chronic Lyme Disease: An appraisal. Infect Dis Clin North Am. 2008 Jun; 22(2): 341–360.



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PLoS one

Distinct Cerebrospinal Fluid Proteomes Differentiate Post-Treatment Lyme Disease from Chronic Fatigue Syndrome

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Abstract

Background: Neurologic Post Treatment Lyme disease (*nPTLS*) and Chronic Fatigue (*CFS*) are syndromes of unknown etiology. They share features of fatigue and cognitive dysfunction, making it difficult to differentiate them. Unresolved is whether *nPTLS* is a subset of *CFS*.

Methods and Principal Findings: Pooled cerebrospinal fluid (CSF) samples from *nPTLS patients*, *CFS* patients, and healthy volunteers were comprehensively analyzed using high-resolution mass spectrometry (MS), coupled with immunoaffinity depletion methods to reduce protein-masking by abundant proteins. Individual patient and healthy control CSF samples were analyzed directly employing a MS-based label-free quantitative proteomics approach. We found that both groups, and individuals within the groups, could be distinguished from each other and normals based on their specific CSF proteins ($p<0.01$). *CFS* ($n = 43$) had 2,783 non-redundant proteins, *nPTLS* ($n = 25$) contained 2,768 proteins, and healthy normals had 2,630 proteins. Preliminary pathway analysis demonstrated that the data could be useful for hypothesis generation on the pathogenetic mechanisms underlying these two related syndromes.

Conclusions: *nPTLS* and *CFS* have distinguishing CSF protein complements. Each condition has a number of CSF proteins

Chronic fatigue syndrome (CFS) and neurological Post Treatment Lyme Syndrome (nPTLS) are distinguishable disorders with distinct CSF proteomes. Distinguishing these conditions from each other and controls will permits more focused study of each condition and lead to novel diagnostics and therapeutic interventions.

Schutzer, 2011

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Neuropsychiatric symptoms of Lyme disease

Depression
Anxiety/Panic attacks
Mood swings
Irritability
Sleep disorders
Seizures
ADHD-like behavior
Autism-like behaviors
Schizophrenia
Bipolar disorder
Peripheral neuropathy

Obsessive –compulsive disorders
PANDAS/PANS
Chronic fatigue Syndrome
Fibromyalgia
Brain fog
Memory issues
Headaches/Migraines
Concentration issues
Dementia
Psychosis/ Paranoia
Eating disorders

Fallon, et al. The Neuropsychiatric Manifestations of Lyme Borreliosis. Psychiatric Quarterly, Vol63, No 1, Spring 1992

Index of suspicion for Persistent Lyme Disease

Cognitive difficulties
Simple and complex attention
Slow processing – visual and auditory
Visual spatial difficulties
Sensory integration disorders
Short-term memory difficulties
Word-finding and communication difficulties
Decline in executive functioning
Confusion – overall decline in intellectual performance

Emotional/Behavioral Difficulties
Anxiety, with panic attacks
Depression
Irritability/rage/impulse control
Oppositional defiant disorders
Sleep disorders
Rapid mood swings (bipolar)
Obsessive compulsive disorder
Hyperactivity
Autism-like spectrum disorders
Antisocial disorders
Eating disorders

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Complicating Factors in Lyme disease as a Chronic Illness

BACTERIA FACTORS
1. Numerous strains of Borrelia
2. Different forms of Borrelia
3. Testing Challenges
4. Co-infections
5. Biofilms
6. Immune evasion and persistent infections
7. Various Treatment Guidelines

PATIENT FACTORS
1. Lyme disease and Co-infections
2. Immune Dysfunction
3. Inflammation
4. Environmental toxins – chemicals and mold
5. Nutritional deficiencies
6. Mitochondrial dysfunction
7. Endocrine abnormalities
8. Neurodegenerative disorders
9. Neuropsychiatric disorders
10. Sleep disorders
11. Autonomic nervous system dysfunction and POTS
12. Allergies
13. GI disorders
14. Liver dysfunction
15. Pain dis./addiction
16. Deconditioning

Patient list from Richard Horowitz, MD

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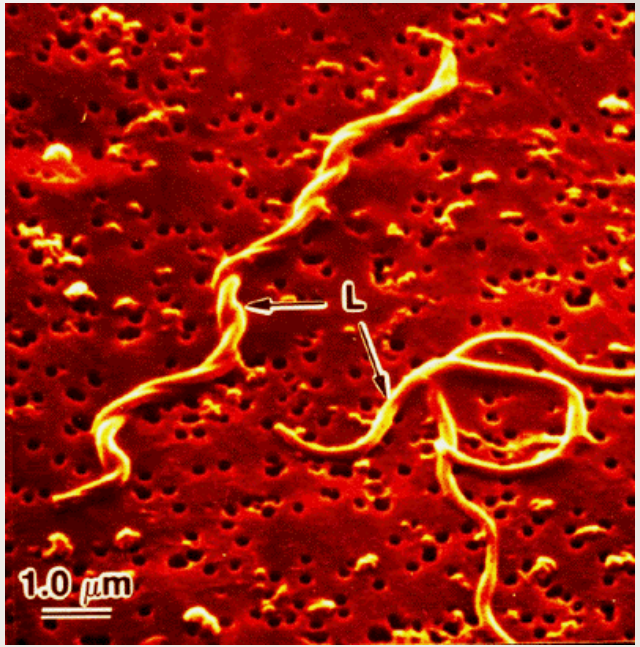
There are many pathogenic bacteria

B. burgdorferi
B. afzelli
B. garinii
B. spielmanii
B. lonestari
B. bissettii
B. carolinensis
B. americana
B. andersonii
B. kurtenbachii

B. lusitaniae
B. valaisiana
B. sinica
B. bavariensis
B. finlandensis
B. japonica
B. miyamoti
B. hermsii
B. yangtze
B. tanuki
B. turdi
Etc…



Pleomorphic bacteria

- Spirochete form
- Atypical forms
- Cyst, rolled, looped, ring
- Cell-less wall or L-form?
- Biofilms

Typical treatment regimens target these forms.

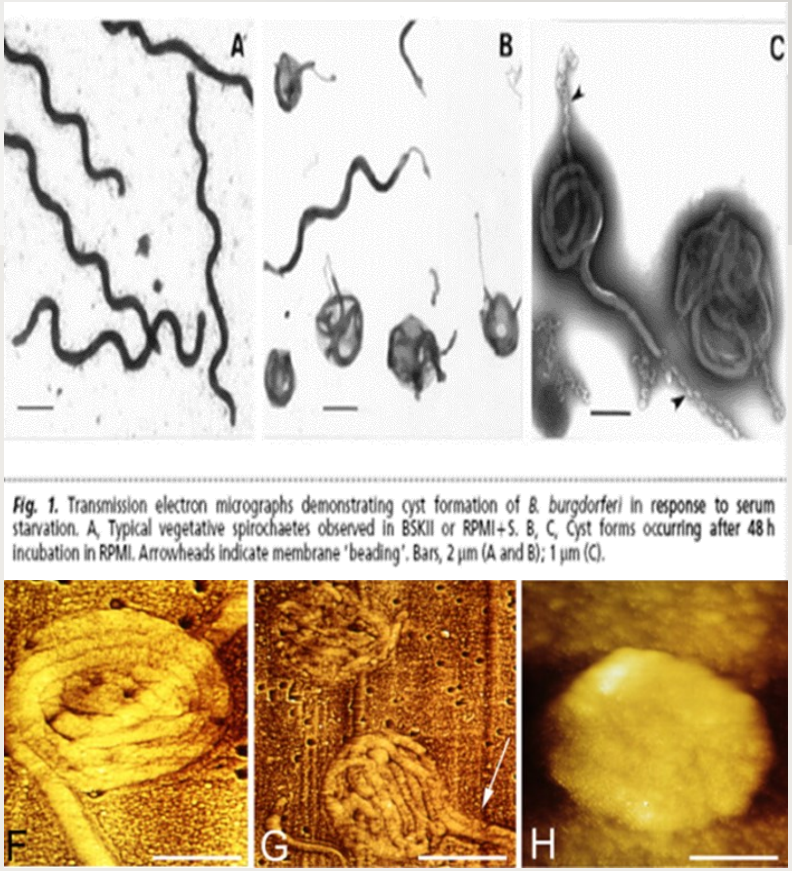


Fig. 1. Transmission electron micrographs demonstrating cyst formation of *B. burgdorferi* in response to serum starvation. A, Typical vegetative spirochaetes observed in BSKII or RPMI+S. B, C, Cyst forms occurring after 48 h incubation in RPMI. Arrowheads indicate membrane 'beading'. Bars, 2 μm (A and B); 1 μm (C).

Possible additional infections

- Anaplasmosis/Ehrlichiosis
- Babesia (B.microti, B. duncani)
- Bartonella (B. henselae, B. quintana, B. bacilliformis)
- Relapsing fever Borrelia (Borrelia miyamotoi, B. hermsii)
- Rickettsia (Rocky Mountain Spotted Fever, R. typhi)
- Coxiella burnetti (Q fever)
- Chlamydia infections
- Mycoplasma infections
- Tularemia
- Brucella
- Tick paralysis
- Colorado Tick fever
- STARI (Southern Tick Associated Rash Illness)

Viral infections

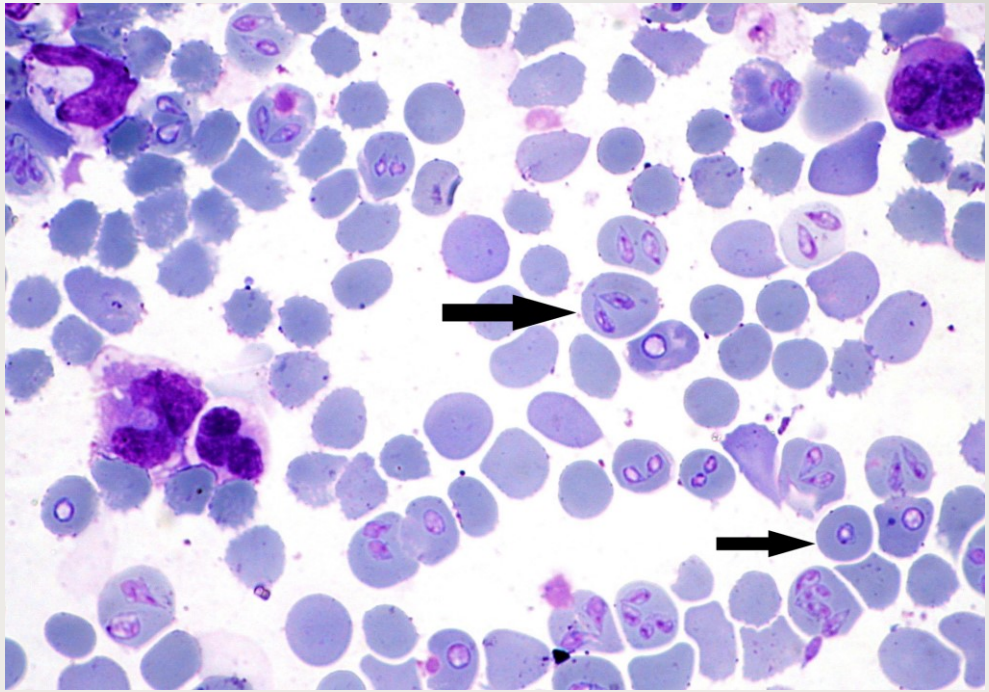
- Heartland Virus
- Powassan Encephalitis
- West Nile
- Human Herpes Virus-6 (HHV-6)
- Epstein Barr Virus (EBV)
- Cytomegalovirus (CMV)

Fungal Infections

Parasitic infections

Seroprevalence of *Babesia microti* in Lyme patients

- 130 patients in New York
- Positive tests for Lyme disease
- 26.9% samples positive for *Babesia microti* IgG and IgM antibodies
- 6.7% of Lyme disease negative controls were positive

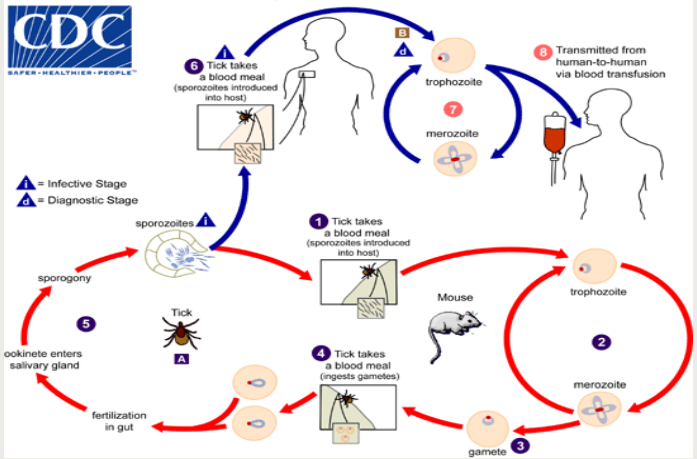


Curcio, SR et al. Seroprevalence of *Babesia microti*. Vector Borne Zoonotic Dis 2016 Dec; 16(12): 737-743.

Babesia-like Organisms

Fever/ Chills
Fatigue
Headaches
Drenching sweats
Muscle aches
Chest pain
Cough
Loss of Appetite
Air hunger/ Shortness of breath
“Brain Fog” /Cognitive problems
Elevation of liver enzymes
Hemolytic anemia

20+ different species.
We can test for 2 species.
Babesia microti
Babesia duncani (Wa-1)
Can be transmitted via tick bite, blood transfusion and via placenta in utero

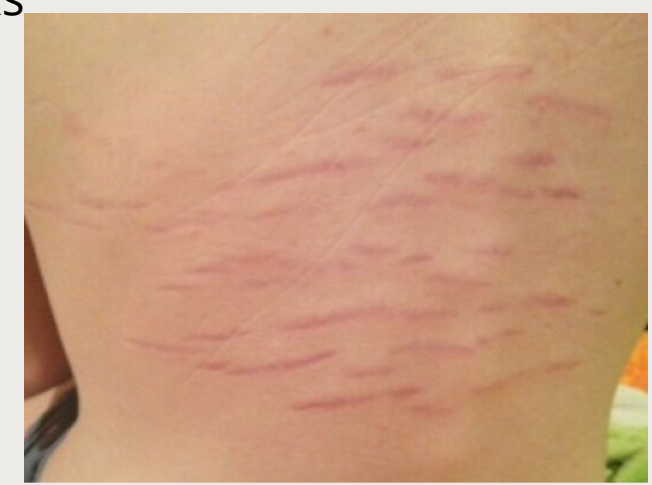


Bartonella-like Organisms (Cat Scratch Fever)

Spread by ticks, other insects and in utero

Symptoms include:

Fatigue
Chronic pain
Pelvic pain/ interstitial cystitis
Pain on the soles of the feet
Chest pain/Palpitations
Headaches
Myalgias/ arthralgias
Abnormal liver enzymes
Encephalopathy
Endocarditis/myocarditis
Hemolysis with anemia
Hepato-splenomegaly
Lymphadenopathy
Papular or angiomatous rash
Weakened immune response
Anxiety/ Panic attacks
Striae
Sore throat
Fever



PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Co-infection of Ticks: The Rule Rather Than the Exception

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Abstract

Introduction

Ticks are the most common arthropod vectors of both human and animal diseases in Europe, and the *Ixodes ricinus* tick species is able to transmit a large number of bacteria, viruses and parasites. Ticks may also be co-infected with several pathogens, with a subsequent high likelihood of co-transmission to humans or animals. However few data exist regarding co-infection prevalences, and these studies only focus on certain well-known pathogens. In addition to pathogens, ticks also carry symbionts that may play important roles in tick biology, and could interfere with pathogen maintenance and transmission. In this study we evaluated the prevalence of 38 pathogens and four symbionts and their co-infection levels as well as possible interactions between pathogens, or between pathogens and symbionts.

Methodology/principal findings

A total of 267 *Ixodes ricinus* female specimens were collected in the French Ardennes and analyzed by high-throughput real-time PCR for the presence of 37 pathogens (bacteria and parasites), by rRT-PCR to detect the presence of Tick-Borne encephalitis virus (TBEV) and by nested PCR to detect four symbionts. Possible multipartite interactions between pathogens, or between pathogens and symbionts were statistically evaluated. Among the infected ticks, 45% were co-infected, and carried up to five different pathogens. When adding symbiont prevalences, all ticks were infected by at least one microorganism, and up to eight microorganisms were identified in the same tick. When considering possible interactions between pathogens, the results suggested a strong association between *Borrelia garinii* and *B. afzelii*, whereas there were no significant interactions between symbionts and pathogens.

Conclusion/significance

Our study reveals high pathogen co-infection rates in ticks, raising questions about possible co-transmission of these agents to humans or animals, and their consequences to human

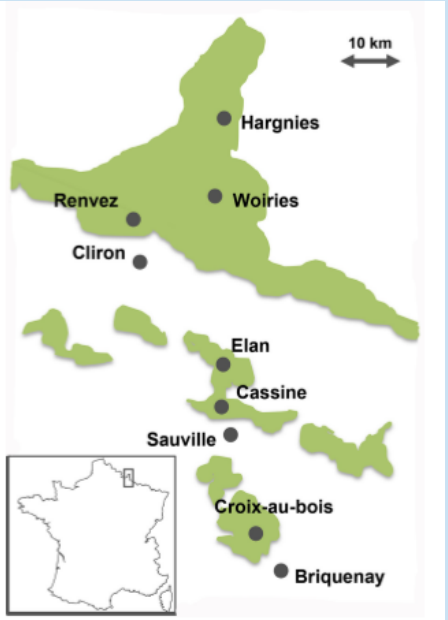

Fig 1. Map of the Ardennes region (France) showing the 9 tick sampling s
green correspond to large forested areas.

doi:10.1371/journal.pntd.0004539.g001

267 *Ixodes ricinus* female ticks tested
45% were co-infected
Carrying up to 5 pathogens

Including symbiont prevalences, all ticks were infected with at least one organism.
Up to 8 pathogens in the same tick.

Ehrlichia (HME) /Anaplasma (HGA)

Ehrlichia Symptoms:
Fever 97%
Headaches 80%
Myalgias 57%
Arthralgia 41%
Rash 66% pediatric
Nausea/vomiting
Abdominal pain
Cough
Meningitis/meningo-encephatitis 20%
42% require hospitalization
3% case fatality

Anaplasma Symptoms:
Similar for fever, HA, myalgias, but less severe than HME
Rash 10%
CNS involvement 1%
PNS higher – peripheral neuropathy, cranial nerve palsies
Both have pancytopenias and elevated LFTs

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Human Ehrlichiosis and Anaplasmosis

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Keywords
Ehrlichiosis; Epidemiology; Immunity; Pathogenesis; Diagnosis; Treatment

OVERVIEW

Human ehrlichiosis and anaplasmosis are acute febrile tick-borne diseases caused by various members from the genera *Ehrlichia* and *Anaplasma* (Anaplasmataceae). Human monocytotropic ehrlichiosis was first reported in the United States in 1987, but during the ensuing 20 years it has become the most prevalent life-threatening tick borne disease in the US. The emergence of ehrlichiosis and anaplasmosis is become more frequently diagnosed as the cause of human infections, as animal reservoirs and tick vectors have increased in numbers and humans have inhabited areas where reservoir and tick populations are high.

Ehrlichia chaffeensis, the etiologic agent of human monocytotropic ehrlichiosis (HME) is an emerging zoonosis that causes clinical manifestations ranging from a mild febrile illness to a fulminant disease characterized by multi-organ system failure. The primary tick vector of HME is the Lone Star tick (*Amblyomma americanum*). *A. phagocytophilum* causes human granulocytotropic anaplasmosis (HGA), previously known as human granulocytotropic ehrlichiosis (HGE). *Anaplasma phagocytophilum* is transmitted by *Ixodes scapularis*, which also transmits agents that cause Lyme disease and babesiosis.

HME and HGA have similar clinical presentations including fever, headache, leukopenia, thrombocytopenia and elevated liver enzymes. Symptoms typically begin a median of 9 days following tick bite, with the majority of patients seeking medical attention within the first 4 days of illness. Neurologic manifestations are most frequently reported with HME. In this article, we review recent advances in the understanding of ehrlichial diseases related to microbiology, epidemiology, diagnosis, pathogenesis, immunity, and treatment of the two prevalent tick-borne diseases found in the United States, HME and HGA.

*Corresponding author. nismail@mmc.edu.

Ehrlichia/Anaplasma/Rickettsia

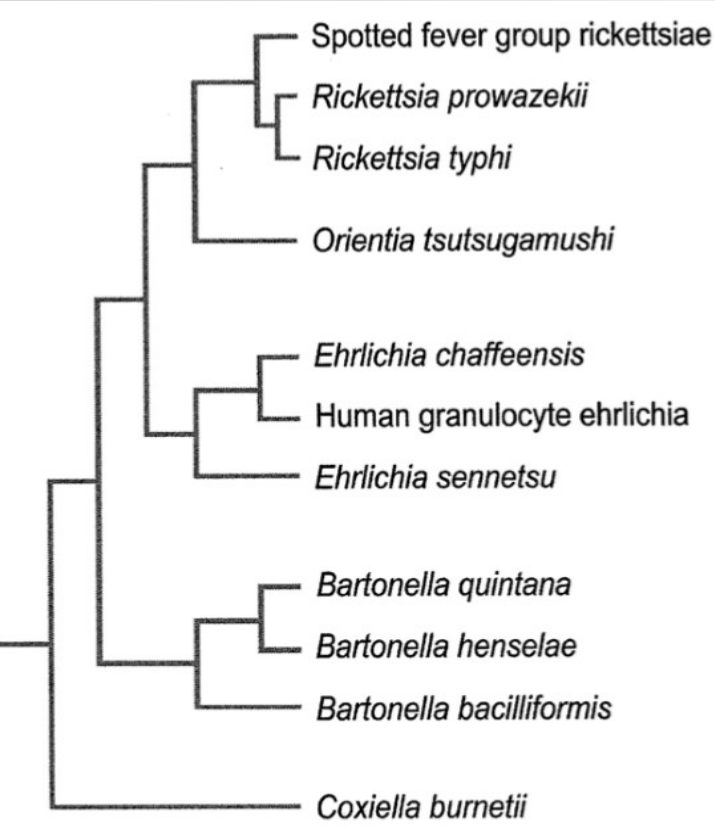
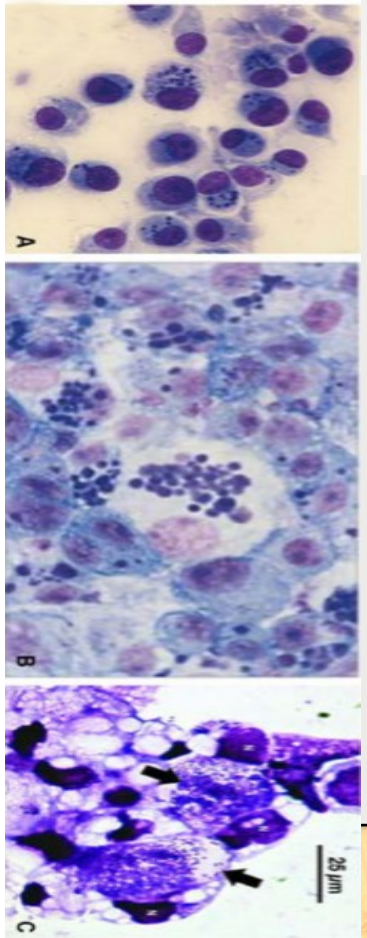


Figure 1.
Phylogenetic relationships between rickettsias based on 16S rRNA gene sequences. (*From* Mason PR, Kelly PJ. Ch. 235: Rickettsia and Rickettsia-Like Organisms. In: Cohen & Powderly, editors. Infectious Diseases, 2nd ed. Mosby; 2004. Permission requested from *Elsevier*.)



- Rickettsial infections are transmitted by fleas, mites, and ticks.
- Can be mild or life threatening.
- Rocky Mountain spotted fever presents as fever, headache, myalgias, petechial rash, and tick exposure.

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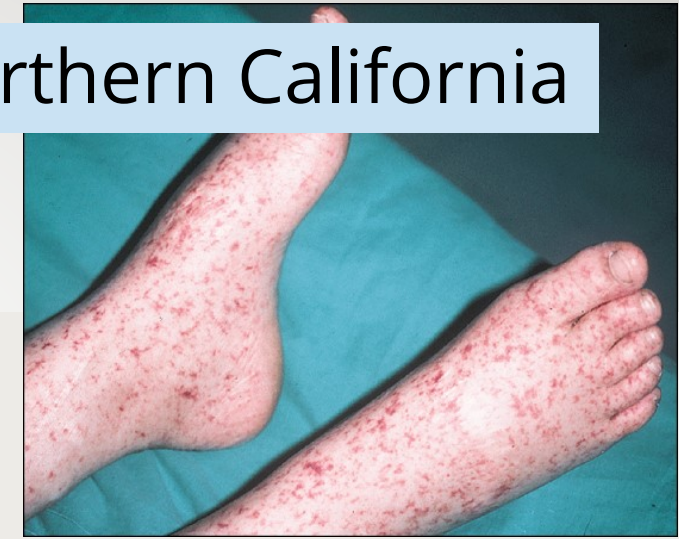
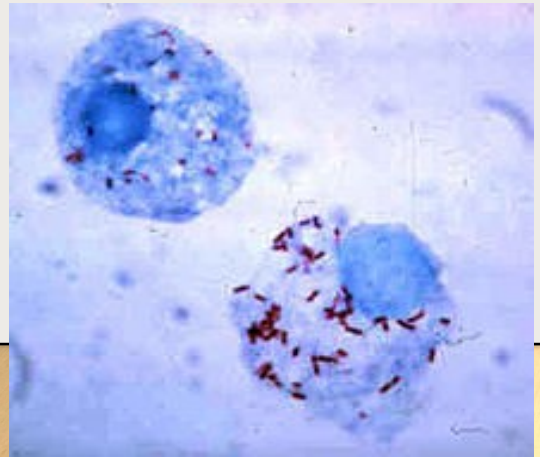
Diversity of Rickettsiae in Rural Northern California



DNA PCR of rickettsia species found in:
3% in humans
33% in grey foxes
42% in dogs
79% in cats
83% in bobcats
Found in fleas, ticks both Ixodes pacificus and Dermacentor varibilis species



Stephenson, et al. Diversity of rickettsiae in a rural community in northern California. Ticks tick Borne Dis. 2017. Feb. pii:s1877-959x(17)30110-3.

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Case: MB

33 yr old woman presented in March 2014 with a number of chronic issues for which she wanted functional medicine approaches.

PMHx: Major depressive disorder
Borderline personality disorder
Hashimoto's thyroiditis
PCOS with infertility issues
Premenstrual syndrome
Chronic back pain from 3 herniated discs
History of SIBO treated with rifaximin.
Corn allergy

PSHx: none

Family Hx: Mom 66, depression
MGM deceased at 81, depression
PGF deceased 70s, psych disorder

Social history: Married, desired children, no drug or tobacco use, +Etoh use.

