LYME DISEASE
EVIDENCE BASED-STATE OF THE ART
VIRGINIA CONGRESSMAN FRANK WOLF HOSTED PHYSICIAN'S LYME FORUM
MAY 1, 2012

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LYME DISEASE
EVIDENCE BASED-STATE OF THE ART
GOALS

To provide a balanced approach to the literature
Identifying those areas better understood
Those that may be controversial
Providing the tools with which to make decisions for your patients

LYME DISEASE
EVIDENCE BASED-STATE OF ART OVERVIEW

Personal interest-chronic fatigue

Historical perspective

Basics

Governor's Task Force on Lyme disease

"State of the Art" the literature:

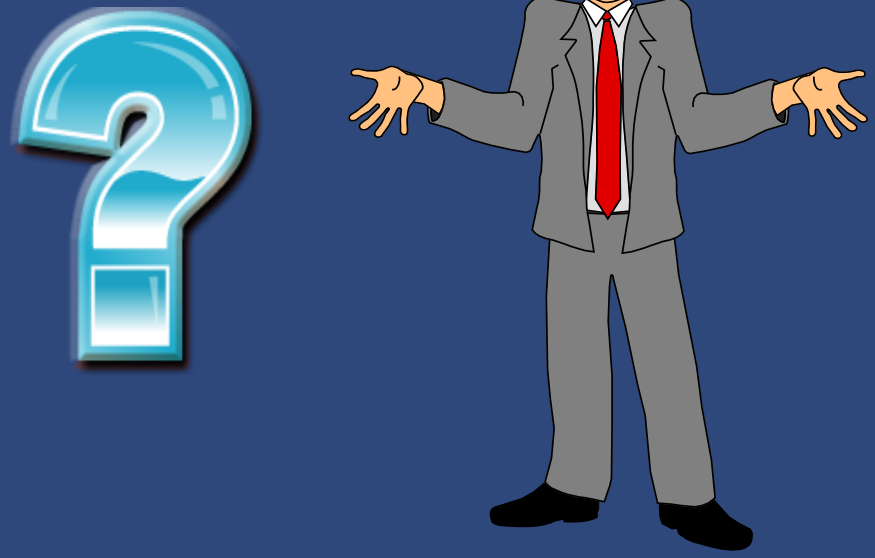
Diagnostic criteria-concept of seronegativity

Clinical presentations-additional/Chronic Lyme

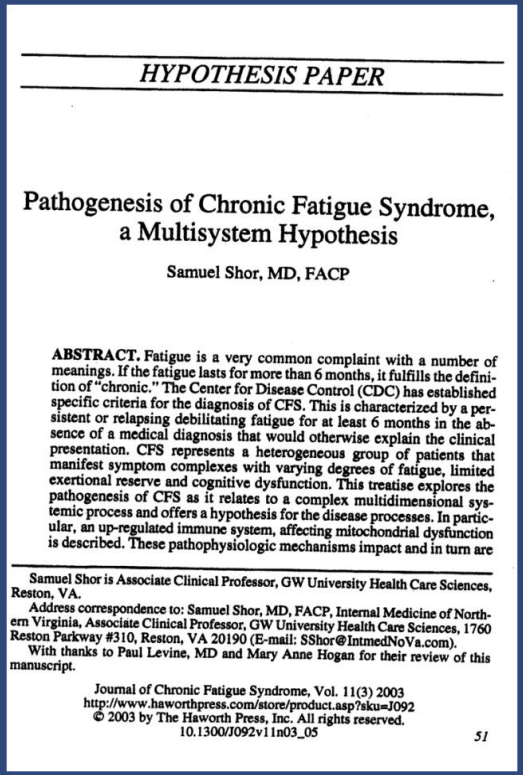
Treatment issues

LYME DISEASE
EVIDENCE BASED-STATE OF THE ART

As a primary care trained physician, why am I even here?



Chronic Fatigue
Personal interest



HYPOTHESIS PAPER

Pathogenesis of Chronic Fatigue Syndrome, a Multisystem Hypothesis

Samuel Shor, MD, FACP

ABSTRACT. Fatigue is a very common complaint with a number of meanings. If the fatigue lasts for more than 6 months, it fulfills the definition of "chronic." The Center for Disease Control (CDC) has established specific criteria for the diagnosis of CFS. This is characterized by a persistent or relapsing debilitating fatigue for at least 6 months in the absence of a medical diagnosis that would otherwise explain the clinical presentation. CFS represents a heterogeneous group of patients that manifest symptom complexes with varying degrees of fatigue, limited exertional reserve and cognitive dysfunction. This treatise explores the pathogenesis of CFS as it relates to a complex multidimensional systemic process and offers a hypothesis for the disease processes. In particular, an up-regulated immune system, affecting mitochondrial dysfunction is described. These pathophysiologic mechanisms impact and in turn are

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With thanks to Paul Levine, MD and Mary Anne Hogan for their review of this manuscript.