She had dissociative episodes in college and started therapy. Had a "breakdown" in the first semester of her MFT program. She is now mentally stable on Pristiq.

Case: MB

3/13/14 labs:
Chol 188 mg/dL = 4.87 mmol/L
LDL 101mg/dL = 2.62 mmol/L
HDL 54 mg/dL = 1.4 mmol/L
trig 206H mg/dL = 2.33 mmol/L
Wbc 6.7 x103, hgb 13.9, plt 266
Glu 86 mg/dL = 4.77 mmol/L
cmp wnl, HgA1c 5.3%,
MTHFR C677t +/-, Celiac neg, ANA neg
Pregnenolone 71 ng/mL =225.8nmol/L
DHEA-S 253 µg/dL = 6.63µmol/L
Ferritin 43 ng/mL = 96 pmol/L
TSH 2.32 mIU/L
free t4 0.89 mg/dL = 11.46 pmol/L
free t3 2.9 pmol/L = 188.31 pg/dL
+thyroid antibodies
Hs CRP 6.79 mg/L = 64.67 nmol/L

Alletess food IgG sensitivities –reactions to gluten, dairy, egg

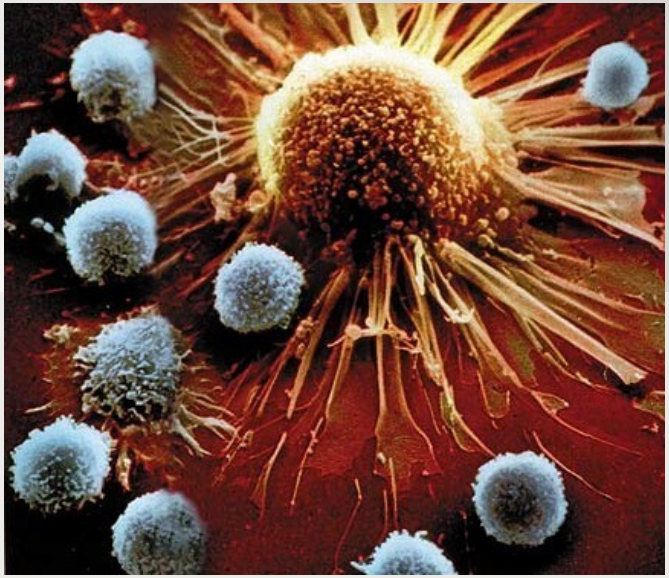
Comprehensive stool analysis - 4+ Candida glabrata. Calprotectin – 68 (<50 is normal) Secretory IgA – 255 (51-204 normal)

Cd 57 was 34 (abs CD8-CD57 +lymph) (optimal >200)
Transforming Growth Factor Beta1 – 11,460 pg/mL (normal is <2382)

Vit D 25 OH - 18.9 ng/mL = 47.17 nmol/L
Vit D 1,25 OH - 64 pg/mL = 166 pmol/L

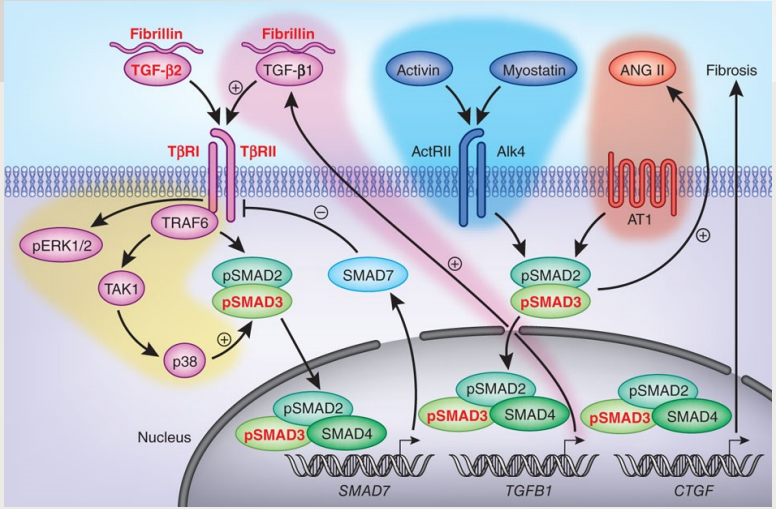
What is CD 57?

- CD57 is a subset of natural killer (NK) cells
- Distinct from CD 56 cells the major subset of NK cells
- Function is poorly understood
- May be suppressed in chronic infections including EBV, CMV, HIV and Lyme disease
- Associations with remission rates in cancers
- Downregulated by TH1 cytokines (IL2, IFN, TNF)
- CD57 marker is found on other cells (T-cells and nerve cells)



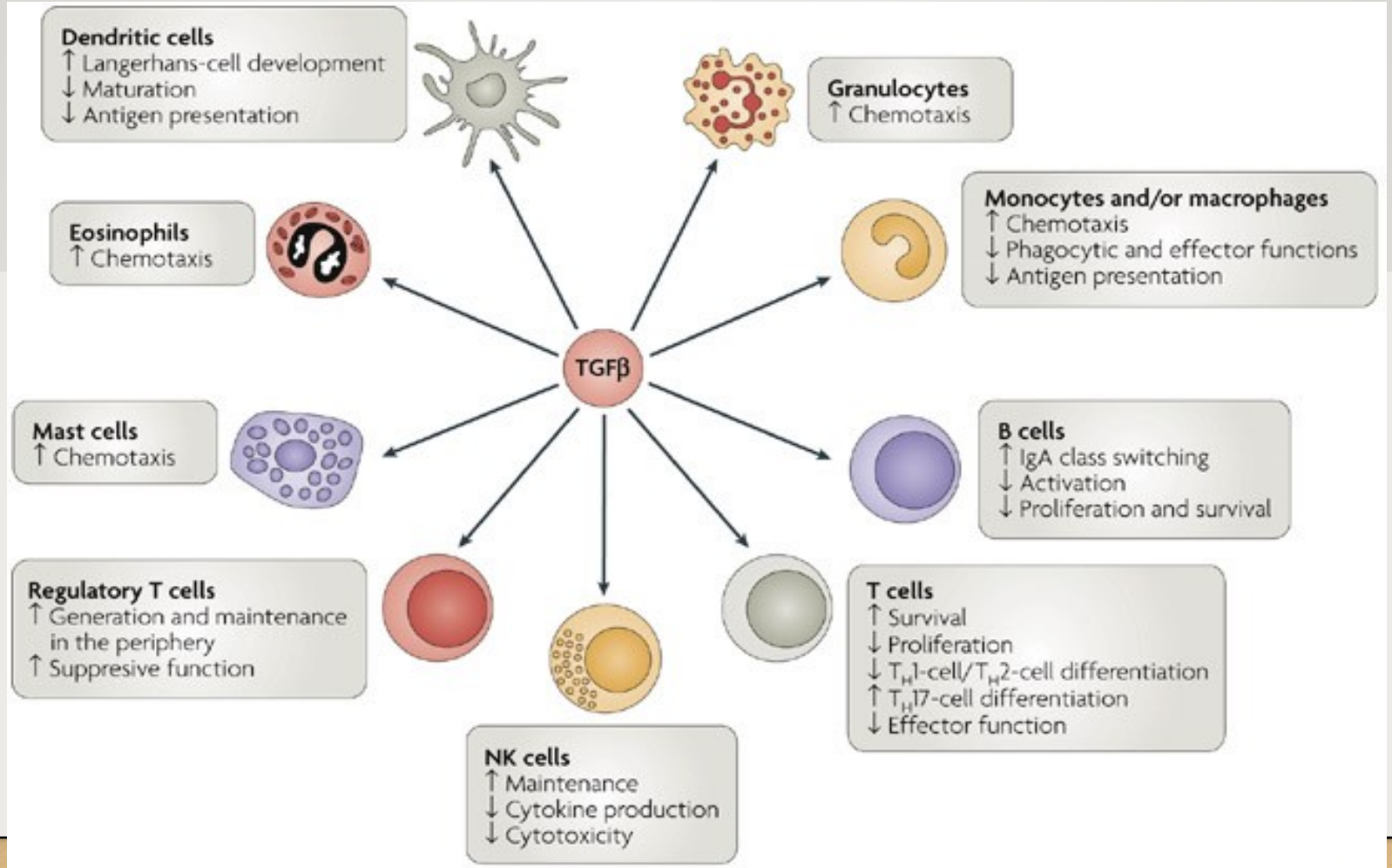
- Stricker RB, Burrascano J, Winger E. Longterm decrease in the CD57 lymphocyte subset in a patient with chronic Lyme disease. Ann Agric Environ Med. 2002;9(1):111-3.
- Marques A, et al. Natural killer cell counts are not different between patients with post-Lyme disease syndrome and controls. Clin Vaccine Immunol. 2009 Aug;16(8):1249-50.
- Nielsen, CM, et al. Functional Significance of CD57 Expression on Human NK Cells and Relevance to Disease. Front Immunol. 2013; 4: 422.

Transforming Growth Factor Beta1



Zhang, et al. TGF-β1 factor in the cerebrovascular diseases of Alzheimer's disease. Eur Rev Med Pharmacol Sci. 2016 Dec;20(24):5178-5185.
Schumann. TGFbeta1 of no avail as prognostic marker in Lyme disease. PeerJ2:e398; DOI 10.7717/peerj.398.

- TGF-beta 1 (Transforming Growth Factor Beta 1) (normal is <2382)
- Immunomodulatory cytokine, has pleiotropic effects.
- A marker of an overactive immune system. Directs immunity towards TH17, often results in autoimmunity.
- Also role in tumor suppression and promoting tolerance to allergens and self-antigens.
- Can be elevated in CIRS from mold or Lyme disease.
- Important in autoimmune hepatitis, IBD, hepatocellular carcinoma and RA



Widhe, M. et al. Cytokines in Lyme borreliosis: lack of early tumour necrosis factor-alpha and transforming growth factor-beta1 responses are associated with chronic neuroborreliosis. Immunology. 2002 Sep;107(1):46-55.

MD

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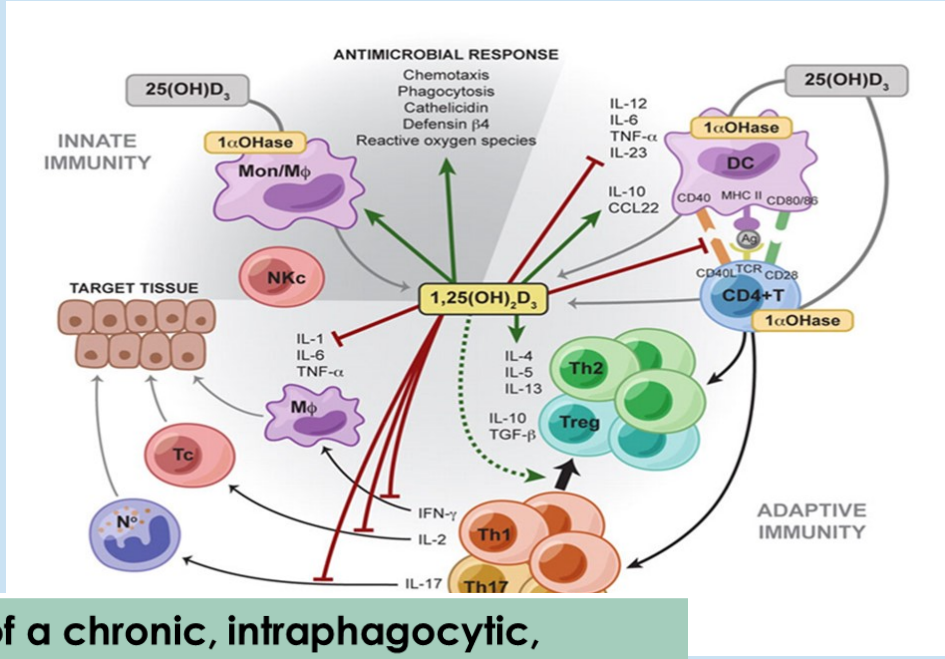
Dysregulation of the Vitamin D Nuclear Receptor May Contribute to the Higher Prevalence of Some Autoimmune Diseases in Women

Amy D. Proal,[a] Paul J. Albert,[b] and Trevor G. Marshall[c]

[a]*Georgetown University, Washington, DC, USA*
[b]*Weill Cornell Medical College, New York, NY, USA*
[c]*Murdoch University, Perth, Australia*

Researchers have noted that the incidence of autoimmune diseases, such as Hashimoto's thyroiditis, is markedly higher in women than in men, but to date the reason for this disparity has been unclear. The vitamin D nuclear receptor (VDR) is expressed in the human cycling endometrium. Because the VDR controls expression of the cathelicidin and β-defensin antimicrobial peptides (AmPs), dysregulation of the receptor greatly compromises the innate immune response. Increasing evidence indicates the presence of a chronic, intraphagocytic, metagenomic microbiota in patients with autoimmune disease that may survive by dysregulating the VDR. VDR dysregulation, in turn, prevents the breakdown of the active vitamin D metabolite 1,25-hydroxyvitamin D (1,25-D) by CYP24. *In silico* data suggest that when 1,25-D rises above its normal range, it binds the α/β thyroid receptors, the glucocorticoid receptor (GCR), and the androgen receptor (AR), displacing their native ligands and causing an array of hormonal imbalances. If T3 is displaced from α-thyroid, thyroiditis may result. Because the VDR, GCR, and AR also express multiple families of AmPs, expression of these natural antibiotics further wanes in response to dysregulation by 1,25-D. The end result is a system-wide drop in AmP expression that may allow pathogens to spread with greater ease. Because women have an extra site of VDR expression in the endometrium, the drop in AmP expression as-



Increasing evidence indicates the presence of a chronic, intraphagocytic, metagenomic microbiota in patients with autoimmune disease that may survive by dysregulating the VDR…which in turn prevents breakdown of the active Vit D metabolite…when 1,25 D rises above its normal range it binds with thyroid receptors, GCR and AR displacing native ligands and causing an array of hormonal imbalances.

Proal et al. 2009.

amy.proal@gmail.com

imately 85% of patients with Hashimoto's

Contemporary Challenges in Autoimmunity: Ann. N.Y. Acad. Sci. 1173: 252–259 (2009).
doi: 10.1111/j.1749-6632.2009.04672.x © 2009 New York Academy of Sciences.

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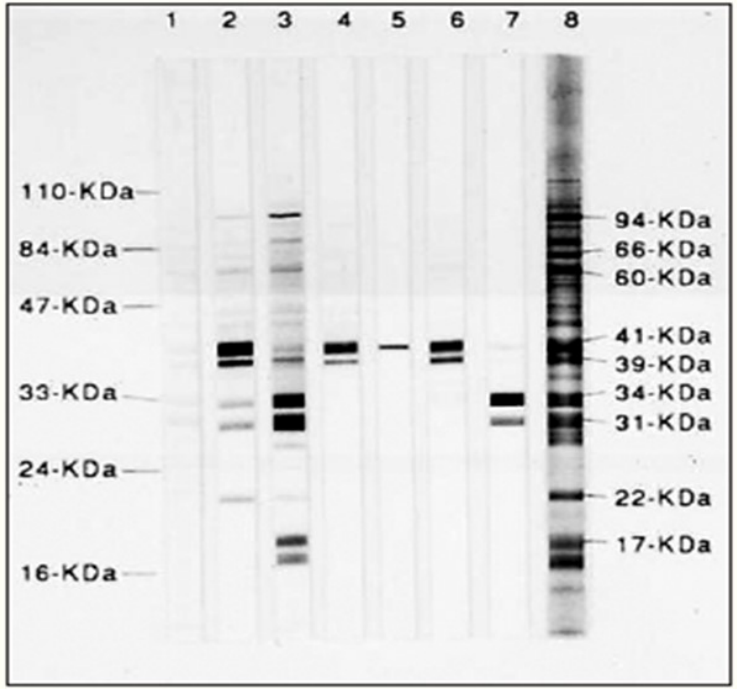
Vitamin D discrepancy

- Inflammatory disease processes appear to be due to alterations in the microbiome.
- Autoimmune diseases may be antibody generation against polymicrobial colonies and infections.
- Intracellular microbes slow innate immune system defense by dysregulating the vitamin D nuclear receptor (VDR).
- VDR affects transcription of at least 913 gene including the expression of key antimicrobial peptides.
- This dysregulation facilitates the ability of other pathogens to persist and slow the immune system further.

- VDR dysregulation prevents the breakdown of the active Vit D metabolite 1,25oh, thus it becomes elevated and 25-OH vit D remains low.
- Elevated 1,25OH – D can interfere with the expression of other nuclear receptors such as the androgen receptor, glucocorticoid receptor and thyroid receptors.

Proal. 2009. Ann NY Acad Sci 1173: 252-9.
Sun. 2010. Cur Opin GI 26(6): 591-595.
Proal. 2013. Curr Opin Rheumatol. Mar 25(2): 234-40.
Proal 2014. Discovery Medicine. 17(95):257-65.
Proal 2011. Cell & Mol Immunol 8: 213-225.



Significant Lyme disease antibodies detected on Western blot test, including 31- and 34-kilodalton bands. Courtesy of IGeneX, Inc.

Laboratory testing

- Stony Brook University

IFA, Western blot plus bands 31 (OspA) and 34 (OspB)

- Igenex

Lyme, relapsing fever borrelias IFA, western blot, PCR
Bartonella henselae antibodies, Bartonella FISH
Babesia microti and duncani antibodies, Babesia FISH
Ehrlichia, Anaplasma, C. pneumonia, Rickesttia
Immunoblot

- Fry Labs

Advanced stains for Protomyxzoa rheumatic and other parasites

- Advanced Lab - Borrelia culture
- Medical Diagnostic Labs (MDL)

Bacteria, vectors, viral antibodies and PCR

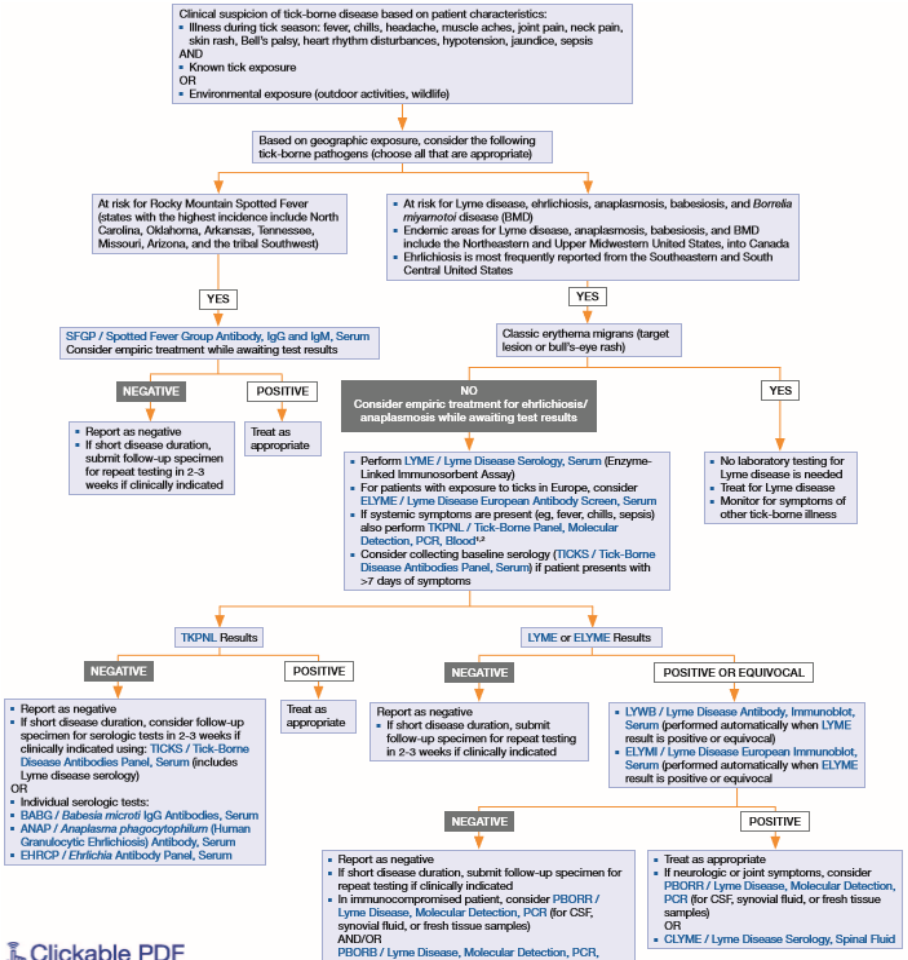
- Galaxy Labs

Bartonella species testing

- Armin Labs (Germany)– Lyme and co-infection urine testing
- Mayo Medical Laboratory – Lyme serology and Immunoblot

MAYO CLINIC
Mayo Medical Laboratories

Acute Tick-Borne Disease Testing Algorithm



Clickable PDF

https://www.mayomedicallaboratories.com/it-mmfiles/Acute_Tick-Borne_Disease_Testing_Algorithm.pdf

Case: MB Lyme western blot through Stonybrook

11/16/15
IFA – nonreactive
IgM – positive for bands 23, 41 and (62 and 93) – positive by CDC criteria
IgG – 41+ band only

2/29/16
IFA – nonreactive
IgM - positive for bands 23, 41 and (36, 62, and 93) – positive by CDC criteria
IgG – positive for 41, 66 and 25

She couldn't afford any co-infection testing other than commercial labs and those tests were all negative.

Case: MB Follow up

- She did antibiotics for 1 year and then had an embryo transfer.
- Continued on a single antibiotic Augmentin as the other antibiotics caused diarrhea during her pregnancy.
- Plus a Chrysanthemum morifolium product as additional antimicrobial.
- Had healthy baby girl. All infant tests so far have been negative for Lyme.

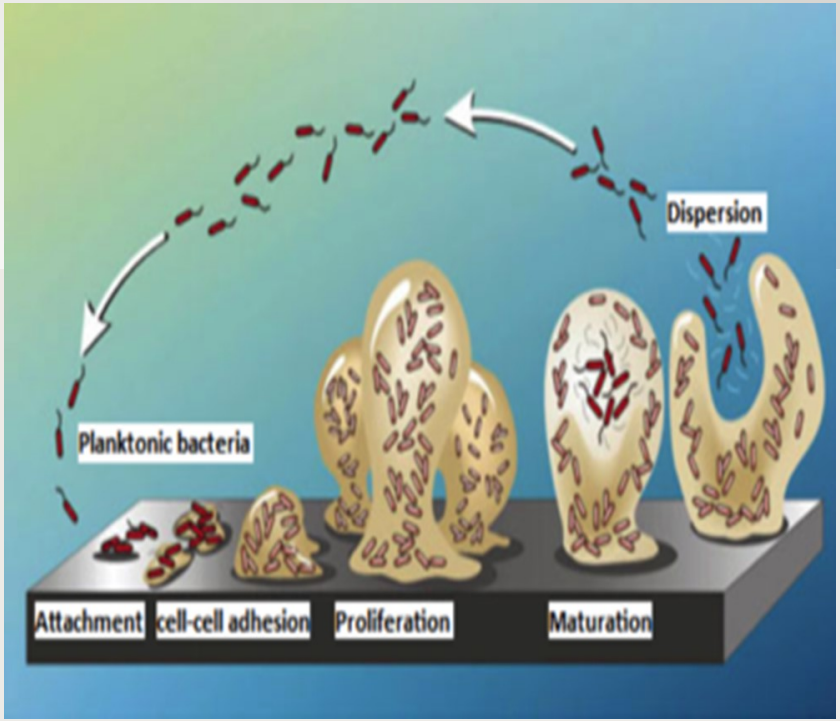
Complicating Factors in Lyme disease as a Chronic Illness

BACTERIA FACTORS

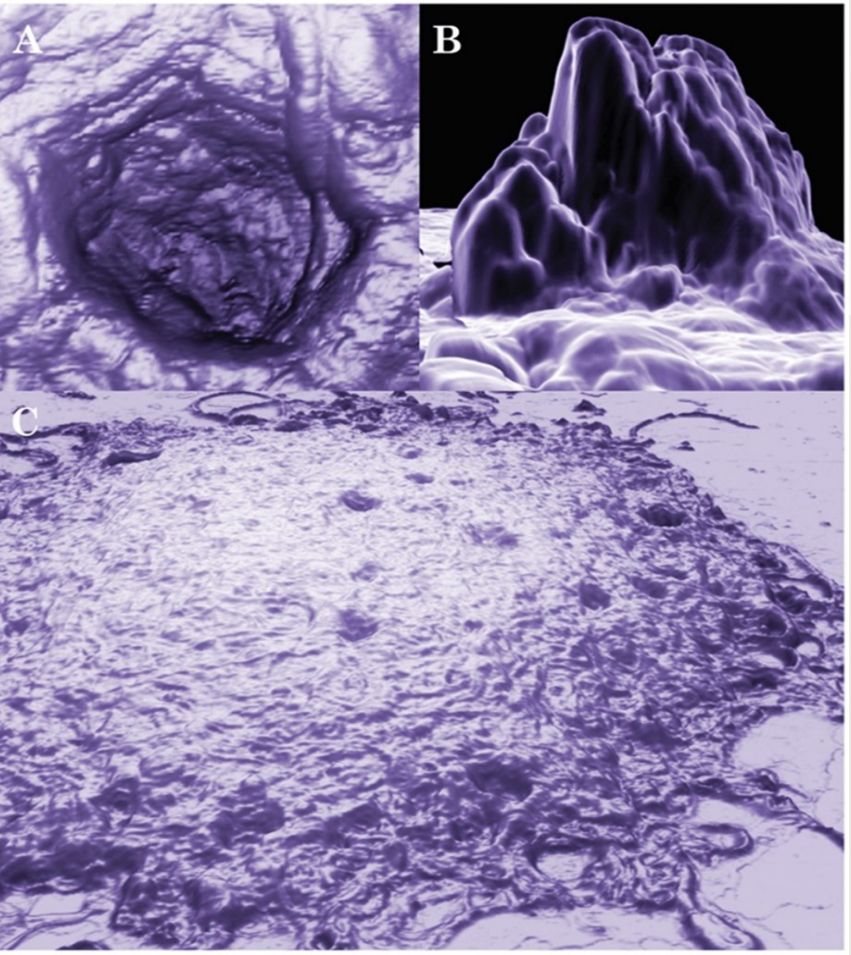
1. Numerous strains of Borrelia
2. Different forms of Borrelia
3. Testing Challenges
4. Co-infections
5. **Biofilms**
6. Immune evasion and persistent infections
7. Various Treatment Guidelines

What's a biofilm?

- Bacterial biofilms are microbial communities held together by an extracellular polymeric substance matrix predominantly composed of polysaccharides, proteins and nucleic acids.
- Biofilms protect the bacteria complicating treatment.



Sapi, E, et al. Characterization of Biofilm Formation by Borrelia burgdorferi In Vitro. PLoS One. 2012; 7(10): e48277.
Sapi, E, et al. Evidence of In Vivo Existence of Borrelia Biofilm in Borrelial Lymphocytomas. Eur J Microbiol Immunol (Bp). 2016 Feb 9;6(1):9-24



Biofilms in 3D

- Biofilms protect the resident individuals from the hostile environment of the host immune system attack or antibiotics or other targeted phytonutrient therapies.
- Dr. Sapi states, “It was demonstrated that pathogenic biofilms possess as much as 1000 fold increased tolerance to antimicrobial agents, making them very difficult to eradicate.”

- Borrelia biofilms have been demonstrated in vitro and in tissue biopsy specimen.

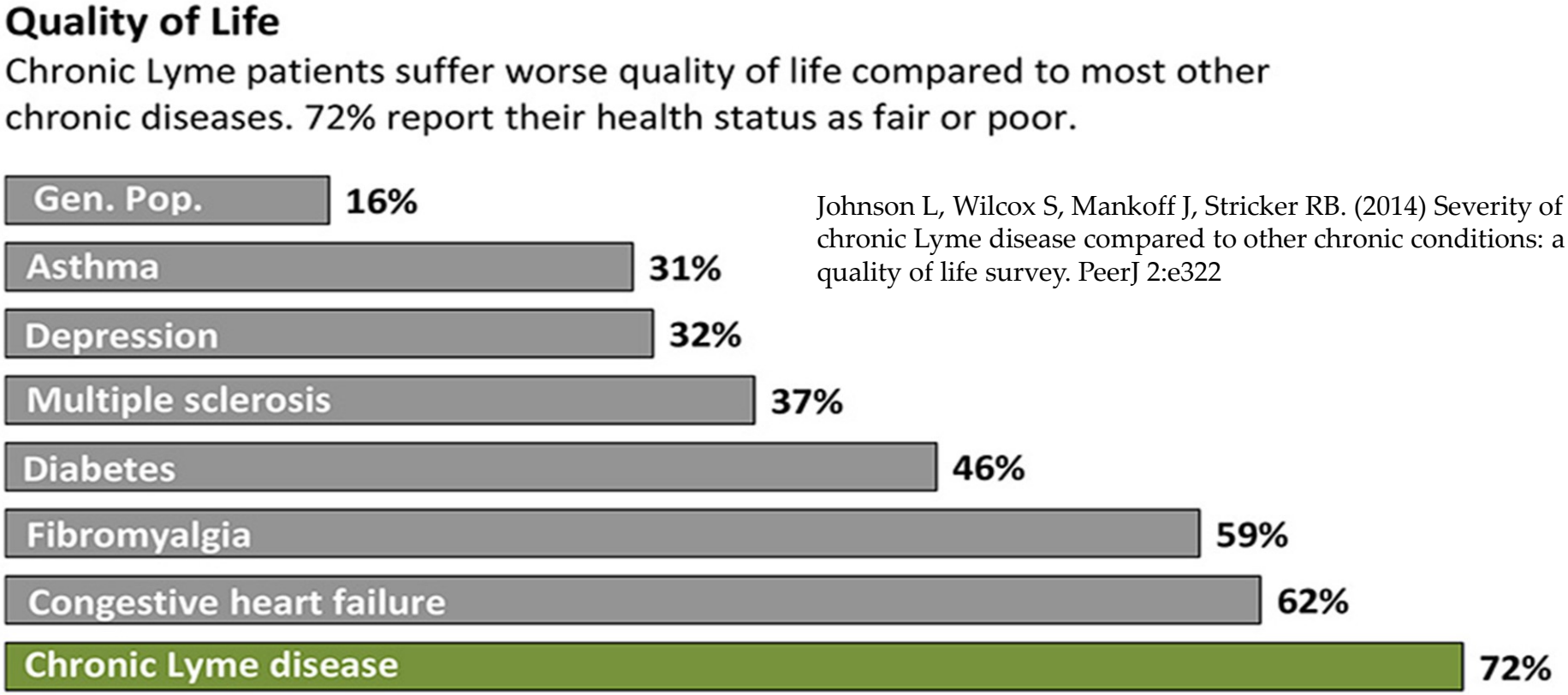
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3480481/

Lyme evades immune system responses

- Lyme causes immune system dysfunction and immune suppression
  - Tick salivary proteins delay early host immune response
  - Atypical morphologies evade immune response
- The spirochete has form changes and antigenic variation
  - Deceives alternative complement pathways
  - Antigenic variation challenges the humoral immune responses
- Physical seclusion to Intracellular and extracellular sites
  - Unique motility skills
  - Seeks niches to evade host immune system.
- Biofilms
- Persister cells

Berndtson, K. Inter Jour Gen med 2013;6: 291-306.
Embers, Microbes Infect 2004;6:312-8.

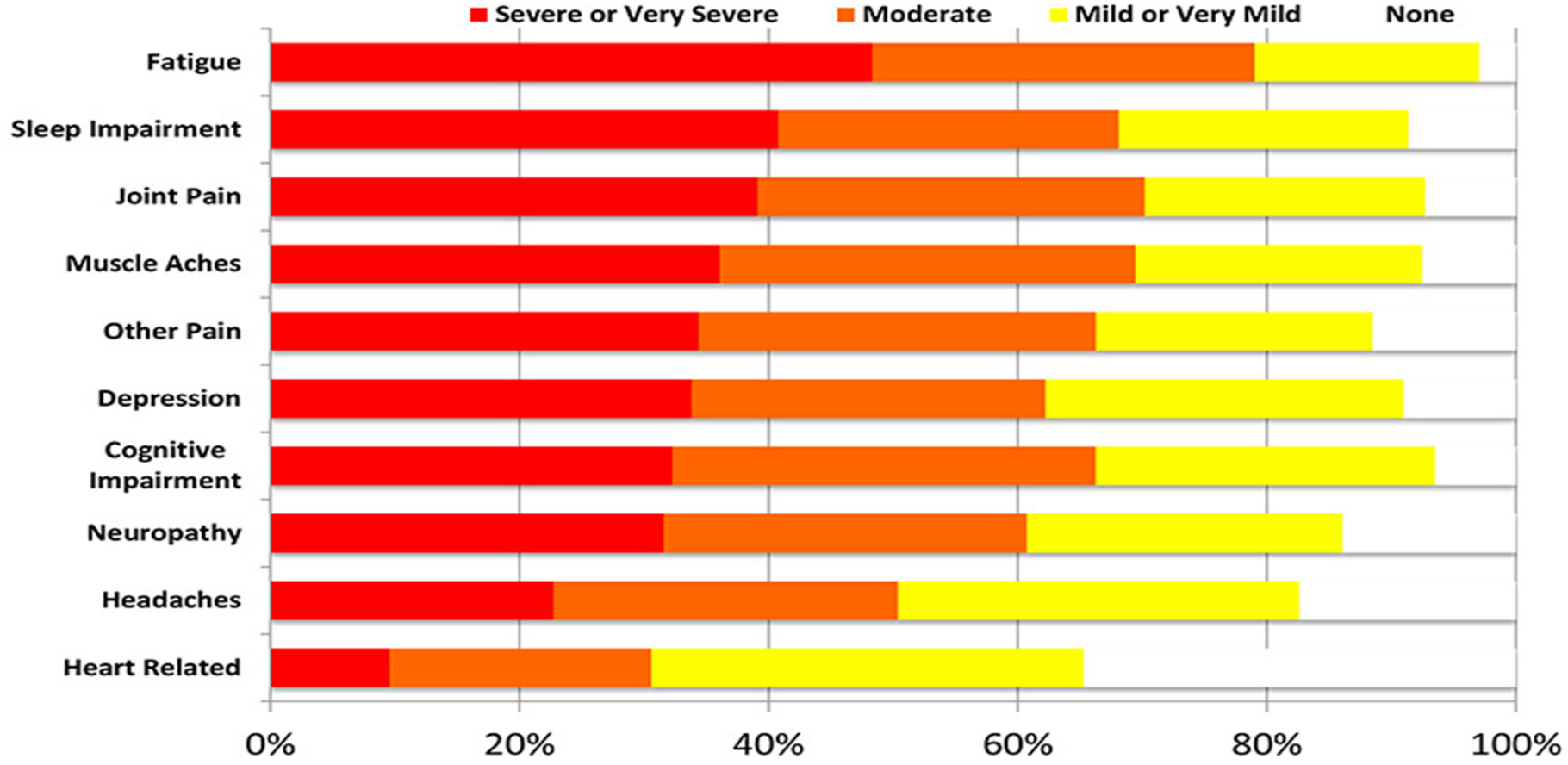
Lyme patients can become chronically ill patients

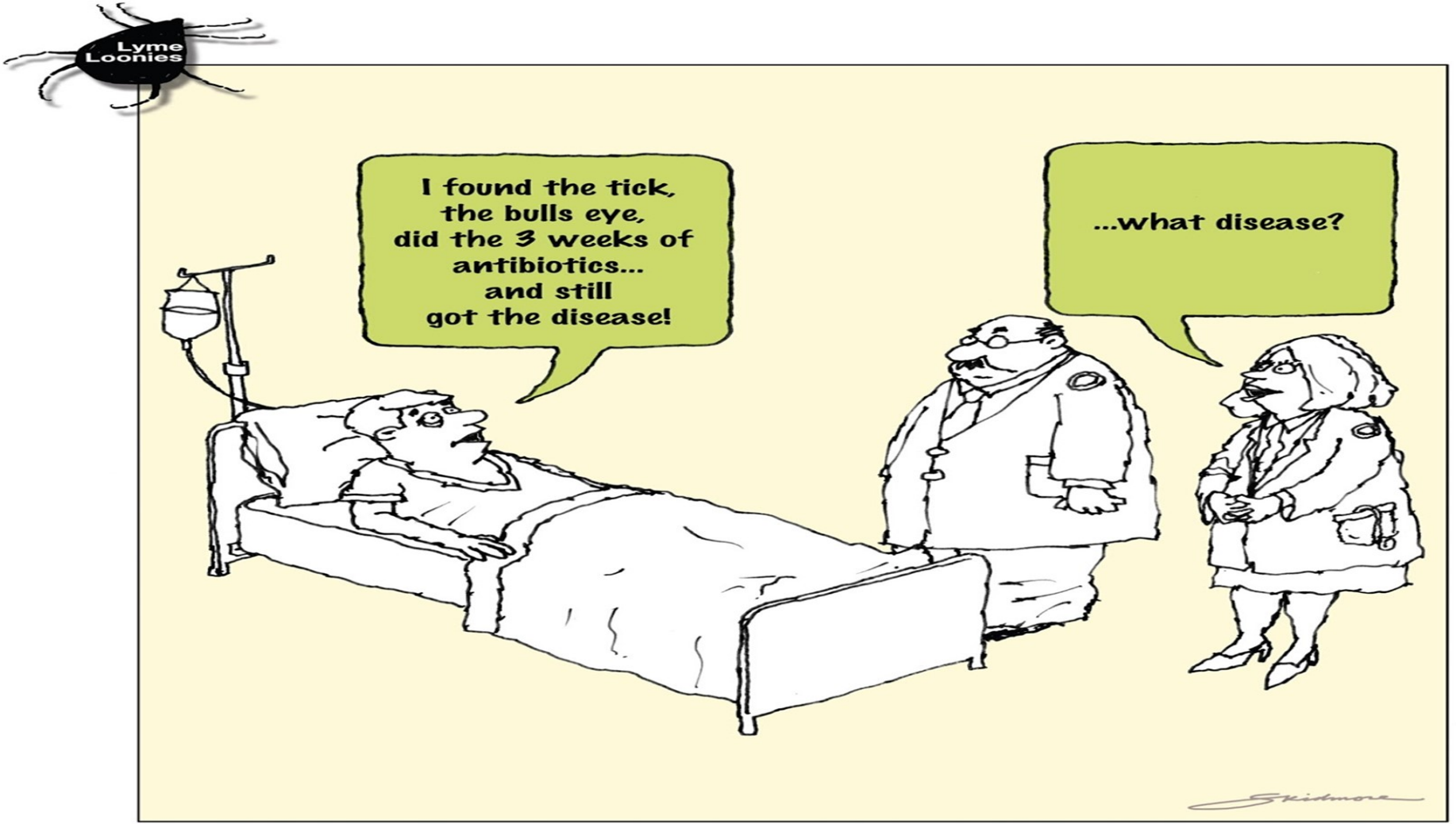


Johnson L, Wilcox S, Mankoff J, Stricker RB. (2014) Severity of chronic Lyme disease compared to other chronic conditions: a quality of life survey. PeerJ 2:e322

Symptom Severity

75% of chronic Lyme patients experience severe or very severe symptoms. 63% describe two or more symptoms as severe or very severe.




Lyme Loonies
I found the tick, the bulls eye, did the 3 weeks of antibiotics... and still got the disease!
...what disease?
Skidmore

Complicating Factors in Lyme disease as a Chronic Illness

PATIENT FACTORS

1. Lyme disease and Co-infections
2. Immune Dysfunction
3. Inflammation
4. Environmental toxins – chemicals and mold
5. Nutritional deficiencies
6. Mitochondrial dysfunction
7. Endocrine abnormalities
8. Neurodegenerative disorders
9. Neuropsychiatric disorders
10. Sleep disorders
11. Autonomic nervous system dysfunction and POTS
12. Allergies
13. GI disorders
14. Liver dysfunction
15. Pain disorders/addiction
16. Deconditioning

Patient list from Richard Horowitz, MD

Horowitz Lyme-MSIDS Questionnaire

The Horowitz Lyme-MSIDS Questionnaire is not intended to replace the advice of your own physician or other medical professional. You should consult a medical professional in matters relating to health, and individuals are solely responsible for their own health care decisions regarding the use of this questionnaire. It is intended for informational purposes only and not for self-treatment or diagnosis.

SECTION 1: SYMPTOM FREQUENCY SCORE

0 None 1 Mild 2 Moderate 3 Severe

1. Unexplained fevers, sweats, chills, or flushing	
2. Unexplained weight change; loss or gain	
3. Fatigue, tiredness	
4. Unexplained hair loss	
5. Swollen glands	
6. Sore throat	
7. Testicular or pelvic pain	
8. Unexplained menstrual irregularity	
9. Unexplained breast milk production; breast pain	
10. Irritable bladder or bladder dysfunction	
11. Sexual dysfunction or loss of libido	
12. Upset stomach	
13. Change in bowel function (constipation or diarrhea)	
14. Chest pain or rib soreness	
15. Shortness of breath or cough	
16. Heart palpitations, pulse skips, heart block	
17. History of a heart murmur or valve prolapse	
18. Joint pain or swelling	
19. Stiffness of the neck or back	
20. Muscle pain or cramps	
21. Twitching of the face or other muscles	
22. Headaches	
23. Neck cracks or neck stiffness	

Horowitz Lyme-MSIDS Questionnaire

24. Tingling, numbness, burning, or stabbing sensations	
25. Facial paralysis (Bell's palsy)	
26. Eyes/vision: double, blurry	
27. Ears/hearing: buzzing, ringing, ear pain	
28. Increased motion sickness, vertigo	
29. Light-headedness, poor balance, difficulty walking	
30. Tremors	
31. Confusion, difficulty thinking	
32. Difficulty with concentration or reading	
33. Forgetfulness, poor short-term memory	
34. Disorientation: getting lost; going to wrong places	
35. Difficulty with speech or writing	
36. Mood swings, irritability, depression	
37. Disturbed sleep: too much, too little, early awakening	
38. Exaggerated symptoms or worse hangover from alcohol	
TOTAL Section 1	

SECTION 2: MOST COMMON LYME SYMPTOMS SCORE

If you rated a 3 for each of the following in section 1, give yourself 5 additional points:	
39. Fatigue	
40. Forgetfulness, poor short-term memory	
41. Joint pain or swelling	
42. Tingling, numbness, burning, or stabbing sensations	
43. Disturbed sleep: too much, too little, early awakening	
TOTAL Section 2	

SECTION 3: LYME INCIDENCE SCORE

Now please circle the points for each of the following statements you can agree with:	If true, transpose points here:
44. You have had a tick bite with no rash or flulike symptoms. *3 points*	
45. You have had a tick bite, an erythema migrans, or an undefined rash, followed by flulike symptoms. *5 points*	
46. You live in what is considered a Lyme-endemic area. *2 points*	
47. You have a family member who has been diagnosed with Lyme and/or other tick-borne infections. *1 point*	
48. You experience migratory muscle pain. *4 points*	
49. You experience migratory joint pain. *4 points*	
50. You experience tingling/burning/numbness that migrates and/or comes and goes. *4 points*	
51. You have received a prior diagnosis of chronic fatigue syndrome or fibromyalgia. *3 points*	
52. You have received a prior diagnosis of a specific autoimmune disorder (lupus, MS, or rheumatoid arthritis), or of a nonspecific autoimmune disorder. *3 points*	
53. You have had a positive Lyme test (IFA, ELISA, Western blot, PCR, and/or borrelia culture). *5 points*	
TOTAL Section 3	

Horowitz Lyme-MSIDS Questionnaire

SECTION 4: OVERALL HEALTH SCORE

	Transpose the points from column A here:
54. Thinking about your overall physical health, for how many of the past thirty days was your physical health not good?_____ days Award yourself the following points based on the total number of days: 0–5 days = 1 point 6–12 days = 2 points 13–20 days = 3 points 21–30 days = 4 points	
55. Thinking about your overall mental health, for how many days during the past thirty days was your mental health not good?_____ days Award yourself the following points based on the total number of days: 0–5 days = 1 point 6–12 days = 2 points 13–20 days = 3 points 21–30 days = 4 points	
TOTAL Section 4	

SCORING:

Record your total scores for each section below and add them together to achieve your final score:

Section 1 Total:	
Section 2 total:	
Section 3 total:	
Section 4 total:	
FINAL SCORE	

If you scored 46 or more, you have a high probability of a tick-borne disorder and should see a health-care provider for further evaluation.

If you scored between 21 and 45, you possibly have a tick-borne disorder and should see a health-care provider for further evaluation.

If you scored under 21, you are not likely to have a tick-borne disorder.

Interpreting the Results

We see a high frequency of Section 1 symptoms in our patients, including fatigue, joint and muscle pain that often migrates, sleep disorders, as well as memory and concentration problems, and a high frequency of Section 3 symptoms, especially neuropathic pain that comes and goes and migrates (tingling, numbness, burning, etc.). These form a cluster of presenting symptoms that are characteristic of those with a high probability of having Lyme-MSIDS.

In one recent study conducted in our office of 100 consecutive patients, we found that more than 25 percent reported that the following symptoms were present most or all of the time in the month preceding their office visit. Many of these patients reported that these symptoms affected their quality of life: 71 percent reported that their physical health was not good and 47 percent reported that their mental health was not good on at least fifteen days in the previous month.

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ORIGINAL RESEARCH

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

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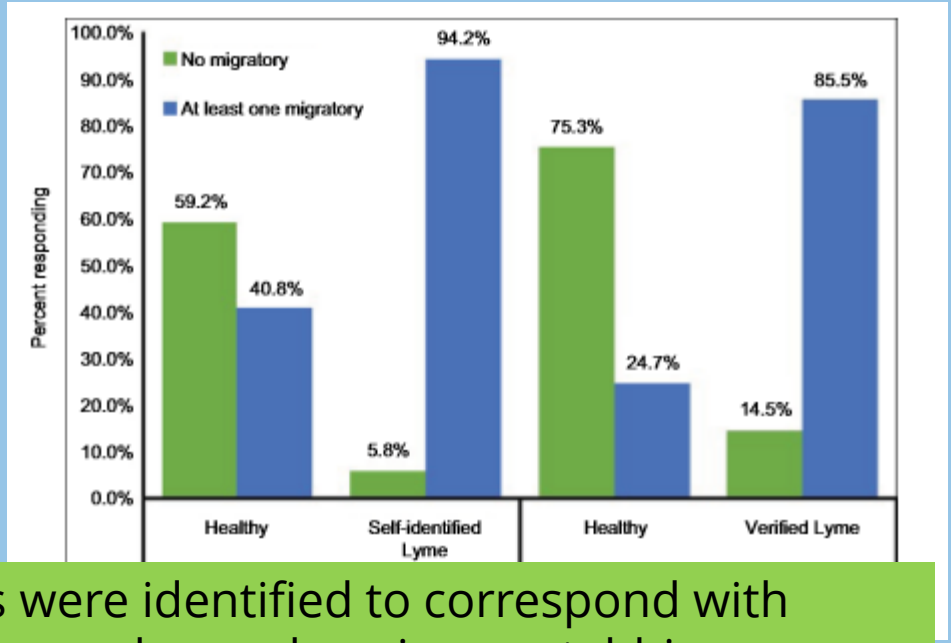
Purpose: Lyme disease is spreading worldwide, with multiple *Borrelia* species causing a broad range of clinical symptoms that mimic other illnesses. A validated Lyme disease screening questionnaire would be clinically useful for both providers and patients. Three studies evaluated such a screening tool, 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 2 involved an online sample of 999 participants, who self-identified as either healthy (N=217) or suffering from Lyme now (N=782) who completed the Horowitz MSIDS Questionnaire (HMQ) along with an outdoor activity survey. We examined convergent validity among components of



Paper includes 3 studies. 6 factors were identified to correspond with Lyme symptoms including tingling, numbness, burning or stabbing sensations, forgetfulness and poor short term memory, joint pain or swelling, fatigue, disturbed sleep; plus dysautonomia and cardio/respiratory symptoms. 85% of Lyme patients had at least one migratory symptom, only 24% of healthy individuals possessed. Focus on migratory joint pain, muscle pain and neuropathic pains.

Citera, 2017

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blood brain barrier, endothelial tissue, and imbed itself in joints, entering certain cells

, MD

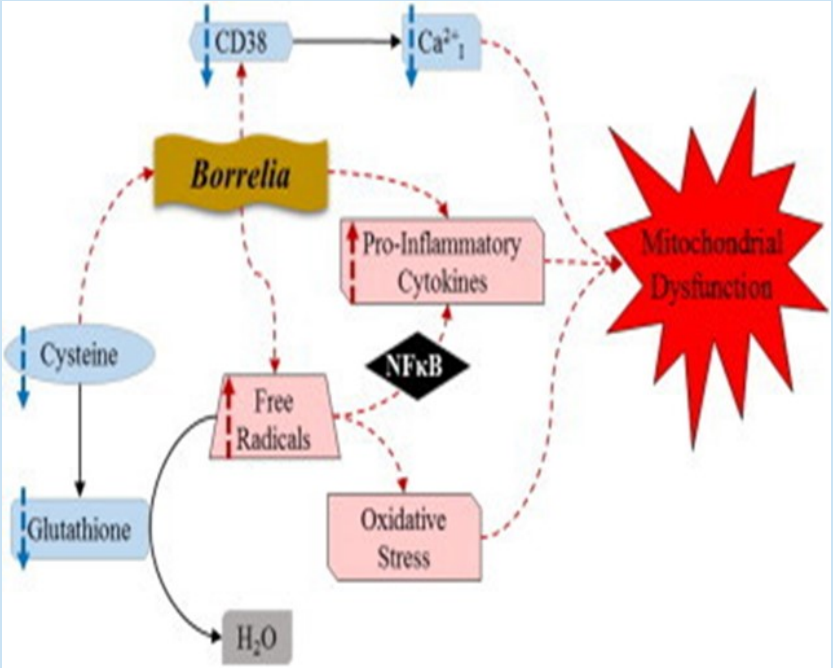

Lyme Loonies
...Bon voyage! Oh, by the way, I can't say when I'll let you off this thing?
LYME HELL RIDE
LYME HELL RIDE
LYME HELL RIDE

Pathophysiology of Lyme and Chronic Illness

Oxidative stress
Inflammation
Immune dysfunction
Autoimmunity
Molecular mimicry
Mitochondrial dysfunction
IDO upregulation
Increased kynurenic acid
Microglial activation
Gastrointestinal disturbances
Endocrine dysfunction
Mineral imbalance – zinc and manganese

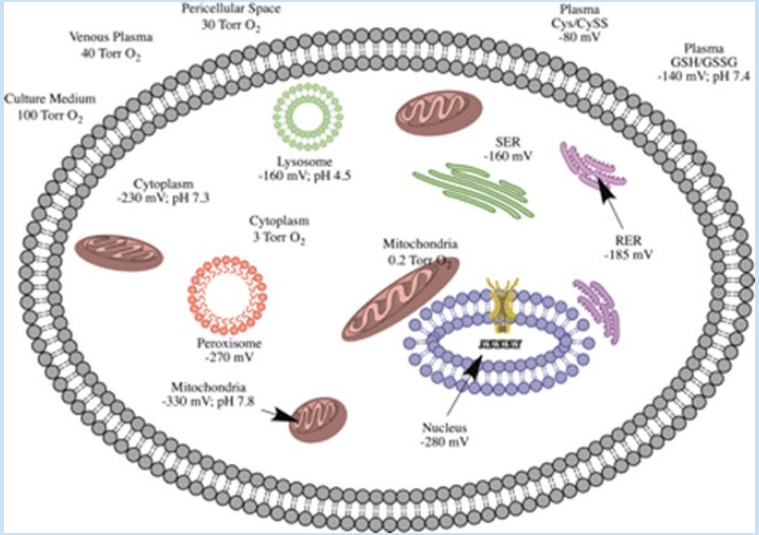
Lyme disease – inflammation and oxidative stress

- Significant rise in mitochondrial superoxide and decrease in ionized calcium indicate oxidative stress, mitochondrial membrane instability and release of pro-inflammatory cytokines in Lyme borreliosis patients.
- Activation of Inflammation and host immune responses cause damage leading to hallmarks of neurodegeneration. Misfolded proteins, oxidative stress, deficient apoptosis, cell death.
- Dexamethasone reverses inflammatory cascade, both lower inflammatory markers and preventing pathological changes in animal neuroborreliosis.



DeChiara, etal. 2012. Mol Neurobiol 46:614-38.
Peacock 2015. Redox Biology 5:66-70.
Ramesh. Amer Journ of Pathology. 2015. 185 (5): 1344-60.

Oxidative shielding rather than oxidative stress

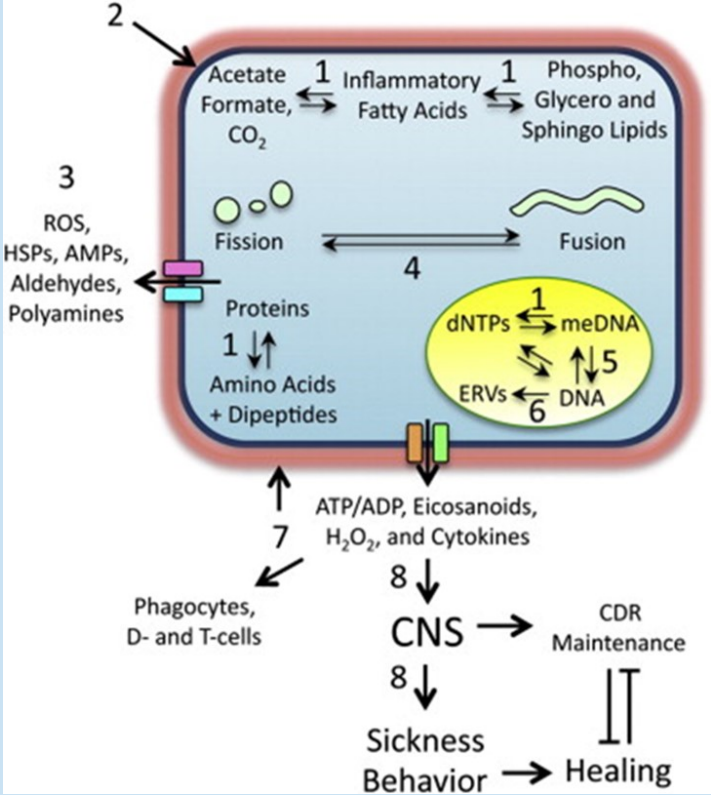


Naviaux. Journal of Pharmacology and Experimental Therapeutics. 2012, 342(3):608-18.