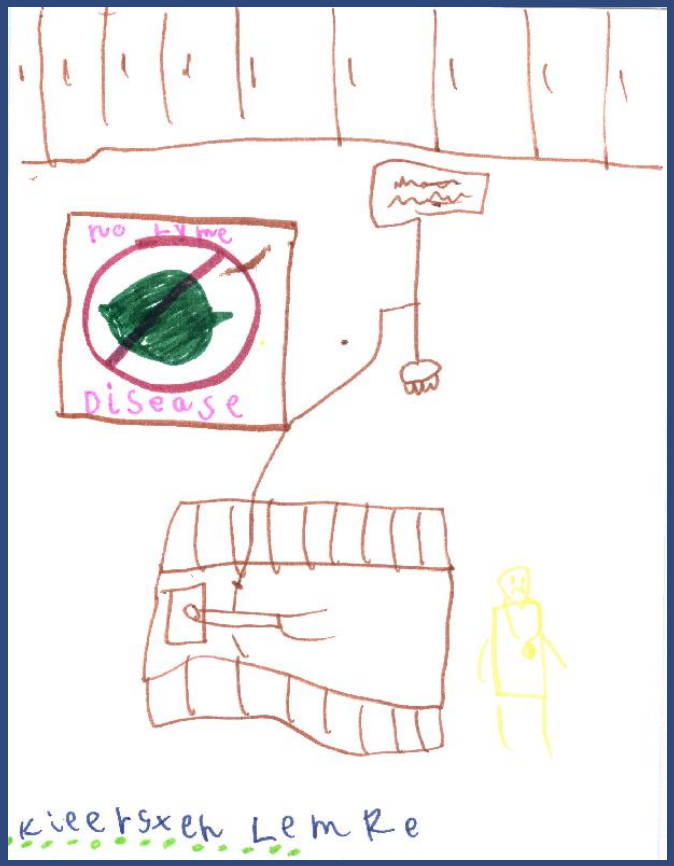
Journal of Chronic Fatigue Syndrome, Vol. 11(3) 2003
http://www.haworthpress.com/store/product.asp?sku=J092

10.1300/J092v11n03_05

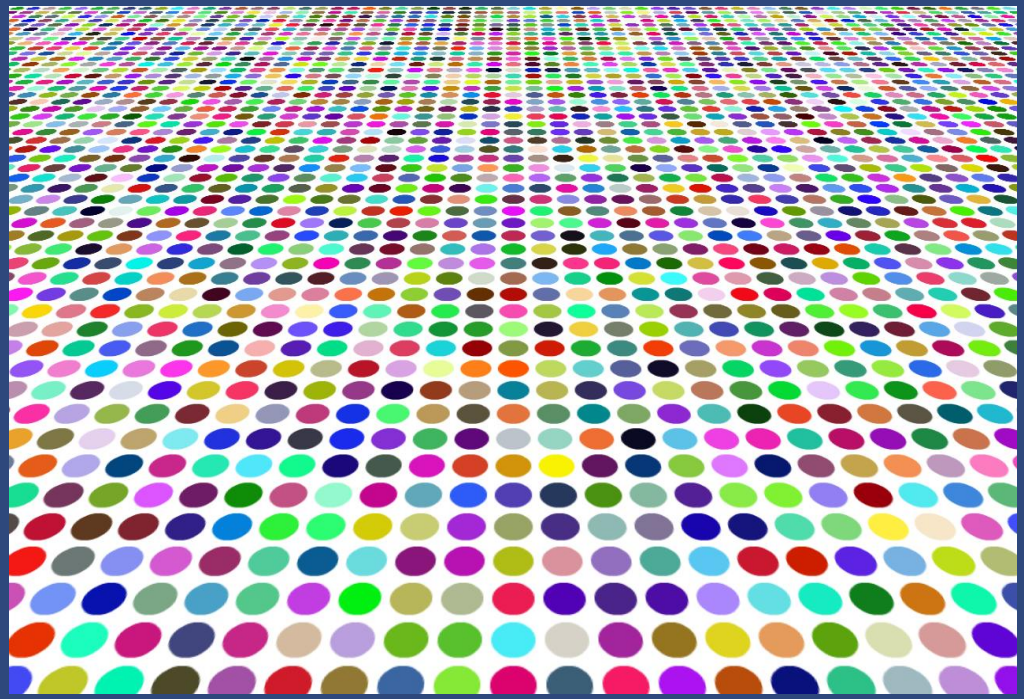
2003

Shor S Pathogenesis of Chronic Fatigue Syndrome, A Multisystem Hypothesis *Journal of Chronic Fatigue Syndrome* Vol. 11(3) 2003: 51-68