- When mitochondria nutrients and substrates are perturbed by viral or microbial infection or toxins, there is a metabolic mismatch.
- Electrons are diverted, oxygen consumption falls, assembly of DNA, RNA, lipids, proteins and carb synthesis stops. ROS/RNS rise and there is a limit to the replication of the invading pathogen.
- Oxidative changes are the symptoms of the disease, not the cause.

The Cell Danger Response

- The cell danger response (CDR) is an evolutionarily conserved cellular metabolic response that is activated when a cell encounters a chemical, physical, or microbial threat that could injure or kill the cell.
- Psychological trauma, particularly during childhood, can also activate the cell danger response, produce chronic inflammation, and increase the risk of many disorders.



Naviaux. Mitochondrion. 2014. 16:7–17

The Cell Danger Response

The acute CDR produces at least 8 functional changes:

1) It shifts cellular metabolism to prevent the hijacking and assembly of cellular resources by intracellular pathogens.
2) It stiffens the membranes of the cell
3) Releases antiviral and antimicrobial chemicals into the pericellular environment
4) Increases autophagy and mitochondrial fission to remove intracellular pathogens

The Cell Danger Response

5) Changes DNA methylation and histone modification to alter gene expression
6) Mobilizes endogenous retroviruses and other mobile genetic elements like the long interspersed nuclear elements (LINEs) to produce genetic variations
7) Warns neighboring cells and distant effector cells of the danger
8) Alters the behavior of the host to prevent the spread of infection to kin and sleep patterns to facilitate healing

Metabolic features of chronic fatigue syndrome

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Edited by Ronald W. Davis, Stanford University School of Medicine, Stanford, CA, and approved July 13, 2016 (received for review May 11, 2016)

More than 2 million people in the United States have myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). We performed targeted, broad-spectrum metabolomics to gain insights into the biology of CFS. We studied a total of 84 subjects using these methods. Forty-five subjects ($n = 22$ men and 23 women) met diagnostic criteria for ME/CFS by Institute of Medicine, Canadian, and Fukuda criteria. Thirty-nine subjects ($n = 18$ men and 21 women) were age- and sex-matched normal controls. Males with CFS were 53 (±2.8) y old (mean ± SEM; range, 21–67 y). Females were 52 (±2.5) y old (range, 20–67 y). The Karnofsky performance scores were 62 (±3.2) for males and 54 (±3.3) for females. We targeted 612 metabolites in plasma from 63 biochemical pathways by hydrophilic interaction liquid chromatography, electrospray ionization, and tandem mass spectrometry in a single-injection method. Patients with CFS showed abnormalities in 20 metabolic pathways. Eighty percent of the diagnostic metabolites were decreased, consistent with a hypometabolic syndrome. Pathway abnormalities included sphingolipid, phospholipid, purine, cholesterol, microbiome, pyrroline-5-carboxylate, riboflavin, branch chain amino acid, peroxisomal, and mitochondrial metabolism. Area under the receiver operator characteristic curve analysis showed diagnostic accuracies of 94% [95% confidence interval (CI), 84–100%] in males using eight metabolites and 96% (95% CI, 86–100%) in females using 13 metabolites. Our data show that despite the heterogeneity of factors leading to CFS, the cellular metabolic response in patients was homogeneous, statistically robust, and chemically similar to the evolutionarily conserved persistence response to environmental stress known as dauer.

chronic fatigue syndrome | metabolomics | mitochondria | dauer | cell danger response

Chronic fatigue syndrome (CFS) is a complex, multiorgan system disease for which no single diagnostic test yet exists. The disease is characterized by profound fatigue and disability lasting for at least 6 mo, episodes of cognitive dysfunction, sleep disturbance, autonomic abnormalities, chronic or intermittent pain syndromes, microbiome abnormalities (1), cerebral cytokine dysregulation (2), natural killer cell dysfunction (3), and other symptoms that are made worse by exertion of any kind (4). The Institute of Medicine (IOM) recently published an update of the diagnostic criteria recommended for CFS (4). These are listed in Box 1.

Complex diseases like CFS are often difficult and expensive to diagnose. Although individual tests may be affordable and possibly covered by medical insurance, many patients undergo a diagnostic odyssey that results in substantial personal expenditures that can exceed $100,000 over years of searching, absence from the workplace, and significant reductions in quality of life. The societal cost of CFS is estimated to be up to $24 billion annually (4). Health care professionals are also frustrated by the lack of an objective technology that can assist with diagnosis. Attempts to use a small number of biomarkers, whether analytes in blood, cerebrospinal fluid, or a handful of genetic loci, have not yielded diagnostically useful tests for CFS.

Metabolomics has several advantages over genomics for the in precision medicine (5). First, fewer than 2,000 metabolites constitute the majority of the parent molecules in the blood that are used for cell-to-cell communication and metabolism, compared with 6 billion bases in the diploid human genome. Second, metabolites reflect the current functional state of the individual. Collective cellular chemistry represents the functional interaction of genes and environment. This is metabolism. In contrast, the genome represents an admixture of ancestral genotypes that were selected for fitness in ancestral environments. The metabolic state of an individual at the time of illness is produced by both current conditions, age, and the aggregate history, timing, and magnitude of exposures to physical and emotional stress, trauma, diet, exercise, infections, and the microbiome recorded as metabolic memory (6, 7). Analysis of metabolites may provide a more technically and bioinformatically tractable, physiologically relevant, chemically comprehensive, and cost-effective method of diagnosis of complex chronic diseases. In addition, because metabolomics provides direct small-molecule information, the results can provide immediately actionable treatment information using readily available small-molecule nutrients, cofactors, and lifestyle interventions. Our results show that CFS has an objectively identifiable chemical signature in

Significance

Chronic fatigue syndrome is a multisystem disease that causes long-term pain and disability. It is difficult to diagnose because of its protean symptoms and the lack of a diagnostic laboratory test. We report that targeted, broad-spectrum metabolomics of plasma not only revealed a characteristic chemical signature but also revealed an unexpected underlying biology. Metabolomics showed that chronic fatigue syndrome is a highly concerted hypometabolic response to environmental stress that traces to mitochondria and was similar to the classically studied developmental state of dauer. This discovery opens a fresh path for the rational development of new therapeutics and identifies metabolomics as a powerful tool to identify the chemical differences that contribute to health and disease.

Author contributions: R.K.N., N.N., W.A., and E.G. designed research; R.K.N., J.C.N., K.L., A.T.B., L.W., A.B., N.N., W.A., and E.G. performed research; R.K.N., J.C.N., K.L., A.T.B., W.A.A., and L.W. contributed new reagents/analytic tools; R.K.N. wrote and managed the human subjects protocol; J.C.N. recruited subjects and developed methods; K.L. developed methods; A.T.B. created the pathway database and developed new bioinformatic methods; W.A.A. prepared the Cytoscape pathway visualizations; A.B. coordinated patient recruitment, medical histories, and clinical data; N.N., W.A., and E.G. identified and recruited patients; R.K.N., J.C.N., K.L., A.T.B., N.N., and E.G. analyzed data; and R.K.N., J.C.N., K.L., A.T.B., and W.A.A. wrote the paper.

The authors declare no conflict of interest.

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Data deposition: The data reported in this paper have been deposited in the NIH Metabolomics Data Repository and Coordinating Center (DRCC) (accession no. ST000450).

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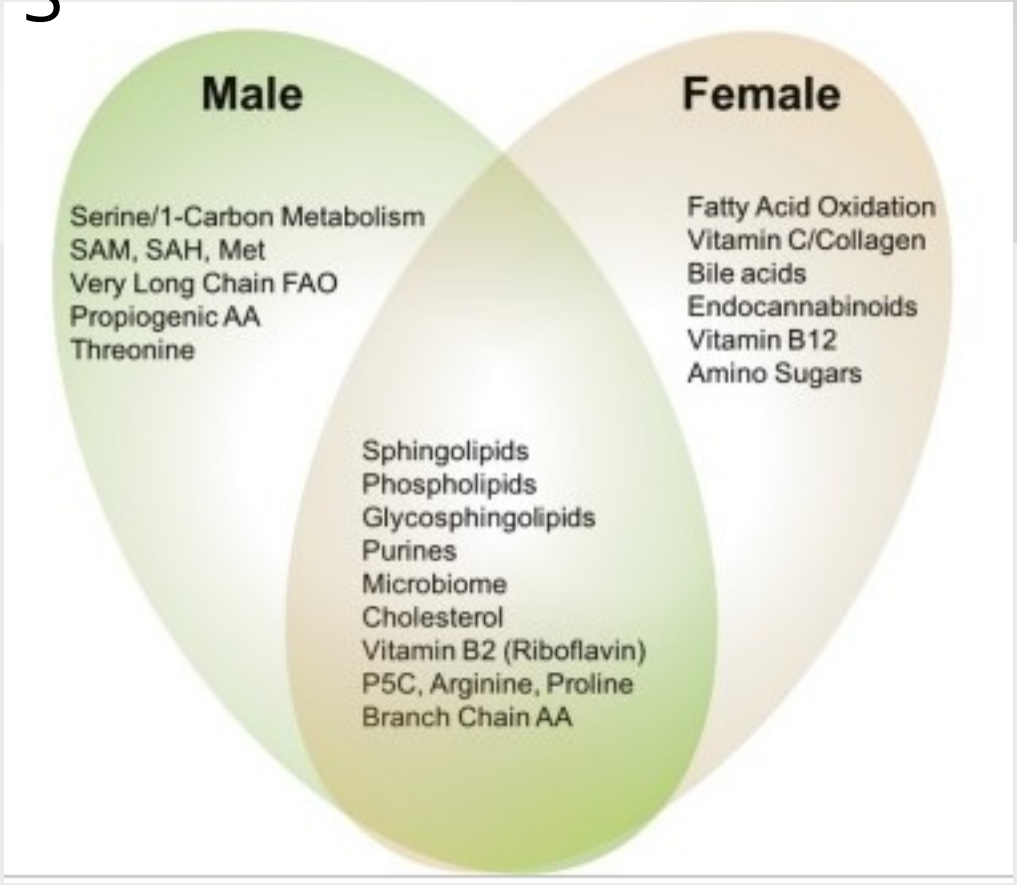
Features of CFS

- Metabolomics of chronic fatigue indicate a hypometabolic state in response to pathologically persist or recurrent cell danger signaling, as in the case of persistent viral or bacterial infections.
- Dauer, which means persistent or long-lived in German, is a hypometabolic state capable of living efficiently by altering basic mitochondrial functions to confer a survival advantage.
- Both males and females with Chronic Fatigue Syndrome had chemical signature that was distinct from healthy controls.

Kelly K. McCann, MD

Metabolic Features of CFS

- Both males and females with Chronic Fatigue Syndrome had chemical signature that was distinct from healthy controls.
- 9 common pathways, 11 showed gender differences.
- Dominant abnormalities in sphingolipids constituted close to 50% of all metabolic changes.
- Phospholipids changes 16% in males, 26% in females.



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Gastrointestinal disturbances
Endocrine dysfunction
Mineral imbalance – zinc and manganese

PLOS | PATHOGENS

RESEARCH ARTICLE

Suppression of Long-Lived Humoral Immunity Following *Borrelia burgdorferi* Infection

Rebecca A. Elsner[1,2¤a], Christine J. Hastey[1,2¤b], Kimberly J. Olsen[1], Nicole Baumgarth[1,2,3]*

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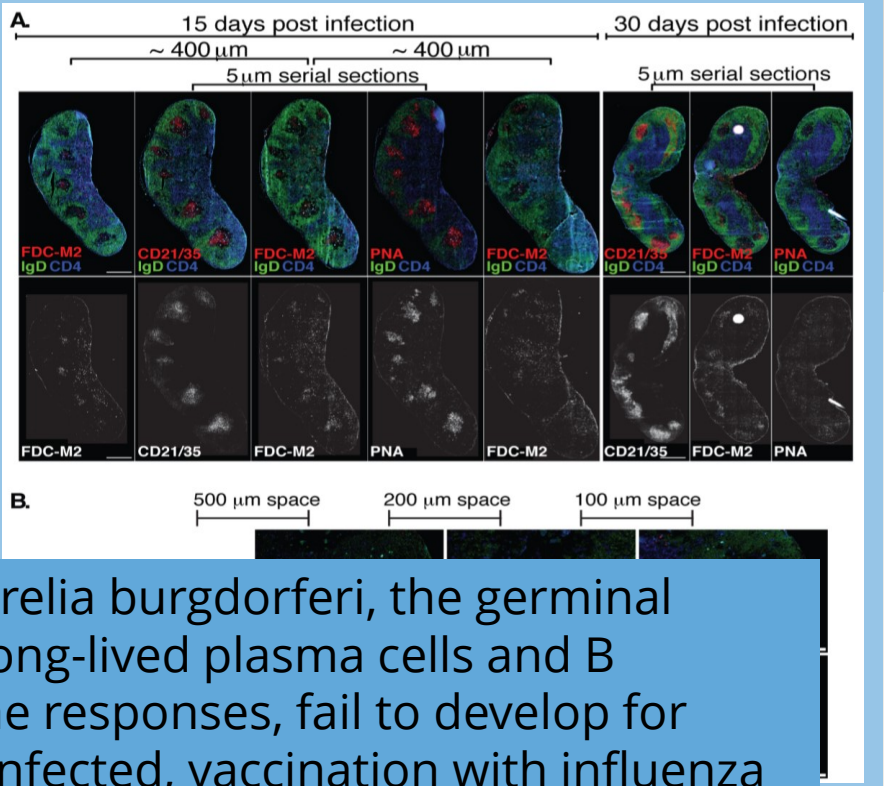

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only short-lived germinal centers, micro-anatomical locations from which long-lived immunity originates. These showed structural abnormalities and failed to induce memory B cells and long-lived plasma cells for months after the infection, rendering the mice susceptible to reinfection with the same strain of *B. burgdorferi*. The inability to induce long-lived immune

Following the infection of mice with Borrelia burgdorferi, the germinal centers are structurally abnormal and long-lived plasma cells and B memory cells, which are normal immune responses, fail to develop for months after the infection…Also when infected, vaccination with influenza fails to induce protective anti-viral immunity. Elsner, et al. 2014

Kelly K. McCann, MD

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Review

Cell PRESS

Autoimmunity and the environment

Infections and autoimmunity – friends or foes?

Shaye Kivity[1,2*], Nancy Agmon-Levin[1,3*], Miri Blank[1] and Yehuda Shoenfeld[1,3,4]

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Autoimmunity can be triggered by many environmental factors, among which infectious agents are pivotal. Here, we summarize current knowledge of the relationship between infection and autoimmunity. An autoimmune disease can be i
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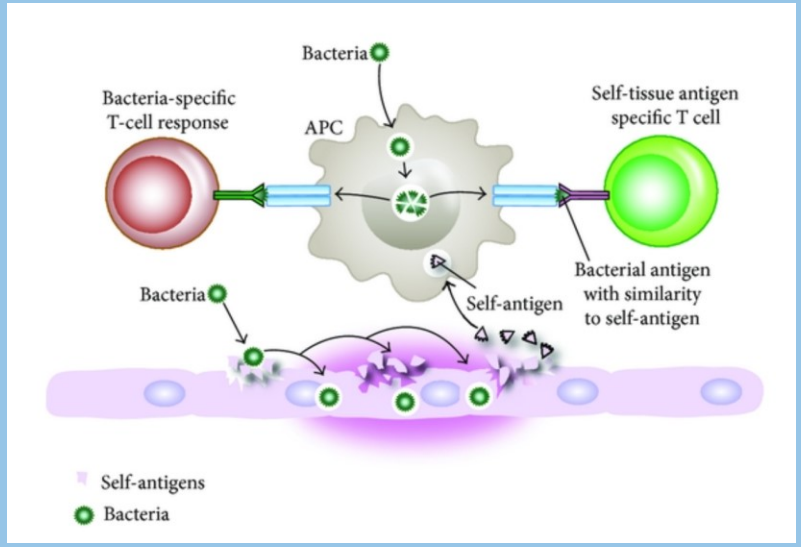
suggested to explain this relationship. In recent years, the compound interplay between infections and autoimmunity has been studied extensively. Here, we summarize the current literature and preliminary results from our

Introduction

The immune sy
processes desig
infectious patl
includes innate, adaptive and memory responses that are constantly activated, adapted and improved to meet the challenge of evading pathogens more efficiently. In

immunity [1]. Almost every autoimmune disease investigated is linked to one or more specific infectious agents. One of the best-recognized examples of this relationship is acute



Most infectious agents can induce autoimmunity disease in genetic susceptible hosts, which in turn increases their risks of additional infections. Post-infectious autoimmunity can be induced by a variety of mechanisms including molecular mimicry, bystander activation, persistent infections and polyclonal activation. Burden of infections are cumulative over lifetime to a breakthrough point. Kivity, et al. 2009

Ten principles of the relationship between infection and autoimmunity

1. Infections can cause autoimmune diseases.
2. Different infectious agents (viruses, bacteria, fungus and parasites) can trigger autoimmunity.
3. An infection can trigger an individual with an underlying immune dysregulation to express an overt autoimmune disease.
4. Infectious agents can determine the presence of disease-specific auto-antibodies and clinical manifestations.
5. In many cases, it is not a single infection, but rather the 'burden of infections' during life that is responsible for induction of autoimmunity.

Ten principles of the relationship between infection and autoimmunity

6. Infections during childhood can be implicated in the development of autoimmune diseases in adulthood.
7. Infections can protect individuals from some autoimmune diseases.
8. The same infectious agent can induce one specific autoimmune disease and protect from another autoimmune disease.
9. Molecular mimicry, epitope spreading, bystander activation and polyclonal activation can induce autoimmunity after infections via innate and adaptive immune responses.
10. Genetic susceptibility might explain why only a subgroup of individuals will develop autoimmunity after infections.

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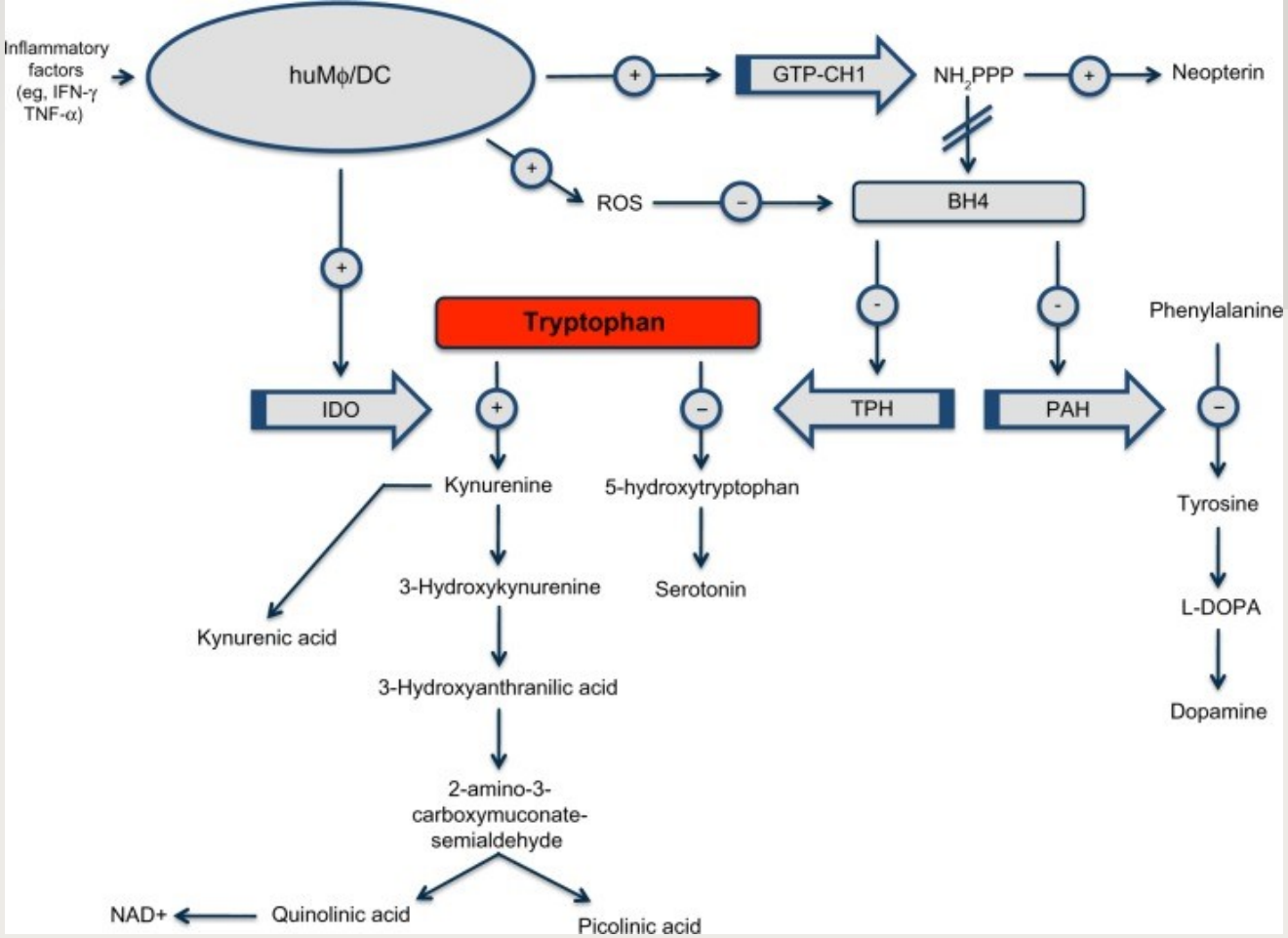
Tryptophan metabolism - Lyme and serotonin



Tryptophan metabolism - Lyme and serotonin

- IDO is induced by interferon (IFN)γ, interleukin-6 and tumor necrosis factor-α, lipopolysaccharides and oxidative stress, factors that play a role in the pathophysiology of depression.
- TRYCATs, like kynurenine and quinolinic acid, are depressogenic and anxiogenic; activate oxidative pathways; cause mitochondrial dysfunctions; and have neuroexcitatory and neurotoxic effects that may lead to neurodegeneration.

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Review

Indoleamine 2,3-dioxygenase in infection: the paradox of an evasive strategy that benefits the host

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Abstract

Initially recognized in infection because of antimicrobial activity ('tryptophan starvation'), indoleamine 2,3-dioxygenase (IDO) is widely involved in host immune homeostasis and even immune evasion by microbes that establish commensalism or chronic infection. This review deals with recent findings that could gain IDO a reputation of Jack-of-all-trades in mammalian host/microbe interactions.

Keywords: Indoleamine 2,3-dioxygenase; Tryptophan starvation; Kynurenines

1. Introduction

Historically, the role of indoleamine 2,3-dioxygenase (IDO) in infection was first centered on the anti-proliferative effects of tryptophan (trp) deprivation by the host, which may hold true of specific intracellular infections. However, like tumor cells [1], eukaryotic microbes may express IDO, and even exploit an IDO-conditioned regulatory environment to evade their host's own defense mechanisms, eventually leading to pathogen persistence or chronic infection [2]. Within a conceptual framework from different areas of immune regulation, the many and apparently disparate functions of IDO in infection are now being reconciled, emphasizing a quite complex role for a metabolic pathway that appears to be conserved—though evolved in function—through the last 600 million years of evolution.

IDO and the downstream enzymes in the metabolic pathway of trp degradation have a central role in chronic infection [2,3]. Present in innate immune cells such as macrophages, polymorphonuclear neutrophils (PMN) [4] and epithelial cells [5], IDO is a key player in the suppression of acute inflammatory responses. Furthermore, its expression by plasmacytoid dendritic cells (pDC) enables the onset of tolerance in adaptive immune [6]. Thus immune regulation by IDO encompasses the inductive and effector phases of the innate and acquired immune responses to infection. On the other hand, IDO activation and trp degradation are regulatory mechanisms whose importance in tolerance is increasingly recognized [6,7]. A number of IDO-dependent events restrain exaggerated, allergic, or autoimmune inflammation, and induce peripheral tolerance to self or other types of antigen [6,7]. As an example, trp starvation, which leads to suppression of T-cell responses, traditionally explains the seminal observation of sustained IDO expression by placental trophoblasts, which would allow mammalian females to tolerate their fetuses [8]. In addition to direct effector activities, largely involving trp deprivation [9], IDO and the other enzymes of the metabolic pathway contribute immunoactive molecules to the generation of regulatory T (Treg) cells with anti-inflammatory and tolerogenic activities (Fig. 1) [10–12].

Continued integration of pro-inflammatory and anti-inflammatory stimuli is required for proper control of infection and T-cell homeostasis. Many of the diseases that afflict mankind are thought to result from dysfunctional innate and/or adaptive immune responses. Unresolved infection and

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Induction of indoleamine 2,3-dioxygenase by *Borrelia burgdorferi* in human immune cells correlates with pathogenic potential

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Abstract

Borrelia burgdorferi, the bacterial agent of Lyme disease, induces the production of type I IFNs by human DCs through TLR7 and TLR9 signaling. This type I IFN response occurs in a genotype-dependent manner, with significantly higher levels of IFN-α elicited by *B. burgdorferi* strains that have a greater capacity for causing disseminated infection. A *B. burgdorferi* strain that was previously shown to induce IFN-α was found to elicit significantly higher levels of IDO1 protein and its downstream metabolite, kynurenine, compared with a *B. burgdorferi* mutant that lacks a single linear plasmid (lp36); this mutant is unable to induce IFN-α and is severely attenuated for infectivity in mice. Production of IDO by mDC and pDC populations, present within human PBMCs, was concomitant with increased expression of the DC maturation markers, CD83 and CCR7. The defects in IDO production and expression of CD83 and CCR7 could be restored by complementation of the mutant with lp36. Maximal IDO production in response to the wild-type strain was dependent on contributions by both type I IFN and IFN-γ, the type II IFN. Induction of IDO was mediated by the same TLR7-dependent recognition of *B. burgdorferi* RNA that contributes to the production of type I IFNs by human DCs. The ability of IFN-α-inducing *B. burgdorferi* strains to stimulate production of IDO and kynurenines may be a mechanism that is used by the pathogen to promote localized immunosuppression and facilitate hematogenous dissemination.