Lyme Disease



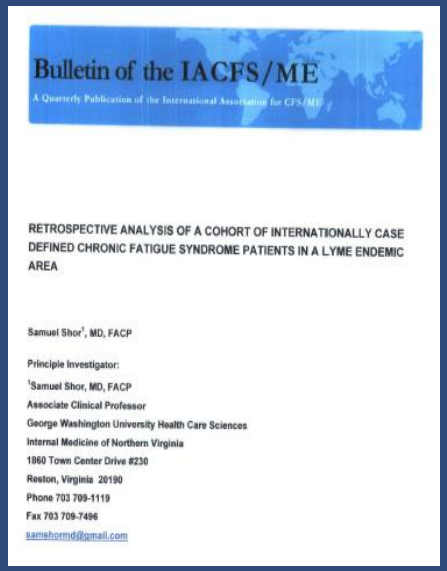
Chronic Fatigue Syndrome
Lyme Disease
"Connecting the Dots"



"Seronegative" Lyme Disease presenting as Chronic Fatigue Syndrome

March 2011

Peer reviewed
Original research



Bulletin of the IACFS/ME

A Quarterly Publication of the International Association for CFS/ME

RETROSPECTIVE ANALYSIS OF A COHORT OF INTERNATIONALLY CASE DEFINED CHRONIC FATIGUE SYNDROME PATIENTS IN A LYME ENDEMIC AREA

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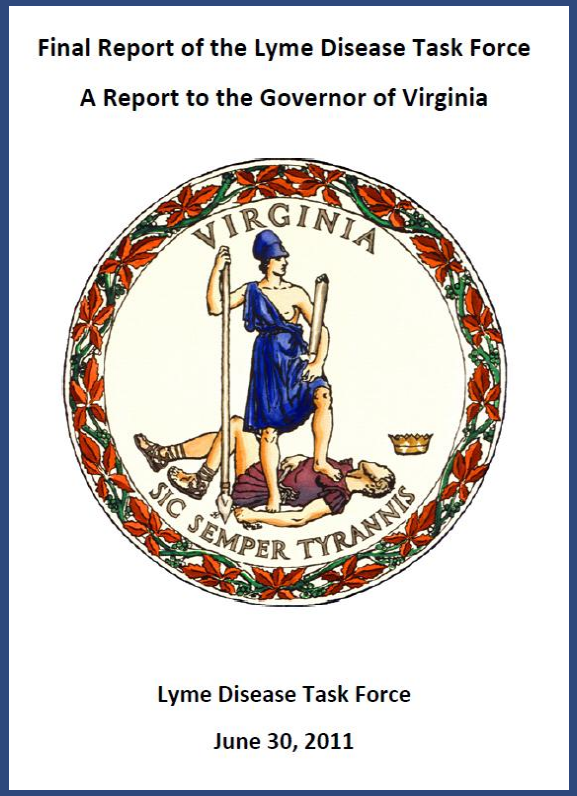
Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123

Commonwealth of Virginia
The Governor's Task Force on Lyme Disease



Commonwealth of Virginia
The Governor's Task Force on Lyme Disease

DIRECTIVE:

- Medical personnel need accurate, fact-based information about prevalence, diagnosis, treatment, and prevention of tick-borne diseases. It is critical to raise awareness in the medical community about Lyme and other tick-borne diseases.

LYME DISEASE
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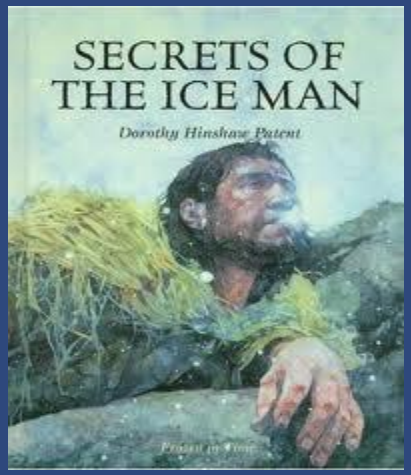
LYME DISEASE-STATE OF ART

HISTORY-FIRST KNOWN CASE

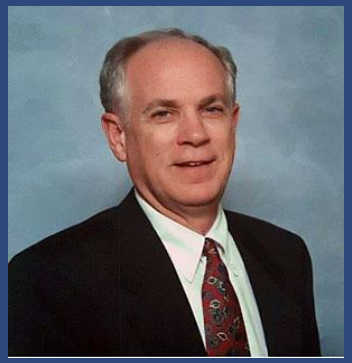


The 5,300-year-old ice mummy dubbed Otzi discovered in the Eastern Alps about 20 years ago