Keywords: Lyme disease, immunosuppression, bacterium, dendritic cells

Introduction

B. burgdorferi is the causative agent of Lyme disease, the most common arthropod-borne disease in the United States. Acquisition of the spirochete through the bite of an infected tick frequently results in a distinctive skin rash, or EM, which is characterized by an influx of immune cells at the site of inoculation [1, 2]. This inflammatory infiltrate contains cellular components of PBMCs, including T lymphocytes, monocytes, and mDCs and pDCs, which participate in the initial host-pathogen interaction [2]. *B. burgdorferi* elicits the production of a wide array of cytokines that underlie the inflammation associated with Lyme disease. The development of inflammation is dependent on host recognition of spirochetal PAMPs by PRRs expressed by cells of the innate immune system, especially the TLRs [3–5]. In some patients, disseminated infection occurs when spirochetes migrate from the initial site of infection to distal sites in the body [6]. Sequelae of disseminated Lyme disease are also distinguished by a robust inflammatory response and include carditis, arthritis, and neuroborreliosis [6].

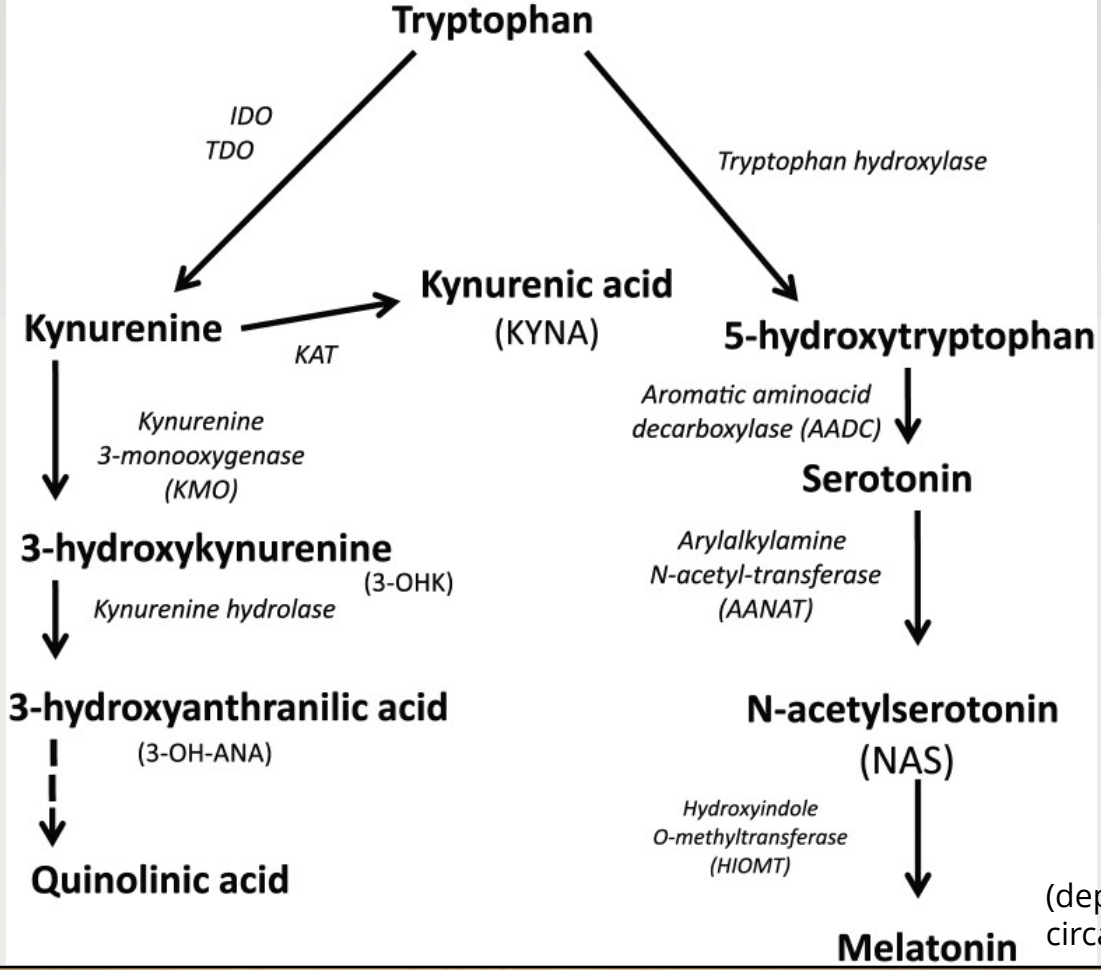
Our group [3, 4] and others [7–9] have shown that this extracellular pathogen induces the production of type I IFNs by human DCs and monocytes, as well as by murine cells. Our previous study [4] used global transcriptional profiling to characterize the response of human PBMCs to a clinical isolate of *B. burgdorferi* by use of an ex vivo coincubation model. This work demonstrated that *B. burgdorferi* stimulates the production of high levels of IFN-α protein and downstream type I IFN-associated gene transcripts via TLR7 and TLR9 signaling in human pDC and mDC subsets [4, 10]. In addition, Cervantes et al. [3] has described IFN-β transcriptional activation in

- Certain strains of *B. burgdorferi* induce IDO as a mechanism to evade the immune system and promote dissemination of the infection.
- Cytokines stimulate release of neopterin and induce IDO to degrade tryptophan.
- Increased concentrations of neopterin and l-kynurenine have been detected in the cerebrospinal fluid of patients with Lyme neuroborreliosis and Lyme encephalopathy.

Gasse, et al. Eur J Clin Chem Clin Biochem. 1994 Sep;32(9):685-9.
Widner, B, et al. Brain Behav Immun. 2002 Oct;16(5):590-5.

Kelly K. McCann, MD

Neuroactive Kynurenines (anxiety, cognitive impairment



(depression, insomnia, circadian dysrhythmia)

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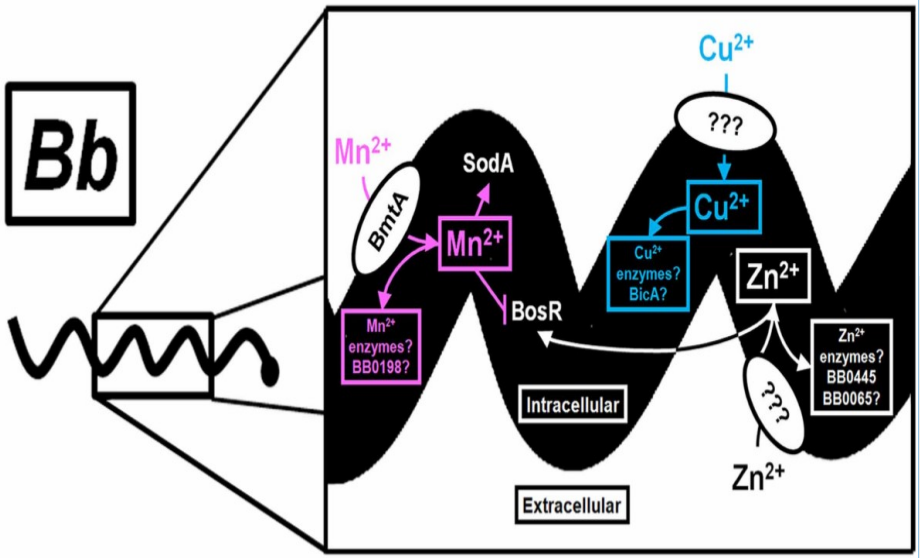
Endocrine dysfunction
Mineral imbalance – zinc and manganese



frontiers in
CELLULAR AND INFECTION MICROBIOLOGY

REVIEW ARTICLE
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Metal-dependent gene regulation in the causative agent of Lyme disease

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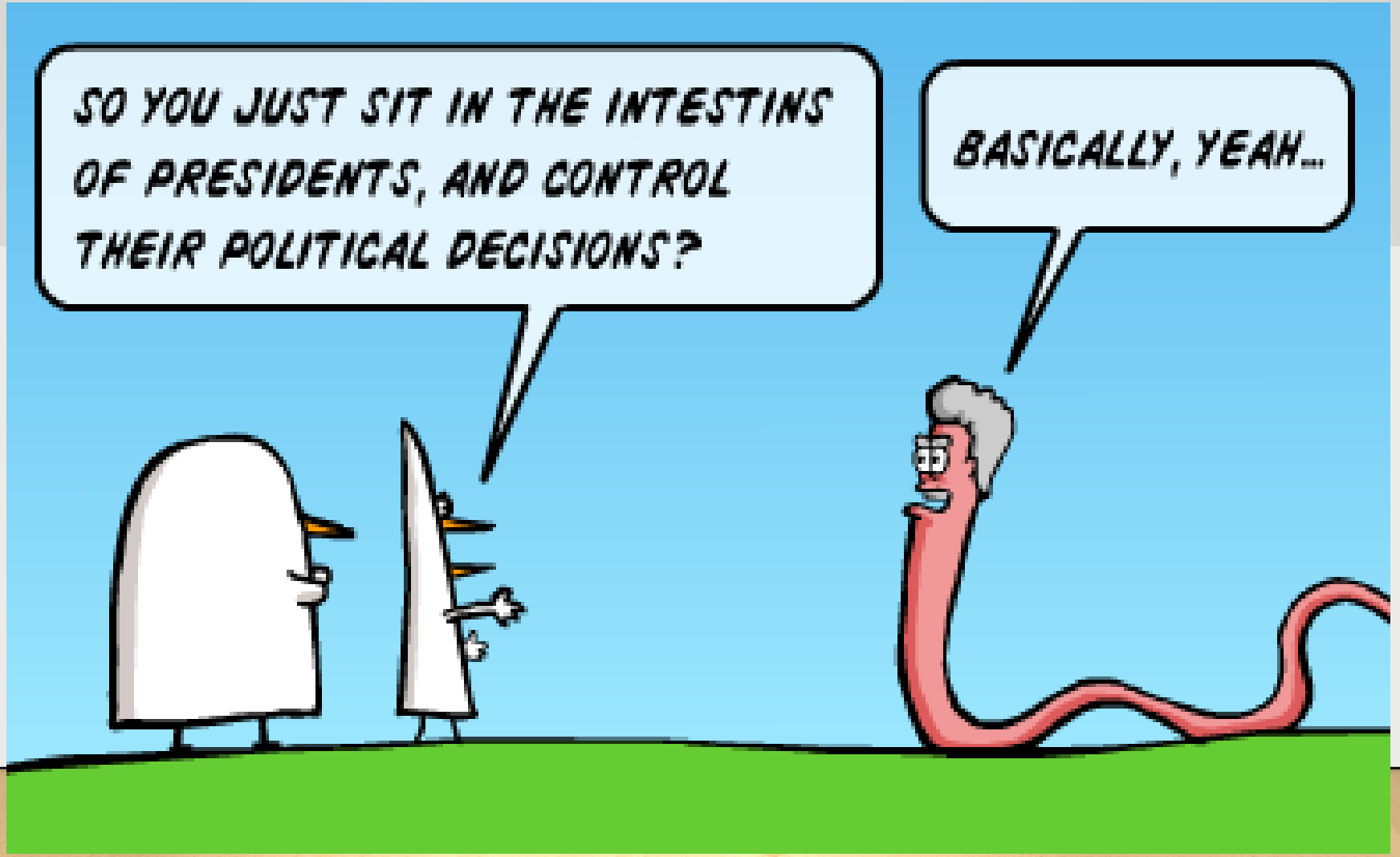
Borrelia burgdorferi (*Bb*) is the causative agent of Lyme disease transmitted to humans by ticks of the *Ixodes* spp. *Bb* is a unique bacterial pathogen because it does not require iron (Fe^{2+}) for its metabolism. *Bb* encodes a ferritin-like Dps homolog called NapA (also called BicA), which can bind Fe or copper (Cu^{2+}), and a manganese (Mn^{2+}) transport protein, *Borrelia* metal transporter A (BmtA); both proteins are required for colonization of the tick vector, but BmtA is also required for the murine host. This demonstrates that *Bb*'s metal homeostasis is a critical facet of the complex enzootic life cycle between the arthropod and murine hosts. Although metals are known to influence the expression of virulence determinants during infection, it is unknown how or if metals regulate virulence in *Bb*. Recent evidence demonstrates that *Bb* modulates the intracellular Mn^{2+} and zinc (Zn^{2+}) content and, in turn, these metals regulate gene expression through influencing the Ferric Uptake Regulator (Fur) homolog *Borrelia* Oxidative Stress Regulator (BosR). This mini-review focuses on the burgeoning study of metal-dependent gene regulation within *Bb*.

Keywords: *Borrelia burgdorferi*, Lyme disease, copper, manganese, zinc, calprotectin

Metalloenzymes are essential for biological systems. Transition metals are tightly regulating and important for gene regulation. Borrelia burgdorferi adapts to two diverse niches, vector and mammalian host in part through its unique metal utilization, thus altering virulence factors. Troxell and Yang, 2013


SO YOU JUST SIT IN THE INTESTINS OF PRESIDENTS, AND CONTROL THEIR POLITICAL DECISIONS?
BASICALLY, YEAH...

Complicating Factors in Lyme disease as a Chronic Illness

PATIENT FACTORS

1. Lyme disease and Co-infections
2. Immune Dysfunction
3. Inflammation
4. Environmental toxins – chemicals and mold
5. Nutritional deficiencies
6. Mitochondrial dysfunction
7. Endocrine abnormalities
8. Neurodegenerative disorders
9. Neuropsychiatric disorders
10. Sleep disorders
11. Autonomic nervous system dysfunction and POTS
12. Allergies
13. GI disorders
14. Liver dysfunction
15. Pain disorders/addiction
16. Deconditioning

Patient list from Richard Horowitz, MD

Case: KF 53 year old woman – May 2015

- Life-time of good health until 2014 during menopause.
- Ran 17 marathons from age 15-46, then ran 25-30 miles a week until 2014
- Vegetarian for 30 years
- On HRT but wanting to optimize. She thought she wasn't on high enough doses.
- Presented with fatigue, decreased stamina and motivation, which she attributed to stress and hormonal imbalances.
- Also complained of night sweats, brain fog, abdominal pain and bloating, back pain and stiffness, leg weakness, new headaches, mood swings, depression, anxiety, sleep issues and a chronic cough.

Case: KF 53 year old woman – May 2015

Past medical history significant for tinnitus, hypothyroidism, chronic sinusitis, and migraines.

Routine labs:

chol 213mg/dL = 5.52mmol/L, LDL 138 mg/dL = 3.57 mmol/L, HDL 85 mg/dL = 2.2mmol/L, pattern A

estradiol - not detectible

hs CRP <0.3mg/dL, HgA1c 5.4%, thyroid wnl. CBC wnl, CMP wnl.

TPO and anti-thyroglobulin were elevated.

- **Vit D25oh 44ng/mL = 109 nmol/L**
- **Vit D1,25oh was 147H = 382 pmol/L**

Case: KF September 2015

- During a return visit review labs, she described an episode when she drank a glass of wine after work and became profoundly exhausted, nauseated with abdominal pain, fever, diarrhea and limb pain.
- The month prior had had increasing fatigue and limb achiness.
- The nausea dissipated over 6 days, but she was left weak with achy arms and legs and brain fog.
- She worked as a college professor and was challenged to organize her thoughts. She describes brain fog and dizziness. She was short of breath.
- She had dental pain and a herpes outbreak in her mouth.
- The college library was under remediation for mold.

Case: KF September 2015

- **Differential diagnosis included:**
- Mold exposure and environmentally acquired illness (previously known as CIRS -chronic inflammatory response syndrome)
- New onset of neurodegenerative disease like Multiple sclerosis or ALS
- Psychosomatic manifestions of depression
- Cardiovascular disease
- Lyme disease and co-infections
- Viral infections
- Toxic exposures – heavy metals
- Small intestinal bacterial overgrowth or profound dysbiosis
- Parasites infestation
- Cancer

Is it Lyme or mold? Could it be both?

Lyme symptoms

Fatigue
Fevers
Rashes
Sweats
Hair loss
Swollen lymph nodes
Sore throat
Chest pain
Shortness of breath
Heart palpitations
Nausea or vomiting
Difficulty eating
Constipation/diarrhea
Bladder dysfunction
Cystitis
Dizziness
Balance problems
Tremor
Psychiatric disorders
Joint pain
Myalgias
Joint swelling
Back pain
Neck stiffness
TMJ pain
Headaches
Muscle twitching
Neurological sensations of tingling, burning or stabbing
Increased motion sickness
Vision changes
Hearing changes
Hypotension
Disturbed sleep
Memory loss
Confusion
Difficulty concentrating

Mold symptoms

Fatigue
Weakness
Decreased assimilation of new knowledge
Myalgias
Headaches
Memory impairment
Word finding problems
Decreased concentration
Light sensitivity
Joint pains
Morning stiffness
Red eyes
Tearing eyes
Blurred vision
Vertigo
Aches
Tingling
Tremors
Unusual pain
Shortness of breath
Sinus congestion
Cough
Excessive thirst
Confusion
Appetite swings
Temperature regulation
Increased urinary frequency
Nocturia
Abdominal pain
Numbness
Disorientation
Metallic taste
Static shocks
Sweats (esp night sweats)
Skin sensitivity/rashes
Ice pick pain
Gluten sensitivity

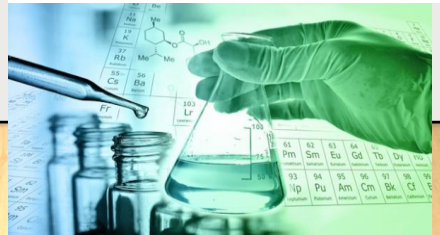
KF specialty labs

- Natural Killer Cell - CD 57 is 34. (nl 60-360)
- Transforming Growth Factor beta1 (TGFBeta1) was 16,140 pg/mL. (nl <2382)
- C4a at quest was 7990 ng/mL (nl <2830)
- Vascular endothelial growth factor (VEGF) <31 pg/mL (nl 31-86)
- Vasointestinal active peptide (VIP) 39.1 pg/mL(nl 23-63)
- Melanocyte Stimulating Hormone (MSH) <8 pg/mL (nl 35-81)

HLA DR - 1-5 low MSH haplotype,

- 7-2-53 mold susceptible haplotype
- She failed her visual contrast test
- Nasal swab was positive for MARCONS

Igenex test result
IFA <40
IgM - 18 kDa++, 30 kDa+, 34 kDa+, 39 kDa IND, 41+, 58+, 83 IND – positive by Igenex criteria
IgG – 41+



Kelly K. McCann, MD

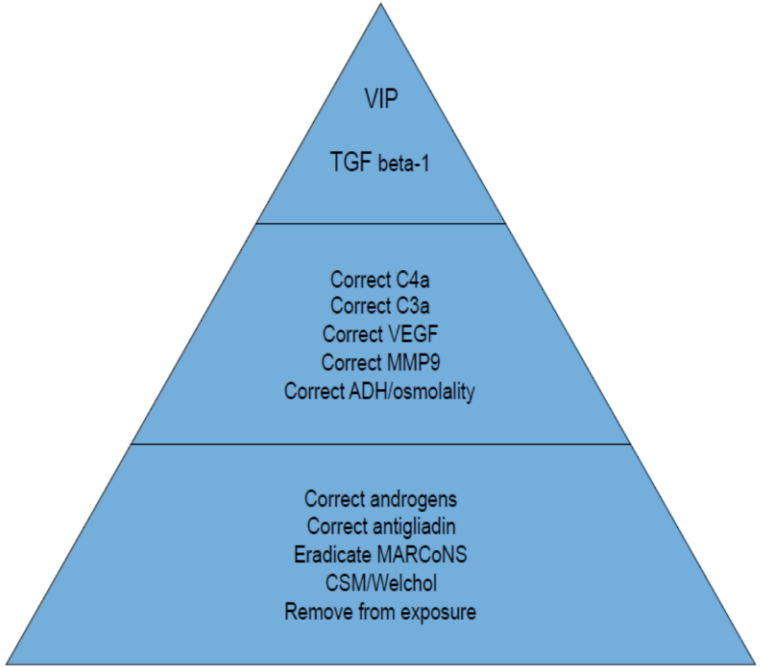
Seven Rules of Lyme Disease Action Plan

1. Symptoms Drive Diagnosis and Treatment
2. Lower Inflammation
3. Detox, Detox, Detox
4. Repair the Damage
5. Provide Internal Balance
6. Master the Big 3: Sleep, Food and Exercise
7. Heal your Emotional Wounds

KF treatment plan

- For the environmentally acquired illness (CIRS) inflammation she needs binders activated charcoal, bentonite clay and short term use of Cholestyramine for lowering biotoxin inflammation due to mold and lyme.
- Then BEG spray for MARCONS
- Short course of antibiotics per patient's choice. Continuation of herbal treatments with Byron White Formulas.
- Biofilm buster – Lumbrokinase added
- Heavy metal retention assessment
- Her partner is a dentist!!

Shoemaker's CIRS treatment protocol



DOCTOR'S DATA INC

CLIENT #: 34225
DOCTOR: Kylie Nuckols, PA

1831 Orange Ave Ste C
Costa Mesa, CA 92627 U.S.A.

Toxic Metals; Urine

TOXIC METALS		RESULT µg/g creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	23	< 35	
Antimony	(Sb)	< dl	< 0.2	
Arsenic	(As)	68	< 80	
Barium	(Ba)	0.6	< 7	
Beryllium	(Be)	< dl	< 1	
Bismuth	(Bi)	< dl	< 4	
Cadmium	(Cd)	0.2	< 1	
Cesium	(Cs)	11	< 10	
Gadolinium	(Gd)	< dl	< 0.8	
Lead	(Pb)	3.2	< 2	
Mercury	(Hg)	0.7	< 4	
Nickel	(Ni)	4.8	< 10	
Palladium	(Pd)	< dl	< 0.15	
Platinum	(Pt)	< dl	< 0.1	
Tellurium	(Te)	< dl	< 0.5	
Thallium	(Tl)	0.5	< 0.5	
Thorium	(Th)	< dl	< 0.03	
Tin	(Sn)	0.2	< 5	
Tungsten	(W)	0.2	< 0.4	
Uranium	(U)	< dl	< 0.04	

URINE CREATININE	RESULT mg/dL	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine	79.4	30- 225	

SPECIMEN DATA

Comments:

Date Collected: 05/04/2016
Date Received: 05/09/2016
Date Completed: 05/10/2016
Method: ICP-MS

pH upon receipt: Acceptable
<dl: less than detection limit
Provoking Agent:
Creatinine by Jaffe Method

Collection Period: Random
Volume:
Provocation: PRE PROVOCATIVE

Results are creatinine corrected to account for urine dilution variations. **Reference intervals and corresponding graphs are representative of a healthy population under non-provoked conditions.** Chelation (provocation) agents can increase urinary excretion of metals/elements. V13

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CLIENT #: 34225
DOCTOR: Kylie Nuckols, PA

1831 Orange Ave Ste C
Costa Mesa, CA 92627 U.S.A.

Toxic Metals; Urine

TOXIC METALS		RESULT µg/g creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	38	< 35	
Antimony	(Sb)	0.3	< 0.2	
Arsenic	(As)	31	< 80	
Barium	(Ba)	2	< 7	
Beryllium	(Be)	< dl	< 1	
Bismuth	(Bi)	< dl	< 4	
Cadmium	(Cd)	1.3	< 1	
Cesium	(Cs)	13	< 10	
Gadolinium	(Gd)	0.2	< 0.8	
Lead	(Pb)	87	< 2	
Mercury	(Hg)	14	< 4	
Nickel	(Ni)	12	< 10	
Palladium	(Pd)	< dl	< 0.15	
Platinum	(Pt)	< dl	< 0.1	
Tellurium	(Te)	< dl	< 0.5	
Thallium	(Tl)	0.8	< 0.5	
Thorium	(Th)	< dl	< 0.03	
Tin	(Sn)	1.3	< 5	
Tungsten	(W)	0.1	< 0.4	
Uranium	(U)	0.09	< 0.04	

URINE CREATININE	RESULT mg/dL	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine	65.9	30- 225	

Provocation done with DMPS and Ca EDTA

SPECIMEN DATA

Comments:

Date Collected: 05/04/2016
Date Received: 05/09/2016
Date Completed: 05/10/2016
Method: ICP-MS

pH upon receipt: Acceptable
<dl: less than detection limit
Provoking Agent:
Creatinine by Jaffe Method

Collection Period: timed: 9 hours
Volume:
Provocation: POST PROVOCATIVE

Results are creatinine corrected to account for urine dilution variations. **Reference intervals and corresponding graphs are representative of a healthy population under non-provoked conditions.** Chelation (provocation) agents can increase urinary excretion of metals/elements. V13

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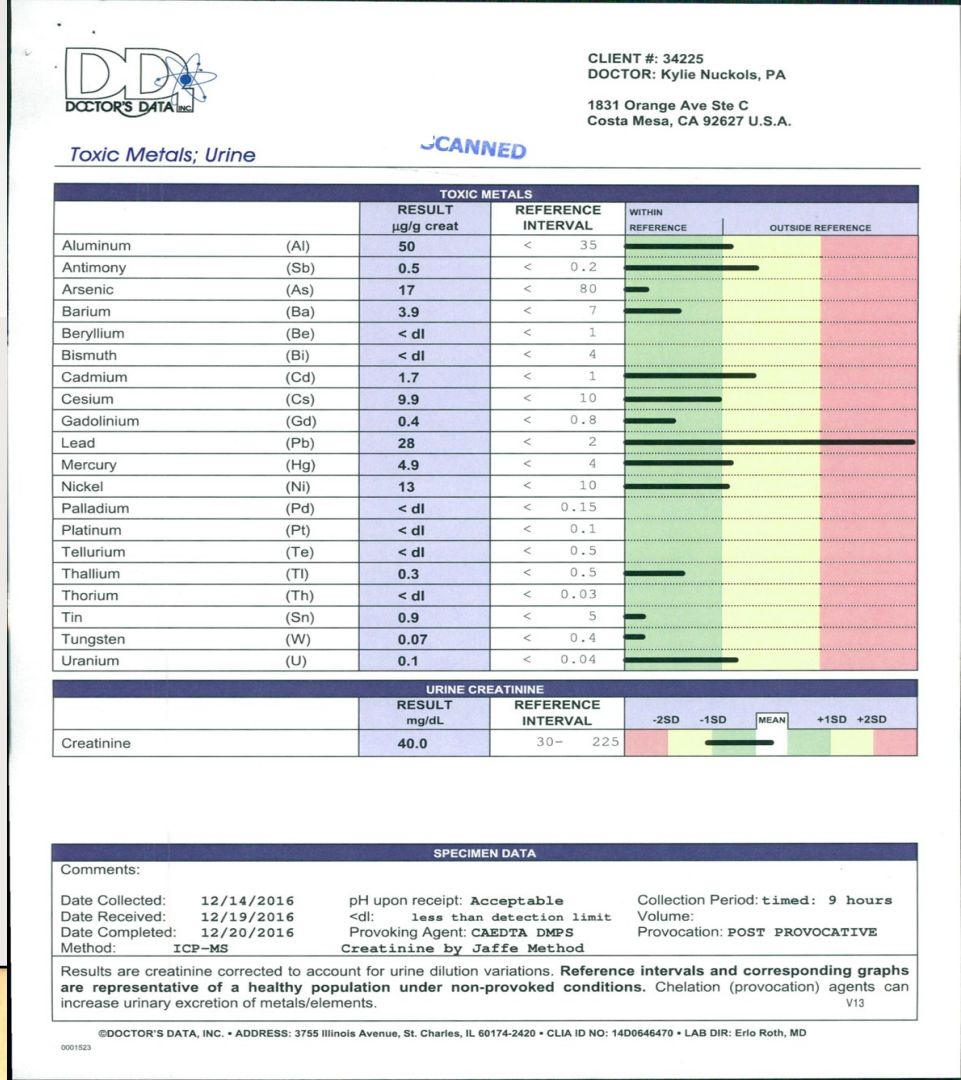
0001523

KF: treatment plan

- She completed 10 rounds of IV chelation with DMPS and CA EDTA.
- Far infrared sauna 2-4 times per week
- Weekly colonics
- Methylation, detox and nutritional support throughout



DOCTOR'S DATA INC

CLIENT #: 34225
DOCTOR: Kylie Nuckols, PA

1831 Orange Ave Ste C
Costa Mesa, CA 92627 U.S.A.

Toxic Metals; Urine

SCANNED

TOXIC METALS

		RESULT µg/g creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	**50**	< 35	
Antimony	(Sb)	**0.5**	< 0.2	
Arsenic	(As)	**17**	< 80	
Barium	(Ba)	**3.9**	< 7	
Beryllium	(Be)	**< dl**	< 1	
Bismuth	(Bi)	**< dl**	< 4	
Cadmium	(Cd)	**1.7**	< 1	
Cesium	(Cs)	**9.9**	< 10	
Gadolinium	(Gd)	**0.4**	< 0.8	
Lead	(Pb)	**28**	< 2	
Mercury	(Hg)	**4.9**	< 4	
Nickel	(Ni)	**13**	< 10	
Palladium	(Pd)	**< dl**	< 0.15	
Platinum	(Pt)	**< dl**	< 0.1	
Tellurium	(Te)	**< dl**	< 0.5	
Thallium	(Tl)	**0.3**	< 0.5	
Thorium	(Th)	**< dl**	< 0.03	
Tin	(Sn)	**0.9**	< 5	
Tungsten	(W)	**0.07**	< 0.4	
Uranium	(U)	**0.1**	< 0.04	

URINE CREATININE

	RESULT mg/dL	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine	**40.0**	30- 225	

SPECIMEN DATA

Comments:

Date Collected: 12/14/2016
Date Received: 12/19/2016
Date Completed: 12/20/2016
Method: ICP-MS

pH upon receipt: Acceptable
<dl: less than detection limit
Provoking Agent: CAEDTA DMPS
Creatinine by Jaffe Method

Collection Period: timed: 9 hours
Volume:
Provocation: POST PROVOCATIVE

Results are creatinine corrected to account for urine dilution variations. **Reference intervals and corresponding graphs are representative of a healthy population under non-provoked conditions.** Chelation (provocation) agents can increase urinary excretion of metals/elements. V13

0001523

Complicating Factors in Lyme disease as a Chronic Illness

PATIENT FACTORS

1. Lyme disease and Co-infections
2. Immune Dysfunction
3. Inflammation
4. Environmental toxins – chemicals and mold
5. Nutritional deficiencies
6. Mitochondrial dysfunction
7. Endocrine abnormalities
8. Neurodegenerative disorders
9. Neuropsychiatric disorders
10. Sleep disorders
11. Autonomic nervous system dysfunction and POTS
12. Allergies
13. GI disorders
14. Liver dysfunction
15. Pain disorders/addiction
16. Deconditioning
17. **Membrane stability/ Fatty acid composition**

Patient list from Richard Horowitz, MD

RBC fatty acid analysis

Red Cell Lipid Biopsy

Specimen Draw Date: 2/10/2016
Practitioner: Dr. Kelly K. McCann (19062)

BURN IT

TRANS ISOMERS			
	VLCFA'S		
	Triacontanoic	50.00	H
SATURATED ODD			
	RENEGADES		
	Vaccenic	46.65	H
	Pristanic	950.00	H
	Gondoic	23.75	

BUILD IT

MYELINATION			STRUCTURAL		
16:0 DMA	-85.60	L	Palmitic	-23.16	
18:0 DMA	-116.11	L	Stearic	-55.04	L
			Oleic	-35.81	L
			Myristic	-56.48	L
			Palmitoleic	-59.43	L
SUMMATION					
Total Saturates	-78.97	L			

Demyelination
Marked lack of structural fatty acids

90% deficient in AA. Gross imbalance in Omega 6: and Omega 3s.

BALANCE IT

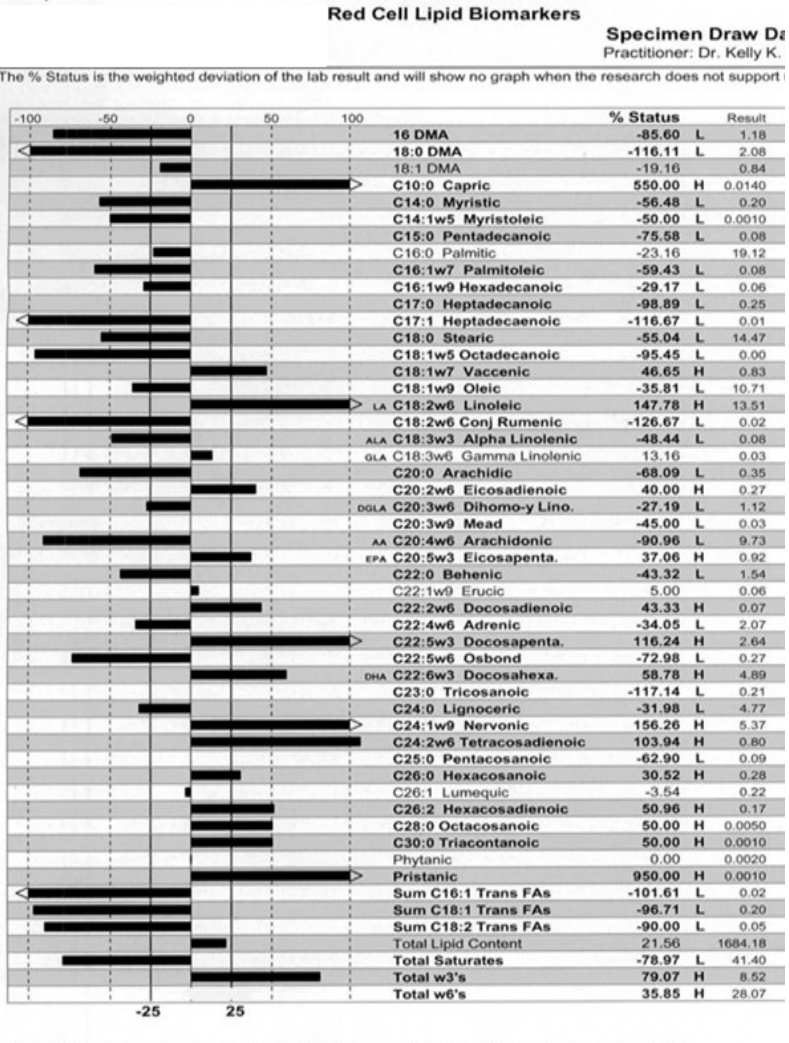
OMEGA 6			OMEGA 3		
Linoleic	147.78	H	Alpha Linolenic	-48.44	L
Gamma Linolenic	13.16		Eicosapentaenoic	37.06	H
Dihomo-y Linolenic	-27.19	L	Docosapentaenoic	116.24	H
Arachidonic	-90.96	L	Docosahexaenoic	58.78	H
Adrenic	-34.05	L			

INDEXES

Fluidity Index	0.00		Myelination Index	-56.79	L
MR Index	-41.67	L			
PR Index	105.65	H			

STABILIZE IT

Kelly K. McCann, MD



- Add eggs to diet.
- Add more flax seeds, chia seeds, hemp seeds and nuts
- Phosphatidylcholine 1 tbsp or 8 caps daily = 9 grams or more if tolerated
- Sodium/potassium Butyrate 2 caps twice daily =500mg butyric acid/cap
- Evening primrose oil 1000mg daily
- Balance oil 4:1 mixture of Omega6:omega3 – 6 tbsp daily
- High dose B vitamins for methylation and detox support
- Bile salts to assist with fat absorption
- Fatty alcohols to repair demyelination along with uridine

Membrane Stabilizing Diet: Modified Ketogenic Diet for Optimal Neurometabolic Health

Permitted foods

- Protein at every meal
- Raw, organic ground seeds and nuts
- Nut and seed butters
- Free range eggs
- Lentils and legume pastas
- Paleo breads and wraps
- Limited starchy vegetables
- Organic ghee, butters and cheeses if tolerated
- Fruits – mostly berries, kiwi
- Veggies
- Bone Broths
- Cook foods in coconut oil or ghee

Kelly K. McCann, MD

Membrane Stabilizing Diet: Modified Ketogenic Diet for Optimal Neurometabolic Health

Omitted foods

All grains, esp gluten

No corn or rice

No peanuts or peanut butter

No mustard (often contaminated with molds and contain VLCFA)

Avoid commercial oils extracted under heat such as canola oil

No sugar or sweeteners

No sodas or diet drinks

No hybridized oleic oils (olive)

No GMO foods

No dried fruits, high sugar fruits

NO fast food

NO Kombucha, No mushrooms

NO moldy or contaminated foods

Kelly K. McCann, MD

KF follow up

- Clinically she is doing well. Minimal fatigue and lower extremity heaviness. Still has occasional "crash days" as of 2/17. She is back running again. But as of 11/17, she is back to normal.
- Off antibiotics and binders.
- Continuing the Byron White formulas and biofilm busters.
- Doing LDI for lyme
- Getting dental work done as we determined she had resistant MARCONS due to dental reservoir.
- Maintaining Oral membrane stabilizing protocol
- Getting IV Phosphatidyl choline. Is up to 0.8 g/kg as of 6/17.

- LABS: 9/26/17
- C4a - 707 ng/mL (nl <2830)
- TGFBeta 1 – 1566 pg/mL (nl <2382)
- VIP – 42 pg/mL (nl 31-86 pg/mL)
- MSH <8 pg/mL (nl 35-81 pg/mL)
- CD 57 – 128 (optimal >300)
- Vit D 25oh is 70 ng/mL = 174 nmol/L
- Vit D1,25oh is 64 pg/mL = 166.4 pmol/L

A LYME MOMENT

Yes, I'd like a menu.
...Oh, and I'll have a glass of water please.

Kelly K. McCann, MD

Case: SD 16 year old with complicated past medical history presented in 2/15. Well until 2 years ago when she got the “flu” for 24 hour and never recovered. Saw ENTs, Neurologists, 3 different rheumatologists, endocrinologist, hematologist, several “holistic” practitioners, pain doctors.

Constant HA
Dizziness
Migraines
Vision Changes
Chronic Fatigue
Joint Pains
Tingling/ shooting pains
Fevers/Chills
Heart palpitations
Chest pains
Constipation
Ovarian cysts
Hashimoto’s thyroiditis
Insulin resistance
Asthma
Bloating
Dysmenorrhea
Sleeping disturbanc

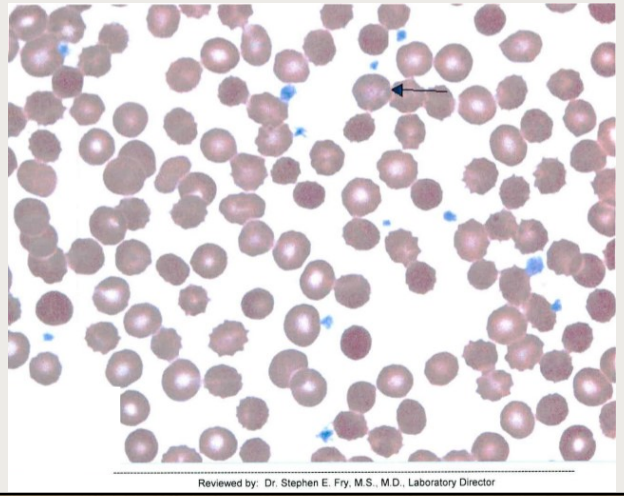
Case: SD 16 year old

Was told she had parasites and Lyme disease by a “holistic” practitioner based on Applied kinesiology testing.
Diagnosed with undifferentiated mixed connective tissue disorder and complex migraines but no medications helped.
Symptoms had waxed and waned over the 2 years prior to her initial appt. Hospitalization with lumbar puncture in mid 2014, ended up in a wheelchair for several months due to extreme joint pains. She was walking when she came into our clinic.

Case: SD

Labs:
2/4/15. wbc 3.1 x10_3, hgb 10.4 g/L, mcv 70, plt 305 x10_3, cd 57 is 24 (low)
Ferritin 9 ng/mL = 20 pmol/L
IgA 62mg/dL (low), IgM 236mg/dL wnl, IgG3 subclass low 16mg/dL (low) rest wnl.
ANA neg. thyroid antibodies+
Vit D25oh 32 ng/mL = 79.87nmol/L
HLA DR 13-6-52A mold susceptible,
14-5-52B multi susceptible
TGFbeta1 9680pg/mL, VIP<16.8pg/mL, MSH 21pg/mL, Homocysteine 14.8µmol/L, hs CRP 1.1mg/L
Igenex –Lyme PCR neg, Indeterminate for Anaplasma, Bartonella.

IGENEX-IGG-RESULT	NEGATIVE
CDC/NYS-RESULT	NEGATIVE
18 kDa	-
**23-25 kDa	-
28 kDa	-
30 kDa	-
**31 kDa	IND
**34 kDa	IND
**39 kDa	IND
**41 kDa	++
45 kDa	-
58 kDa	++
66 kDa	-
**83-93 kDa	-

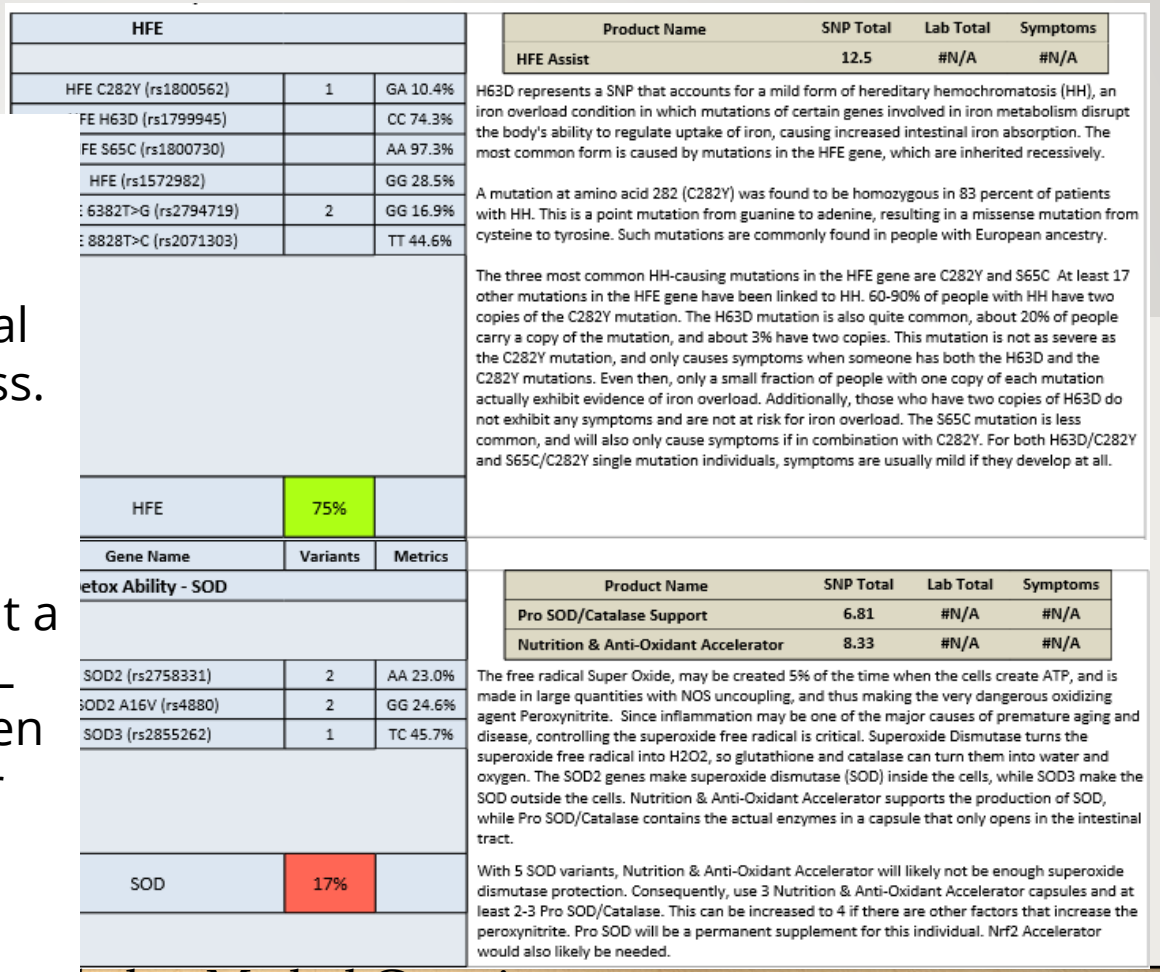


Case: SD

- The hematologist gave her Iron infusion weekly for 10 weeks until 1/16 and her energy improved. Joint pains persisted in hands, feet, back.
- Started on LDN. Supplements for sleep. Probiotics helped her GI tract.
- Started on Herbals immediately for Lyme and Bartonella. MC-BB1 and MC-BAR1
- Layered in antibiotics for Lyme and Bart including plaquenil, rifampin, doxycycline and azithromax.
- Stopped doxy due to intolerance
- 8 weeks post infusions her ferritin was 345, hgb 13.7.
- Repeat labs show persistent ferritin levels in the 200s-300s.
- By 4/16 cd 57 was still only 27, wbc 5.3, hgb 15.1, tgfbeta1 1724, vit D 33.5, Vit D1,25oh 36.6, hs CRP 2.38
- She stopped the rifampin and zithro. Continue plaquenil, LDN, herbals.
- Started an essential oil protocol for infections.
- 9/16 labs showed **ferritin 266**, %iron sat 78%, total iron 188, TIBC 240L, hgb 14.1. **Homocysteine 27.3,** folate level was 2.4. Clinically energy is ok. Joints are fine. No HA. Feels Lyme is under control. Iron/minerals off. Why?

Case: SD

- She is heterozygous for HFE C282Y plus another HFE gene.
- She has significant variants in SOD expression which is critical for dealing with oxidative stress.
- She also variants in Catalase enzymes and glutathione enzymes systems.
- WHO published statement that a serum ferritin above 300mcg/L in men and 200mcg/L in women could be considered at risk for severe iron overload.
- She was experiencing Fenton reactions!



HFE		
HFE C282Y (rs1800562)	1	GA 10.4%
FE H63D (rs1799945)		CC 74.3%
FE S65C (rs1800730)		AA 97.3%
HFE (rs1572982)		GG 28.5%
6382T>G (rs2794719)	2	GG 16.9%
8828T>C (rs2071303)		TT 44.6%
HFE	75%	

Product Name	SNP Total	Lab Total	Symptoms
HFE Assist	12.5	#N/A	#N/A

H63D represents a SNP that accounts for a mild form of hereditary hemochromatosis (HH), an iron overload condition in which mutations of certain genes involved in iron metabolism disrupt the body's ability to regulate uptake of iron, causing increased intestinal iron absorption. The most common form is caused by mutations in the HFE gene, which are inherited recessively.

A mutation at amino acid 282 (C282Y) was found to be homozygous in 83 percent of patients with HH. This is a point mutation from guanine to adenine, resulting in a missense mutation from cysteine to tyrosine. Such mutations are commonly found in people with European ancestry.

The three most common HH-causing mutations in the HFE gene are C282Y and S65C At least 17 other mutations in the HFE gene have been linked to HH. 60-90% of people with HH have two copies of the C282Y mutation. The H63D mutation is also quite common, about 20% of people carry a copy of the mutation, and about 3% have two copies. This mutation is not as severe as the C282Y mutation, and only causes symptoms when someone has both the H63D and the C282Y mutations. Even then, only a small fraction of people with one copy of each mutation actually exhibit evidence of iron overload. Additionally, those who have two copies of H63D do not exhibit any symptoms and are not at risk for iron overload. The S65C mutation is less common, and will also only cause symptoms if in combination with C282Y. For both H63D/C282Y and S65C/C282Y single mutation individuals, symptoms are usually mild if they develop at all.

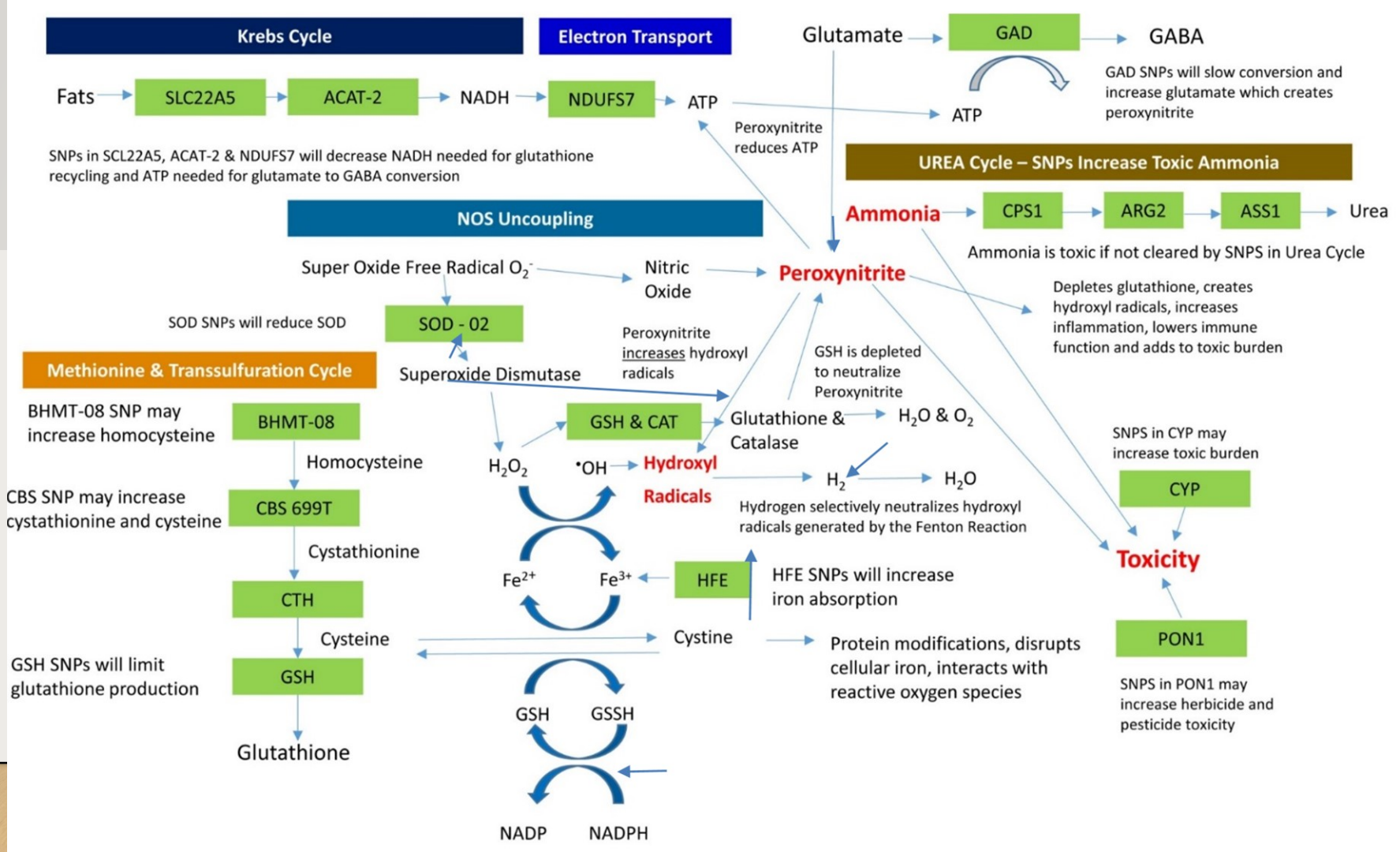
Gene Name	Variants	Metrics
etox Ability - SOD		
SOD2 (rs2758331)	2	AA 23.0%
OD2 A16V (rs4880)	2	GG 24.6%
SOD3 (rs2855262)	1	TC 45.7%
SOD	17%	

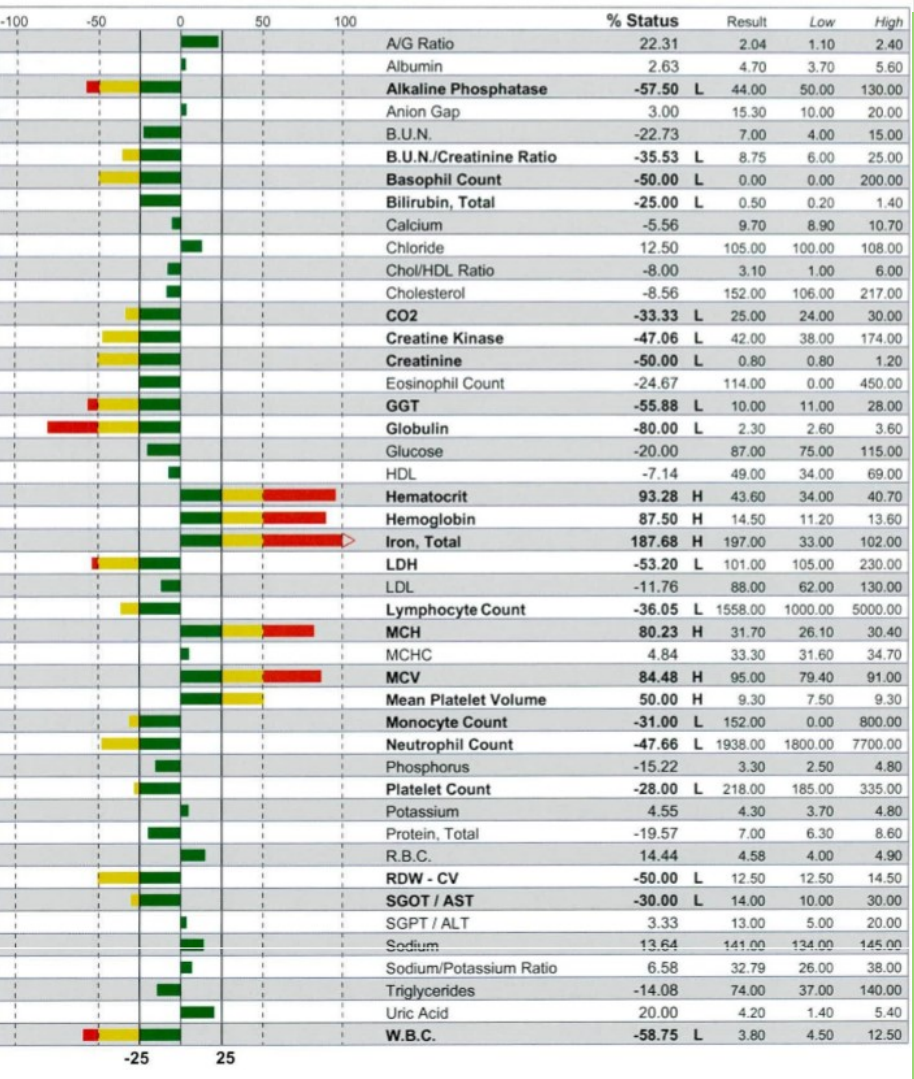
Product Name	SNP Total	Lab Total	Symptoms
Pro SOD/Catalase Support	6.81	#N/A	#N/A
Nutrition & Anti-Oxidant Accelerator	8.33	#N/A	#N/A

The free radical Super Oxide, may be created 5% of the time when the cells create ATP, and is made in large quantities with NOS uncoupling, and thus making the very dangerous oxidizing agent Peroxynitrite. Since inflammation may be one of the major causes of premature aging and disease, controlling the superoxide free radical is critical. Superoxide Dismutase turns the superoxide free radical into H2O2, so glutathione and catalase can turn them into water and oxygen. The SOD2 genes make superoxide dismutase (SOD) inside the cells, while SOD3 make the SOD outside the cells. Nutrition & Anti-Oxidant Accelerator supports the production of SOD, while Pro SOD/Catalase contains the actual enzymes in a capsule that only opens in the intestinal tract.

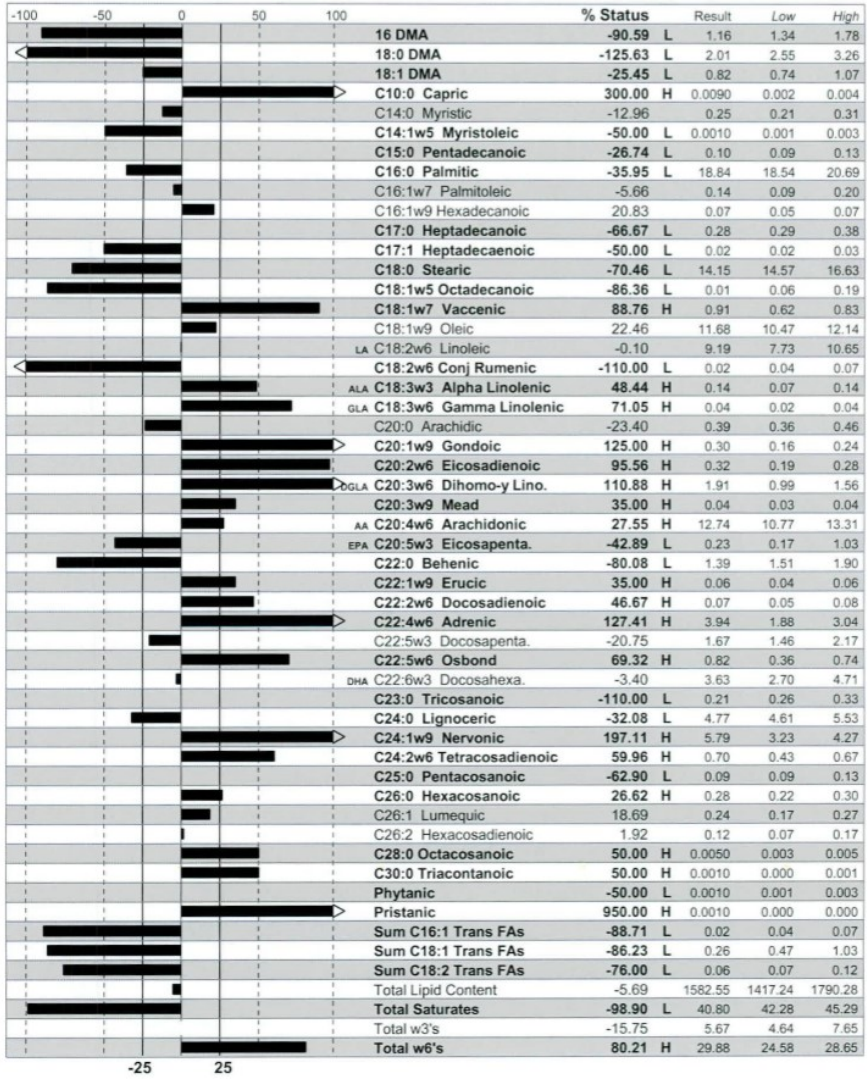
With 5 SOD variants, Nutrition & Anti-Oxidant Accelerator will likely not be enough superoxide dismutase protection. Consequently, use 3 Nutrition & Anti-Oxidant Accelerator capsules and at least 2-3 Pro SOD/Catalase. This can be increased to 4 if there are other factors that increase the peroxynitrite. Pro SOD will be a permanent supplement for this individual. Nrf2 Accelerator would also likely be needed.

led to Methyl Genetic
on.com


Krebs Cycle
Electron Transport
Fats
SLC22A5
ACAT-2
NADH
NDUFS7
ATP
SNPs in SCL22A5, ACAT-2 & NDUFS7 will decrease NADH needed for glutathione recycling and ATP needed for glutamate to GABA conversion
Glutamate
GAD
GABA
GAD SNPs will slow conversion and increase glutamate which creates peroxynitrite
ATP
Peroxynitrite reduces ATP
UREA Cycle – SNPs Increase Toxic Ammonia
Ammonia
CPS1
ARG2
ASS1
Urea
Ammonia is toxic if not cleared by SNPS in Urea Cycle
NOS Uncoupling
Super Oxide Free Radical O_2^-
Nitric Oxide
Peroxynitrite
Depletes glutathione, creates hydroxyl radicals, increases inflammation, lowers immune function and adds to toxic burden
SOD SNPs will reduce SOD
SOD - 02
Superoxide Dismutase
Peroxynitrite increases hydroxyl radicals
GSH is depleted to neutralize Peroxynitrite
Methionine & Transsulfuration Cycle
BHMT-08 SNP may increase homocysteine
BHMT-08
Homocysteine
CBS SNP may increase cystathionine and cysteine
CBS 699T
Cystathionine
CTH
Cysteine
GSH SNPs will limit glutathione production
GSH
Glutathione
GSH & CAT
Glutathione & Catalase
H_2O & O_2
H_2O_2
•OH
Hydroxyl Radicals
H_2
H_2O
Hydrogen selectively neutralizes hydroxyl radicals generated by the Fenton Reaction
SNPS in CYP may increase toxic burden
CYP
Toxicity
Fe^{2+}
Fe^{3+}
HFE
HFE SNPs will increase iron absorption
Cystine
Protein modifications, disrupts cellular iron, interacts with reactive oxygen species
PON1
SNPS in PON1 may increase herbicide and pesticide toxicity
GSH
GSSH
NADP
NADPH



	% Status		Result	Low	High
A/G Ratio	22.31		2.04	1.10	2.40
Albumin	2.63		4.70	3.70	5.60
Alkaline Phosphatase	**-57.50**	**L**	44.00	50.00	130.00
Anion Gap	3.00		15.30	10.00	20.00
B.U.N.	-22.73		7.00	4.00	15.00
B.U.N./Creatinine Ratio	**-35.53**	**L**	8.75	6.00	25.00
Basophil Count	**-50.00**	**L**	0.00	0.00	200.00
Bilirubin, Total	**-25.00**	**L**	0.50	0.20	1.40
Calcium	-5.56		9.70	8.90	10.70
Chloride	12.50		105.00	100.00	108.00
Chol/HDL Ratio	-8.00		3.10	1.00	6.00
Cholesterol	-8.56		152.00	106.00	217.00
CO2	**-33.33**	**L**	25.00	24.00	30.00
Creatine Kinase	**-47.06**	**L**	42.00	38.00	174.00
Creatinine	**-50.00**	**L**	0.80	0.80	1.20
Eosinophil Count	-24.67		114.00	0.00	450.00
GGT	**-55.88**	**L**	10.00	11.00	28.00
Globulin	**-80.00**	**L**	2.30	2.60	3.60
Glucose	-20.00		87.00	75.00	115.00
HDL	-7.14		49.00	34.00	69.00
Hematocrit	**93.28**	**H**	43.60	34.00	40.70
Hemoglobin	**87.50**	**H**	14.50	11.20	13.60
Iron, Total	**187.68**	**H**	197.00	33.00	102.00
LDH	**-53.20**	**L**	101.00	105.00	230.00
LDL	-11.76		88.00	62.00	130.00
Lymphocyte Count	**-36.05**	**L**	1558.00	1000.00	5000.00
MCH	**80.23**	**H**	31.70	26.10	30.40
MCHC	4.84		33.30	31.60	34.70
MCV	**84.48**	**H**	95.00	79.40	91.00
Mean Platelet Volume	**50.00**	**H**	9.30	7.50	9.30
Monocyte Count	**-31.00**	**L**	152.00	0.00	800.00
Neutrophil Count	**-47.66**	**L**	1938.00	1800.00	7700.00
Phosphorus	-15.22		3.30	2.50	4.80
Platelet Count	**-28.00**	**L**	218.00	185.00	335.00
Potassium	4.55		4.30	3.70	4.80
Protein, Total	-19.57		7.00	6.30	8.60
R.B.C.	14.44		4.58	4.00	4.90
RDW - CV	**-50.00**	**L**	12.50	12.50	14.50
SGOT / AST	**-30.00**	**L**	14.00	10.00	30.00
SGPT / ALT	3.33		13.00	5.00	20.00
~~Sodium~~	~~13.64~~		~~141.00~~	~~134.00~~	~~145.00~~
Sodium/Potassium Ratio	6.58		32.79	26.00	38.00
Triglycerides	-14.08		74.00	37.00	140.00
Uric Acid	20.00		4.20	1.40	5.40
W.B.C.	**-58.75**	**L**	3.80	4.50	12.50



	% Status		Result	Low	High
16 DMA	**-90.59**	**L**	1.16	1.34	1.78
18:0 DMA	**-125.63**	**L**	2.01	2.55	3.26
18:1 DMA	**-25.45**	**L**	0.82	0.74	1.07
C10:0 Capric	**300.00**	**H**	0.0090	0.002	0.004
C14:0 Myristic	-12.96		0.25	0.21	0.31
C14:1w5 Myristoleic	**-50.00**	**L**	0.0010	0.001	0.003
C15:0 Pentadecanoic	**-26.74**	**L**	0.10	0.09	0.13
C16:0 Palmitic	**-35.95**	**L**	18.84	18.54	20.69
C16:1w7 Palmitoleic	-5.66		0.14	0.09	0.20
C16:1w9 Hexadecanoic	20.83		0.07	0.05	0.07
C17:0 Heptadecanoic	**-66.67**	**L**	0.28	0.29	0.38
C17:1 Heptadecaenoic	**-50.00**	**L**	0.02	0.02	0.03
C18:0 Stearic	**-70.46**	**L**	14.15	14.57	16.63
C18:1w5 Octadecanoic	**-86.36**	**L**	0.01	0.06	0.19
C18:1w7 Vaccenic	**88.76**	**H**	0.91	0.62	0.83
C18:1w9 Oleic	22.46		11.68	10.47	12.14
LA C18:2w6 Linoleic	-0.10		9.19	7.73	10.65
C18:2w6 Conj Rumenic	**-110.00**	**L**	0.02	0.04	0.07
ALA **C18:3w3 Alpha Linolenic**	**48.44**	**H**	0.14	0.07	0.14
GLA **C18:3w6 Gamma Linolenic**	**71.05**	**H**	0.04	0.02	0.04
C20:0 Arachidic	-23.40		0.39	0.36	0.46
C20:1w9 Gondoic	**125.00**	**H**	0.30	0.16	0.24
C20:2w6 Eicosadienoic	**95.56**	**H**	0.32	0.19	0.28
DGLA **C20:3w6 Dihomo-y Lino.**	**110.88**	**H**	1.91	0.99	1.56
C20:3w9 Mead	**35.00**	**H**	0.04	0.03	0.04
AA **C20:4w6 Arachidonic**	**27.55**	**H**	12.74	10.77	13.31
EPA **C20:5w3 Eicosapenta.**	**-42.89**	**L**	0.23	0.17	1.03
C22:0 Behenic	**-80.08**	**L**	1.39	1.51	1.90
C22:1w9 Erucic	**35.00**	**H**	0.06	0.04	0.06
C22:2w6 Docosadienoic	**46.67**	**H**	0.07	0.05	0.08
C22:4w6 Adrenic	**127.41**	**H**	3.94	1.88	3.04
C22:5w3 Docosapenta.	-20.75		1.67	1.46	2.17
C22:5w6 Osbond	**69.32**	**H**	0.82	0.36	0.74
DHA C22:6w3 Docosahexa.	-3.40		3.63	2.70	4.71
C23:0 Tricosanoic	**-110.00**	**L**	0.21	0.26	0.33
C24:0 Lignoceric	**-32.08**	**L**	4.77	4.61	5.53
C24:1w9 Nervonic	**197.11**	**H**	5.79	3.23	4.27
C24:2w6 Tetracosadienoic	**59.96**	**H**	0.70	0.43	0.67
C25:0 Pentacosanoic	**-62.90**	**L**	0.09	0.09	0.13
C26:0 Hexacosanoic	**26.62**	**H**	0.28	0.22	0.30
C26:1 Lumequic	18.69		0.24	0.17	0.27
C26:2 Hexacosadienoic	1.92		0.12	0.07	0.17
C28:0 Octacosanoic	**50.00**	**H**	0.0050	0.003	0.005
C30:0 Triacontanoic	**50.00**	**H**	0.0010	0.000	0.001
Phytanic	**-50.00**	**L**	0.0010	0.001	0.003
Pristanic	**950.00**	**H**	0.0010	0.000	0.000
Sum C16:1 Trans FAs	**-88.71**	**L**	0.02	0.04	0.07
Sum C18:1 Trans FAs	**-86.23**	**L**	0.26	0.47	1.03
Sum C18:2 Trans FAs	**-76.00**	**L**	0.06	0.07	0.12
Total Lipid Content	-5.69		1582.55	1417.24	1790.28
Total Saturates	**-98.90**	**L**	40.80	42.28	45.29
Total w3's	-15.75		5.67	4.64	7.65
Total w6's	**80.21**	**H**	29.88	24.58	28.65

BURN IT

TRANS ISOMERS			
VLCFA'S			
	Erucic	35.00	H
	Osbond	69.32	H
	Triacontanoic	50.00	H
SATURATED ODD			
RENEGADES			
	Vaccenic	88.76	H
	Mead	35.00	H
	Eicosanoic	35.00	H
	Pristanic	950.00	H
	Gondoic	125.00	H

BUILD IT

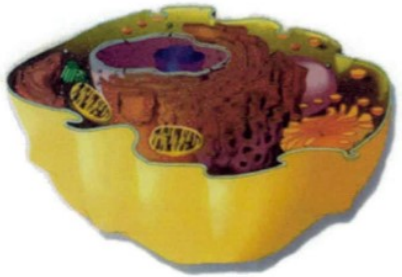
MYELINATION			STRUCTURAL		
16:0 DMA	-90.59	L	Palmitic	-35.95	L
18:0 DMA	-125.63	L	Stearic	-70.46	L
18:1 DMA	-25.45	L			
SUMMATION					
Total Saturates	-98.90	L			

BALANCE IT

OMEGA 6			OMEGA 3		
Linoleic	-0.10		Alpha Linolenic	48.44	H
Gamma Linolenic	71.05	H	Eicosapentaenoic	-42.89	L
Dihomo-γ Linolenic	110.88	H	Docosapentaenoic	-20.75	
Arachidonic	27.55	H	Docosahexaenoic	-3.40	
Adrenic	127.41	H			
INDEXES					
Fluidity Index	-5.00		Myelination Index	-61.74	L
MR Index	-9.39				
PR Index	152.02	H			

STABILIZE IT

PR Index	152.02	H



Lots of undesirable fats which need to be removed

Actively demyelinating with low DMAs
Very low saturated fats
Lacking structural building blocks

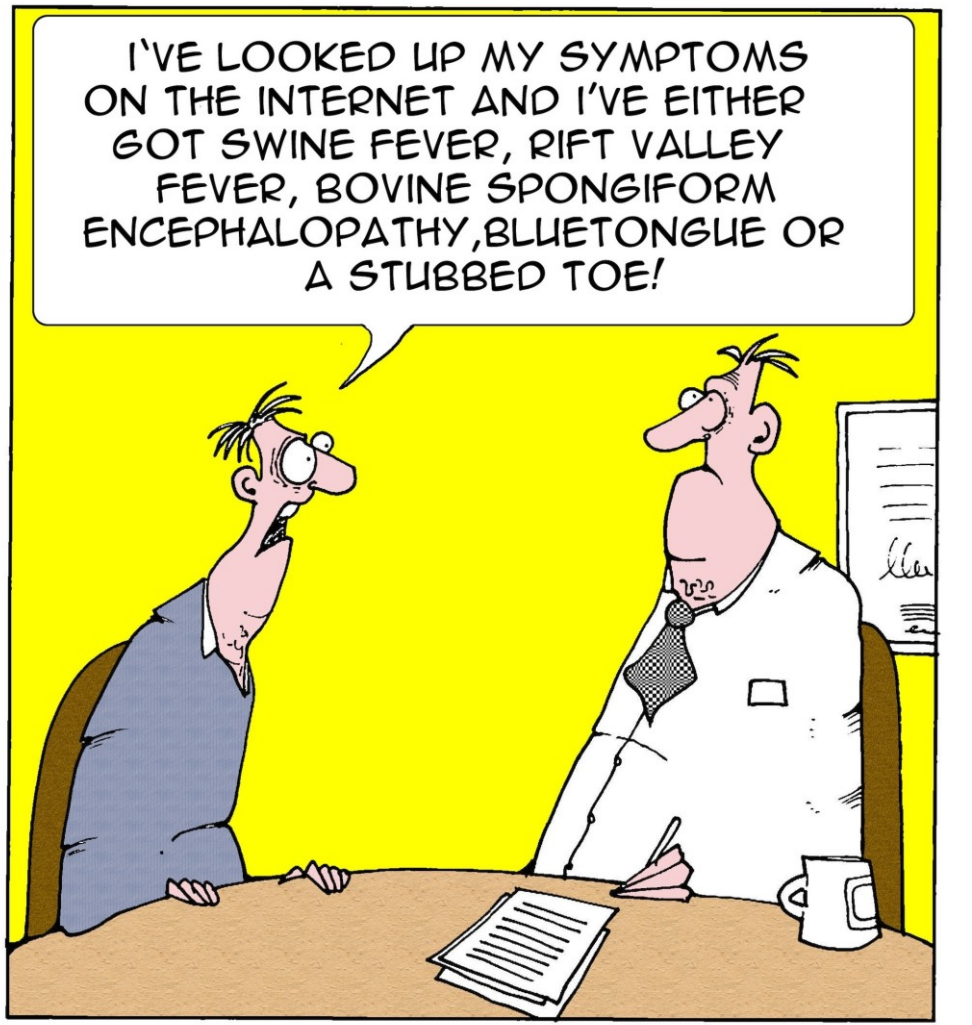
Imbalances between omega6s and omega3s

Test performed by Kennedy Krieger at John Hopkins and then analyzed and report generated by Body Bio.

Case: SD

Treatment Plan:
- Phosphatidyl choline 1 tbsp
- SR3 oil which is sunflower omega6:flax omega3 in a 4:1 ratio 3-6 tbsp. daily
- Evening primrose oil
- high EPA fish oil
- methylated B vitamins
- Butryate for breaking down the VLCFA
- Prometol fatty alcohol for myelin support
- **IV phosphatidyl choline infusions**

- HFE Assist brought her ferritin down from 230-250s to 79
- Next treatment, LDI – low dose immunotherapy!



Case: KK

17 yr old adolescent with OCD on Prozac, Wellbutrin, Effexor, autism spectrum disorder, common variable immunodeficiency on IVIG, growth hormone deficiency, scoliosis, anxiety, hypothryoidism, chronic constipation, intestinal yeast overgrowth, sleep disturbance, cystic acne, chronic viral infections with emotional stability of acyclovir.

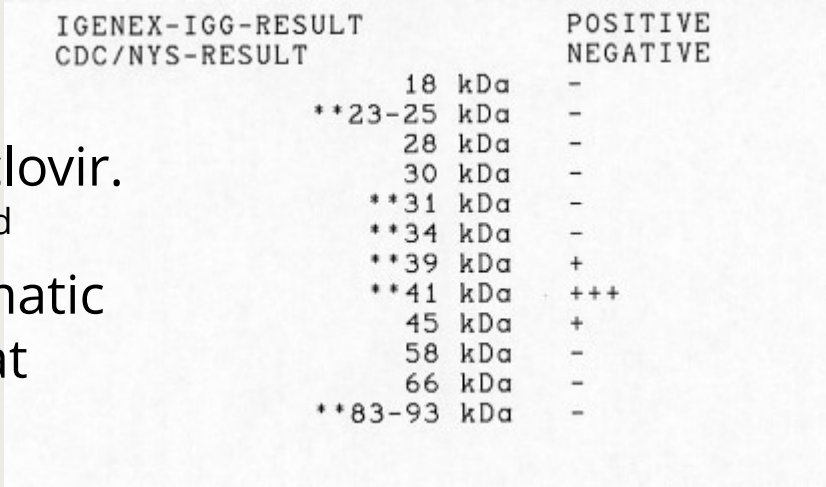
PMHx: Mom was sick with "cold" in the 3rd trimester.
No antibiotics given.
Full term. Traumatic birth.
Vacuum extraction.
Apgars 7/9. O2 given at birth.
He has been "sick" since birth.

Case: KK

17 yr old adolescent with OCD on Prozac, Wellbutrin, Effexor, autism spectrum disorder, common variable immunodeficiency on IVIG, growth hormone deficiency, scoliosis, anxiety, hypothryoidism, chronic constipation, intestinal yeast overgrowth, sleep disturbance, cystic acne, chronic viral infections with emotional stability of acyclovir.

PMHx: Mom was sick with "cold" in the 3rd trimester. No antibiotics given. FT, traumatic birth, apgars7/9. vacuum extraction. O2 at birth. He has been "sick" since birth.

PSHx: 2003 eye surgery for strabismus
2004 – PE tube placement
2005 – adenoidectomy
2006 – eye surgery for strabismus



IGENEX-IGG-RESULT	POSITIVE
CDC/NYS-RESULT	NEGATIVE
18 kDa	-
**23-25 kDa	-
28 kDa	-
30 kDa	-
**31 kDa	-
**34 kDa	-
**39 kDa	+
**41 kDa	+++
45 kDa	+
58 kDa	-
66 kDa	-
**83-93 kDa	-

Relationship of Gestational Lyme and Chronic Infections

Dr. Jones performed chart reviews on 102 gestational borrelia cases.
14% Babesia, 7% Strep,
6% Ehrlichiosis
9% autism
56% attention deficit disorder

Psychological symptoms:
Mood swing 54%
Anger 23%
Anxiety 21%
Depression 13%
OCD 11%, Suicidal thoughts 7%

Neurological symptoms:
HA 50%, Vertigo 30%
Developmental delay 18%
Tic disorders 14%, seizure disorders 11%
Photophobia 43%, hyperacuity 36%
Poor memory 39%
Cognitive impairments 27%, speech delays 21%, read/writing delays 19%, auditory/visual processing 13%, dyslexia 18%

Physical symptoms:
GERD 27%, abd pain 29%, diarrhea or constipation 32%, nausea 23%

Jones, et al. Case studies of 102 Live births. Lyme Times 2005:34-6. summer

A Controlled Study of Cognitive Deficits in Children With Chronic Lyme Disease

Felice A. Tager, Ph.D.
Brian A. Fallon, M.D.
John Keilp, Ph.D.
Marian Rissenberg, Ph.D.
Charles Ray Jones, M.D.
Michael R. Liebowitz, M.D.

Although neurologic Lyme disease is known to cause cognitive dysfunction in adults, little is known about its long-term sequelae in children. Twenty children with a history of new-onset cognitive complaints after Lyme disease were compared with 20 matched healthy control subjects. Each child was assessed with measures of cognition and psychopathology. Children with Lyme disease had significantly more cognitive and psychiatric disturbances. Cognitive deficits were still found after controlling for anxiety, depression, and fatigue. Lyme disease in children may be accompanied by long-term neuropsychiatric disturbances, resulting in psychosocial and academic impairments. Areas for further study are discussed.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2001; 13:500–507)

Lyme disease (LYD) is a multisystemic illness caused by the tick-borne spirochete *Borrelia burgdorferi* (Bb). LYD, the most common tick-borne illness in the United States,[1] may manifest in a variety of ways: dermatologic, arthritic, ophthalmologic, cardiac, and neuropsychiatric.[2] The incidence and spread of the disease increased during the 1980s,[3] stabilizing somewhat in the late 1990s. Children below the age of 9 are at a high risk for Bb infection,[4] with many new cases of Lyme occurring among persons younger than 14 years.[5]

The neuropsychiatric symptoms of LYD in adults have been described,[6,7] but little has been published about the neuropsychiatric effect of the disease in children and adolescents. In adults, deficits in attention and memory have been reported.[8,9] In children, a controlled study of cognitive symptoms investigated a sample of all children and adolescents who presented to a LYD clinic, most of whom presented with rheumatological symptoms, had been diagnosed early, and had been treated appropriately for LD.[10] These children were found to have an excellent prognosis for unimpaired functioning. However, this sample may not be representative of all children diagnosed with LYD, especially those who present initially with neurocognitive problems and/or those who were not treated until many months after the initial infection. Our preliminary data

Received August 7, 2000; revised January 3, 2001; accepted January 10, 2001. From the Columbia University Department of Psychiatry, Division of Behavioral Medicine, New York, New York. Address correspondence to Dr. Tager, Columbia Presbyterian Medical Center, 622 West 168th Street, Box 427, New York, NY 10032. E-mail: ft49@columbia.edu.

Neurocognitive testing revealed:

Headaches (100%)
Brain fog (88%)
Short term memory loss (94%)
Word finding problems (82%)
Distractibility (82%)
School work deterioration (94%
Irritability/depression (94%)
Insomnia (82%)
Sensitivity to sound (58%)
Sensitivity to light (74%)

Tager FA, et al. A controlled study of cognitive deficits in children with chronic Lyme disease. J Neuropsychiatry Clin Neurosci. 2001;13(4):500–507.

Children and Lyme and Cognitive functioning

Pilot study: 8 children with Lyme age 7-13
Completed 1-5 months of antibiotics

Initial evaluation symptoms: fatigue, joint pains, headache, irritability, Trouble with schoolwork, Concentration, Memory, Sleep disturbance, Sensory sensitivity, Mood swings, Impulsivity, Depressed mood, Anxiety, Motor tics, Word retrieval difficulty, Balance problems, temper outbursts

Cognitive defects: Deficient in Performance IQ and verbal IQ, Scores were lowest on processing speed, visual scanning, sequencing, and causal reasoning; attention deficits, visual and sustained

http://www.neuro-lyme.com/Psychological_Evaluation_of_Pediatric,_Neurologic_Lyme_Disease.html

Children and Lyme and Cognitive functioning

Re-eval after antibiotics, (10-32 months)

All improved, 1 had HA, another sleep issues. 5/8 had improvements in cognition and academics, but 4 had cognitive, 5 had emotional, 2 had both and 1 had physical and emotional symptoms.

Cognitive testing showed global improvements

http://www.neuro-lyme.com/Psychological_Evaluation_of_Pediatric,_Neurologic_Lyme_Disease.html

Pilot studies of ASD and Lyme

Vojdani identified 22% of ASD patients via CDC criteria +Lyme

LIAF study found 26% of ASD children positive for Lyme vs 0 controls

Levine tests 9 ASD children. All had Igenex positive WB.

Nicholson tested 48 ASD patients found 20-30% PCR or southern blot positive
and 68% co-infection with Mycoplasma, Bartonella, Ehrlichia and Babesia.
29% positive for HHV-6

Bransfield, et al. Association between tick-borne infections, Lyme borreliosis and autism spectrum disorders. Medical Hypotheses 2008 7, 967-974.

Gevi et al. Molecular Autism (2016) 7:47
DOI 10.1186/s13229-016-0109-5

Molecular Autism

RESEARCH Open Access

Urinary metabolomics of young Italian autistic children supports abnormal tryptophan and purine metabolism

Federica Gevi[1], Lello Zolla[1*], Stefano Gabriele[2] and Antonio M. Persico[3,4*]

Abstract

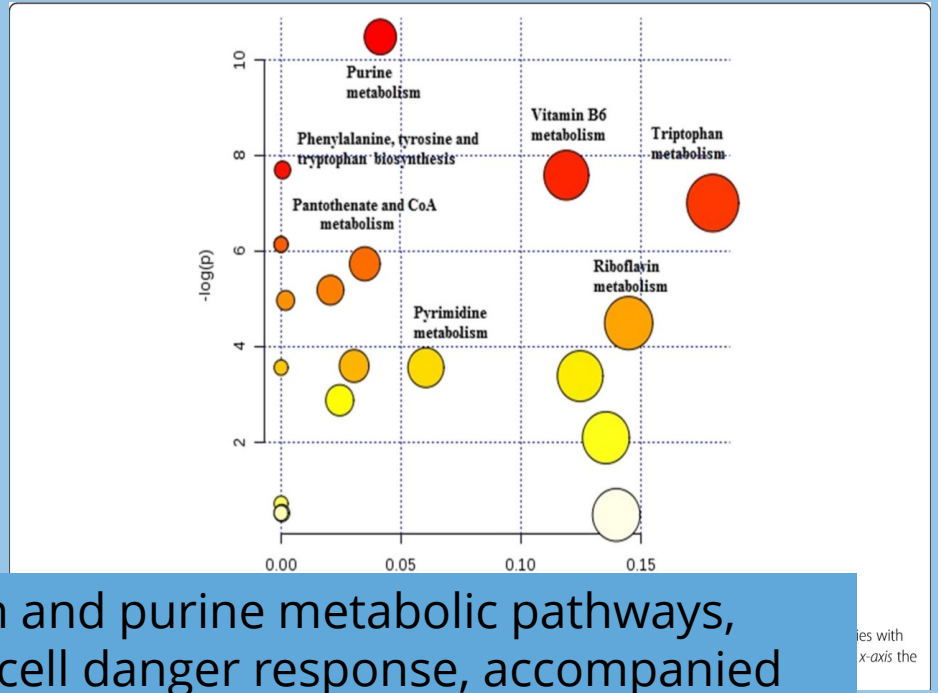
Background: Autism spectrum disorder (ASD) is still diagnosed through behavioral observation, due to a lack of laboratory biomarkers, which could greatly aid clinicians in providing earlier and more reliable diagnoses. Metabolomics on human biofluids provides a sensitive tool to identify metabolite profiles potentially usable as biomarkers for ASD. Initial metabolomic studies, analyzing urines and plasma of ASD and control individuals, suggested that autistic patients may share some metabolic abnormalities, despite several inconsistencies stemming from differences in technology, ethnicity, age range, and definition of "control" status.

Methods: ASD-specific
matched controls (age
mass spectrometry, a hi
multivariate statistical a

Results: Urinary metabo
to the tryptophan and p
biosynthesis, pantothen
transform tryptophan in
expense of kynurenic ac
metabolism, yielding in

Conclusions: The meta
found in rodent models
consistent with the prop
epileptogenic and excit
metabolic abnormalities
disorders, and gastrointestinal symptoms, and could contribute to autism severity. Their diagnostic sensitivity, disease-specificity, and interethnic variability will merit further investigation.

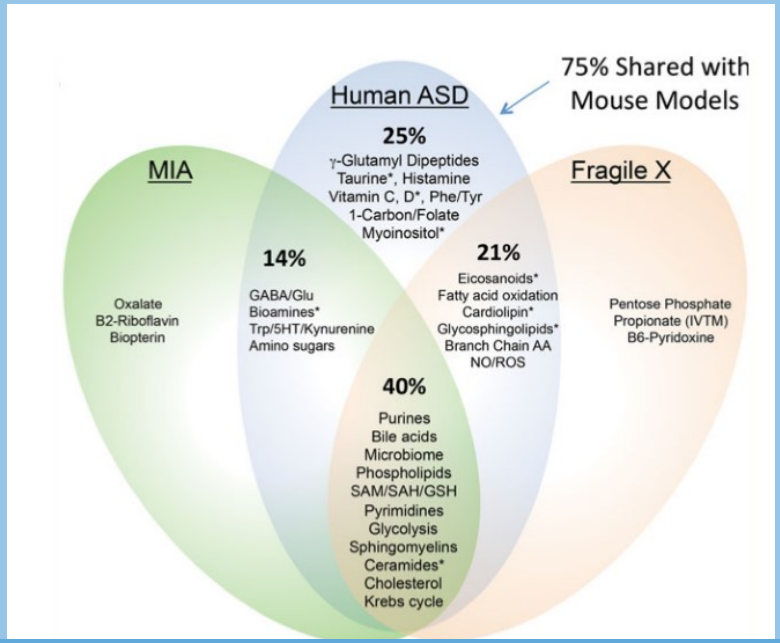
Keywords: Autism, Autism spectrum disorder, Kynurenine, Melatonin, Metabolomics, Purinergic signaling, Quinolinic acid, Serotonin, Tryptophan



Urinary metabolites of tryptophan and purine metabolic pathways, consistent with the purine-driven cell danger response, accompanied by overproduction of quinolinic acid, large reductions in melatonin synthesis and gut dysbiosis. These metabolic abnormalities could underlie several associations to ASD such as sleep and GI disorders.

Gevi, 2016

Kelly K. McCann, MD



ANNALS of Clinical and Translational Neurology
Open Access

RESEARCH ARTICLE

Low-dose suramin in autism spectrum disorder: a small, phase I/II, randomized clinical trial

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Targeted plasma metabolomics revealed that the suramin decreased the cell danger response and restore more normal metabolism and the purine metabolism was the single most changed pathway, consistent with previous mouse models of ASD… Parents reported after treatment there were language, social, behavioral and developmental improvements for 3 weeks after the suramin. Naviaux, 2017

Research Institute (ARI), the Lennox Foundation, the Gupta Family and Satya Fund, the Agrawal Family, Linda Clark, the N of One Autism Research Foundation, the

clinical global impression questionnaire. **Results**: Blood levels of suramin were 12 ± 1.5 μmol/L (mean ± SD) at 2 days and 1.5 ± 0.5 μmol/L after 6 weeks. The terminal half-life was 14.7 ± 0.7 days. A self-limited, asymptomatic rash

Case: KK

BURN IT

TRANS ISOMERS				
	VLCFA'S			
	Triacontanoic	50.00	H	
SATURATED ODD				
oic	24.19			
	RENEGADES			
	Vaccenic	21.29		
	Phytanic	50.00	H	
	Pristanic	950.00	H	

BUILD IT

MYELINATION			STRUCTURAL		
18:0 DMA	-41.18	L	Palmitic	-41.35	L
18:1 DMA	-39.52	L	Oleic	-24.98	
			Myristic	-59.26	L
SUMMATION					
Total Saturates	-44.55	L			
Total w3	-55.75	L			

BALANCE IT

OMEGA 6			OMEGA 3		
Linoleic	49.59	H	Alpha Linolenic	-17.19	
Gamma Linolenic	-13.16		Eicosapentaenoic	-44.29	L
Dihomo-γ Linolenic	-3.33		Docosapentaenoic	-3.16	
Arachidonic	55.55	H	Docosahexaenoic	-66.58	L
Adrenic	66.29	H			

INDEXES

Fluidity Index	-30.00	L	Myelination Index	-19.17	
MR Index	-48.38	L	Odd Chain Index	-24.51	
PR Index	27.91	H			

STABILIZE IT

Odd chain fats created by viruses. Needs butyrate to break up the VLCFA and renegade fats

Needs better dietary fats, phosphatidyl choline and fatty alcohol to support remyelination

Needs sources of ALA (flax, chia, hemp) Evening primrose oil (GLA) and more fish oil Omega3s

Herbal protocols for Lyme were also instituted

moleculera labs

Cunningham Panel™ Testing Results

PATIENT REPORT

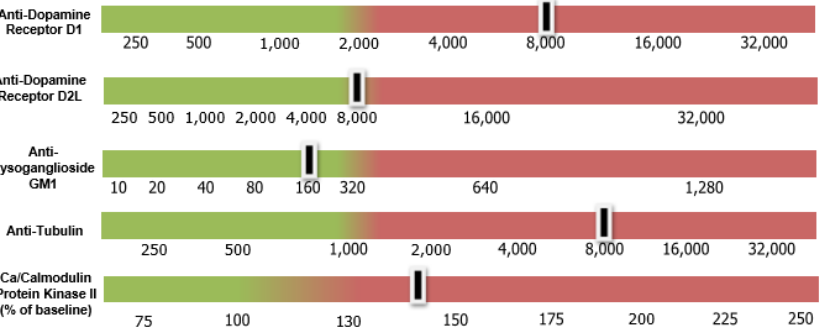
Submitting Prescriber: Kelly McCann, MD
Date of Collection: 09/20/2017
Date of Receipt: 09/21/2017

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	1:8,000	1:8,000	1:160	1:8,000	143
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95
INTERPRETATION*	ELEVATED	BORDERLINE	NORMAL	ELEVATED	ELEVATED

***Report Guidance:** If any one (1) or more of these five (5) assay values is elevated, it may indicate a clinically significant autoimmune neurological condition. This is a condition in which the patient's autoantibodies cross-react and are directed against selected neuronal targets which are involved in normal neuropsychiatric and/or motor functions. It is important to note that the degree of elevation in assay values may not necessarily correlate with degree of symptom severity, as any value above normal ranges may correlate with symptomatology.

LABORATORY TEST RESULTS



The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D1 Receptor (DRD1), Dopamine D2L Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). ELISA results are determined by measuring the colorimetric intensity at a specific wavelength which is directly proportional to the amount of antibody in the sample. The fifth assay of this panel measures the specific activity of calcium/calmodulin-dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel

This patient has PANS – Pediatric Autoimmune encephalitis likely due to post natal trigger on top of possible gestational Lyme.

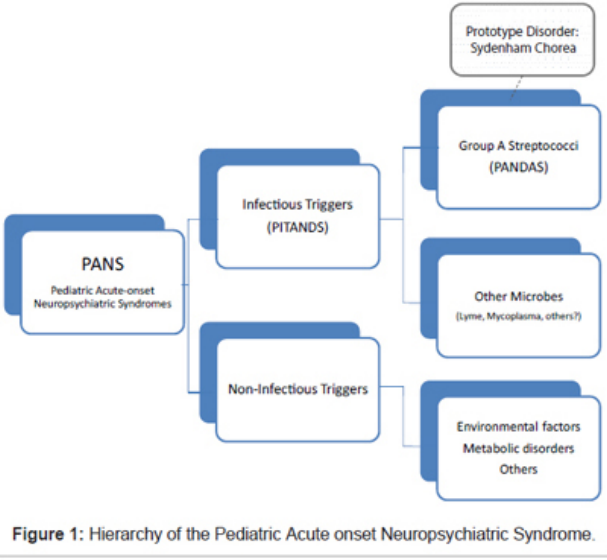


Figure 1: Hierarchy of the Pediatric Acute onset Neuropsychiatric Syndrome.

Image borrowed from "From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)"

Kelly K. McCann, MD

Complicating Factors in Lyme disease as a Chronic Illness

BACTERIA FACTORS

1. Numerous strains of Borrelia
2. Different forms of Borrelia
3. Testing Challenges
4. Co-infections
5. Biofilms
6. Immune evasion and persistent infections
7. **Various Treatment Guidelines**

EXPERT REVIEWS

Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease

Expert Rev. Anti Infect. Ther. 12(9), 1103–1135 (2014)

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Evidence-based guidelines for the management of patients with Lyme disease were develope
by the International Lyme and Associated Diseases Society (ILADS). The guidelines addres
three clinical questions – the usefulness of antibiotic prophylaxis for known tick bites, th
effectiveness of erythema migrans treatment and the role of antibiotic retreatment in patient
with persistent manifestations of Lyme disease. Healthcare providers who evaluate an
manage patients with Lyme disease are the intended users of the new ILADS guidelines
which replace those issued in 2004 (Exp Rev Anti-infect Ther 2004;2:S1–13). These clinica
practice guidelines are intended to assist clinicians by presenting evidence-based treatmen
recommendations, which follow the Grading of Recommendations Assessment, Developmen
and Evaluation system. ILADS guidelines are not intended to be the sole source of guidanc
in managing Lyme disease and they should not be viewed as a substitute for clinica
judgment nor used to establish treatment protocols.

KEYWORDS: antibiotic prophylaxis • antibiotics • erythema migrans • GRADE • Lyme disease • persistent disease • treatment

Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values [1]. The International Lyme and Associated Diseases Society (ILADS) has adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as its basis for evidence assessment and the development of recommendations to ensure a transparent and trustworthy guideline process [2–5].

These guidelines address three fundamental

with persistent manifestations of Lyme disease
ILADS anticipates performing GRADE assess
ments on additional topics related to the diag
nosis and treatment of tick-borne diseases i
the future.

The GRADE scheme classifies the qualit
of the evidence as high, moderate, low o
very low. The quality of evidence from ran
domized controlled trials (RCTs) is initiall
rated as high, but may be downgraded base
on five limitations: study bias, publicatio

The guidelines address 3 treatment questions:

1. Usefulness of antibiotics for known tick bites.
2. The effectiveness of erythema migrains (EM) treatment.
3. The role of antibiotic treatment in patients with persistent manifestation of Lyme disease.

With regard to the 3rd question, reassess diagnosis, screen for co-infections, evaluate for other causes, and start with 4-6 weeks of antibiotics if so agreed.

Extensive treatment options exist. Consider previous responsiveness, progression of illness, patient impairments.

Phytochemicals and Micronutrients for anti-borrelia efficacy

Dipsacus Sylvestris
(Teasel root)
Grapefruit Seed Extract
Uncaria tomentosa
Otoba parvifolia
Stevia rebaudiana
Wild cherry
Black walnut green hull

Apricot seed
Anise
Vitamin B- complex
Vitamin C
Vitamin D3
Kelp (iodine)
Serrapeptase

Teasel root

Goc, et al. Ther Adv Infectious Dis 2016. 3(3-4): 75-82.
Goc, et al. Int Jour Bio Sci. 2016. 12(9): 1093-1103.

Table 3. Efficacy of phytochemicals against *Borrelia sp.*

Phytochemicals	Spirochetes (μg/ml)		Rounded forms (μg/ml)	Biofilm (μg/ml)
Apigenin	MIC_{40} at 125	NS	NS	NS
Malvidin	MIC_{65} at 75	NS	NS	NS
Quercetin	MIC_{70} at 75	MBC_{45} at 125	MBC_{40} at 250	NS
E-viniferin	MIC_{70} at 75	MBC_{40} at 125	MBC_{40} at 250	NS
Resveratrol	MIC_{70} at 125	MBC_{40} at 250	MBC_{40} at 300	NS
Ellagic acid	MIC_{70} at100	MIC_{65} at 250	NS	NS
Oleuropein	MIC_{45} at 250	NS	MBC_{30} at 500	NS
Nordihydrogualaretic acid	MIC_{40} at 125	NS	NS	NS
Amygdalin	MIC_{90} at 75	MBC_{65} at 100	MBC_{50} at 150	NS
Fucoidan	NS	NS	NS	NS
Berberine sulfate	MIC_{90} at 100	MBC_{80} at 150	MBC_{50} at 250	NS

BSH medium, Buffered Schamm and Hestrin's; BSK; Barbour–Stoenner–Kelly; EC, effective concentration eradicating biofilm; MBC, minimal bactericidal concentration; MIC, minimal inhibitory concentration; NS, not susceptible.
Testing was performed with two species such as *Borrelia burgdorferi* and *Borrelia garinii*. Subscript index at the MIC value indicates the percent of inhibition at the provided concentration expressed as μg/ml in 1.5 ml of BSK complete medium at 33°C after 72 h; the MBC value indicates the percent of killing at the provided concentration expressed as μg/ml in 1.5 ml of BSH complete medium at 33°C after 72 h, according to [Goc *et al.* 2015].

Table 1. CAM treatment of Lyme disease with a combination of different antibiotics, herbal remedies, and nutritional supplements, with pertinent references

Antibiotics used for treatment of Lyme disease (Refs 6–8, 10, 11)	Herbal remedies	Ref	Nutritional supplements	Ref
Doxycycline	Samento	(24)	Omega-3 Fatty Acids	(26)
Minocycline	Cumada	(24)	Coenzyme-Q10	(26)
Amoxicillin	Burbur	(24)	S-Adenosylmethionine	(8, 24, 25)
Augmentin	Allicin	(25)	Grapeseed Extract	(26)
Azithromycin	Dragon's blood	(25)	Magnesium	(24)
Biaxin	Cat's claw	(25)	L-Carnitine	(4, 8)
Erythromycin	Devil's claw	(24)	α-Lipoic acid	(14, 15)
Vaucomycin	Echinacea	(25–28)	Dimethylglycine	(27)
Clarithromycin (biaxin)	Citriodiol (lemon eucalyptus extract)	(9)	Vitamin B-complex	(4, 8)
Cefuroxime axetil	Astragallus	(29)	Methylcobalamin	(4, 8)
Penicillin	Nettle	(24)	Vitamin C and D	(12, 13)
Ceftriaxone	Ginkgo biloba	(4, 8)	Hydrolytic enzymes	(16, 17)
Rifampin	Curcumin	(19–20)	Mushroom extracts and Beta-glucan	(22)
Flagyl	Oregano tea	(25)	Thymic peptides	(29)
Plaquenil	Boswellia	(26)	Pycnogenol	(27)
Taurox SB™	Parsley extract	(24)	*N*-Acetylcysteine and glutathione	(26)
Colloidal silver	Red chili pepper (capsaicin)	(18)	Probiotics	(23)
Imipinem	Quercetin	(21)	Dehydroepiandrosterone	(12)
			Royal Jelly	(26)

Doi:10.1093/ecam/nem138

Beyond Balance Products for Lyme and Co-infections

Core Immune Support

MC-BB1 - for Lyme
MC-BB2 – stronger formula for relapsing fever Borrelia, Erhlichia
MC-BAR-1 – for Bartonella
MC-BAR-2 – stronger formula for bartonella
MC-BAB-1 – for Babesia microti
MC-BAB-2 – for Babesia duncani and Protomyxoma rheumatica
MC-BAB-3 –broad spectrum blood parasites

MC-BB1

Supplement Facts

Serving size 1 ml
Servings per container 30

Amount Per Serving	%DV
Proprietary Blend	
Queen's Root (Root) *(Stillingia sylvatica)*	*
Motherwort (Tops) *(Leonurus cardiaca)*	*
Plantain Leaf (Tops) *(Plantago lanceolata)*	*
Black Walnut (Green Hull) *(Juglans nigra)*	*
Licorice (Root) *(Glycyrrhiza glabra)*	*
Calendula (Flower) *(Calendula officinalis)*	*

*** Daily Value Not Established**

Other Ingredients: Kosher vegetable glycerin (80% by volume), Filtered water

Allergens: This product contains no soy, corn, or any other known allergens. Free from preservatives, artificial colorings, or flavorings.

Warning: If pregnant, nursing, or taking medications, consult your healthcare professional before use.

Beyond Balance Products for Lyme and Co-infections

Tox-Ease GL

Supplement Facts

Serving size 1 ml
Servings per container 59

Amount Per Serving 100 mg	%DV
Proprietary Blend	
Slippery Elm (Bark) *(Ulmus fulva)*	*
Bilberry (Berry) *(Vaccinium myrtillus)*	*
Grape Seed (Seed) Extract *(Vitis vinifera)*	*
Mullein (Leaf) *(Verbascum thapsus)*	*
Elder (Berry) *(Sambucus nigra)*	*
Rosehips (Bud) *(Rosa canina)*	*
Red Clover (Blossom) *(Trifolium pratense)*	*
Licorice (Root) *(Glycyrrhiza glabra)*	*
Dandelion (Leaf) *(Taraxacum officinale)*	*
Rhubarb (Root) *(Rheum spp.)*	*
Fresh Skullcap (Flowering tops) *(Scutellaria lateriflora)*	*
Milk Thistle (Seed) *(Silybum marianum)*	*
Cayenne (Fruit) *(Capsicum annum)*	*

*** Daily Value Not Established**

Detox support
Tox-Ease – general detox/digest aid
Tox-Ease II – heavy metal detox
Tox-Ease GL –gentle cellular detox
Cognease Detox

Biofilm Breakdown
MC-BFM-1 – made from Guggul
MC-BFM-P – pediatric doses

Fungal Products
Pro-Myco
Mycoregen

Parasite Products
MC-PZ
Parazomin

Beyond Balance Products for Lyme and Co-infections

Immune Support Products
IMN-B – guard against bacteria
IMN-GI – support GI immunity
IMN-R –Immune modulatory
IMN-V – guard against viruses
IMN-V-III – for neurological viral symptoms

Environmental Detox Support
ENL-BT-1 – for Biotoxins
ENL-MC – for Mycoplasma
ENL-NM - for environmental toxins
ENL-RD – for radiation exposure

Inflammation
Cyflacalm
Cyflacalm II- for vascular/nervous inflammation

IMN-V-III

Supplement Facts
Serving size 1 ml
Servings per container 60

Amount Per Serving 100 mg	**%DV**
Proprietary Blend	
Cat's Claw (Bark) *(Uncaria tomentosa)*	*
Licorice (Root) *(Glycyrrhiza glabra)*	*
Skullcap (Flowering Tops) *(Scutellaria lateriflora)*	*
Rosehips (Hip) *(Rosa canina)*	*
Coptis (Rhizome) *(Coptis chinensis)*	*
Cleavers (Tops) *(Galium aparine)*	*
Dandelion (Whole Plant) *(Taraxacum officinale)*	*
Kelp (Thallus) *(Laminaria digitata)*	*
Elderberry (Berry) *(Sambucus nigra)*	*
Mistletoe (Leaf) *(Viscum album)*	*
Valerian (Root) *(Valeriana officinalis)*	*
Wild Lettuce (Leaf) *(Lactuca spp.)*	*
Cornsilk (Green Silk) *(Zea Mays)*	*
Grape Seed (Seed) *(Vitis vinifera)*	*
Horsetail (Spring Shoots) *(Equisetum arvense)*	*
Rosemary (Leaf) *(Rosmarinus officinalis)*	*
Gotu Kola (Leaf) *(Centella asiatica)*	*
Thyme (Leaf) *(Thymus vulgaris)*	*
Marshmallow (Root) *(Althaea officinalis)*	*
White Willow (Bark) *(Salix alba)*	*

*** Daily Value Not Established**

Beyond Balance Products for Lyme and Co-infections

Begin by Layering Formulas

1. Start with Detox of the terrain first
2. Antimicrobial treatment
3. Ensure solid nutritional support
4. Support reduction of inflammation
5. Address biofilm
6. Continue detox support
7. Continue evaluating and supporting as clinical indicated.

Sample protocol for multiply infected patient with brain fog:

1. Start **Tox-Ease GL** 3 drops BID, gradually increase by 1 drop BID up to 12-15 drops 2-3 times per day.
2. Add **MC-BB-1** 1 drop BID. Slowly increase as tolerated up to 10-12 drops BID
3. **Cyflacalm II** 3-4 drops BID
4. Next **MC-BAR-1** for bartonella. (adjust like MC-BB-1)
5. Add **MC-BFM-P** –pinch once daily, then ½ cap once daily, work up to 1 cap BID.
6. **Cognease Detox** 1 drop BID, increase up to 10-15 drops 2-3 times daily.

Integrative and Functional approaches to Lyme disease and chronic infections

- Identify infections
- Determine all areas of dysfunction
- Lifestyle Modifications
- Dietary adjustments
- Detoxification and reduction of exposures to toxins/molds/EMF
- Nutritional supplementation
- Immune support
- Genetic analyses and appropriate support
- Gastrointestinal assessments and support
- Mitochondrial support
- Adrenal/endocrine support
- Methylation support
- Membrane stabilizing therapies

Integrative and Functional approaches to Lyme disease and chronic infections

- Low dose immunotherapy
- Emotional and psychological issues/Trauma
- Structural dysfunctional support
- Physical therapy
- OMT/craniosacral therapy
- Chiropractic manipulation
- Visceral manipulation
- Acupuncture/TCM referrals
- Energy medicine/Rife
- Movement/exercise
- Spiritual counseling
- Family counseling

"According to my research, laughter is the best medicine, giggling is good for mild infections, chuckling works for minor cuts and bruises, and snickering only makes things worse."

How to manage a patient whom you suspect has Lyme disease

- Patients often need a team approach to their care.
- Locate and meet with Lyme literate practitioners in your area.
- Check out www.ILADS.org or your state or local Lyme advocacy groups for referrals.
- Begin the work up, if comfortable. If not, refer.
- You may also need functional and integrative medicine practitioners with whom to partner, if you can't find a Lyme literate, functional practitioner.
- Know that these patients have often been neglected and dismissed by the medical system. They need your support and acknowledgment that you believe them, even if you can't explain all their symptoms.
- If the psychological and emotional and even spiritual aspects don't get addressed, they will continue to struggle.
- Metaphor of immune system – boundary issues

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