Iceman may have suffered from Lyme disease
Gene evidence of Borrelia and clinical evidence of arthritis

LYME DISEASE HISTORY

1975
Alan Steere, MD:
JRA epidemic in Lyme CT.



1982
Willy Burgdorfer, Ph.D.
Borrelia burgdorferi, first isolated

Infectious Diseases Society of America

2000

GUIDELINES FROM THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Practice Guidelines for the Treatment of Lyme Disease

Gary P. Wormser,[1] Robert B. Nadelman,[1] Raymond J. Dattwyler,[2] David T. Dennis,[6] Eugene D. Shapiro,[7] Allen C. Steere,[8] Thomas J. Rush,[3] Daniel W. Rahn,[10] Patricia K. Coyle,[5] David H. Persing,[11] Durland Fish,[4] and Benjamin J. Luft[9]

[1]*Division of Infectious Diseases, Department of Medicine, New York Medical College, Valhalla,* [2]*Division of Allergy, Immunology and Lyme Disease, Department of Medicine,* [3]*Department of Neurology, and* [4]*Department of Medicine, Health Sciences Center, State University of New York at Stony Brook, and* [5]*private practice, Briarcliff Manor, New York;* [6]*Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado; Departments of* [7]*Pediatrics and* [8]*Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut;* [9]*Tufts University School of Medicine, New England Medical Center, Boston, Massachusetts;* [10]*Office of Medical Management, Medical College of Georgia, Augusta; and* [11]*Diagnostics Development, Corixa Corporation, and Infectious Disease Research Institute, Seattle Life Sciences Center, Seattle, Washington*

Executive Summary

Tick bites and prophylaxis. The best currently available method for preventing infection with *Borrelia burgdorferi* is to avoid vector tick exposure. If exposure to *Ixodes scapularis* or *Ixodes pacificus* ticks is unavoidable, measures recommended to reduce the risk of infection include using both protective clothing and tick repellents, checking the entire body for ticks daily, and promptly removing attached ticks, before transmission of *B. burgdorferi* can occur (A-III [see tables 1 and 2 for recommendation categories, indicated in parentheses throughout this text]).

Routine use of either antimicrobial prophylaxis (E-I) or serological tests (D-III) after a tick bite is not recommended. Some experts recommend antibiotic therapy for patients bitten by *I. scapularis* ticks that are estimated to have been attached for >48 h (on the basis of the degree of engorgement of the tick with blood), in conjunction with epidemiological information regarding the prevalence of tick-transmitted infection (C-III). However, accurate determinations of species of tick and degree of engorgement are not routinely possible, and data are insufficient to demonstrate efficacy of antimicrobial therapy in this setting.

Persons who remove attached ticks should be monitored closely for signs and symptoms of tick-borne diseases for up to 30 days and specifically for the occurrence of a skin lesion at the site of the tick bite (which may suggest Lyme disease) or a temperature >38°C (which may suggest human granulocytic ehrlichiosis [HGE] or babesiosis). Persons who develop a skin lesion or other illness within 1 month after removing an attached tick should promptly seek medical attention for assessment of the possibility of having acquired a tick-borne disease (A-II).

Health care practitioners, particularly those in areas where Lyme disease is endemic, should become familiar with its clinical manifestations, recommended practices for testing for it, and therapy for the disease, as well as for HGE and babesiosis (A-III).

Testing of ticks for tick-borne infectious organisms is not recommended, except in research studies (D-III).

Prior vaccination with the recently licensed recombinant outer-surface protein A (OspA) vaccine preparation reduces the risk of developing Lyme disease associated with tick bites but should not alter the above recommendations (A-I).

Early Lyme disease. Administration of doxycycline (100 mg twice daily) or amoxicillin (500 mg 3 times daily) for 14–21 days is recommended for treatment of early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of neurological involvement or third-degree atrioventricular heart block (A-I). In prospective studies, these agents have been shown to be effective in treating erythema migrans and associated symptoms. Doxycycline has the advantage of being efficacious for treatment of HGE, which may occur simultaneously with early Lyme disease. Doxycycline is relatively contraindicated during pregnancy or lactation and for children aged <8 years.

Because of its higher cost, cefuroxime axetil (500 mg orally twice daily), which is as effective as doxycycline in the treatment of erythema migrans (A-I), should be reserved as an alternative agent for those patients who can take neither doxycycline nor amoxicillin. For children, we recommend amoxicillin at a dos-

Reprints or correspondence: Dr. Gary P. Wormser, Room 209 SE, Macy Pavilion, Westchester Medical Center, Valhalla, NY 10595.

Clinical Infectious Diseases 2000; 31(Suppl 1):S1–14

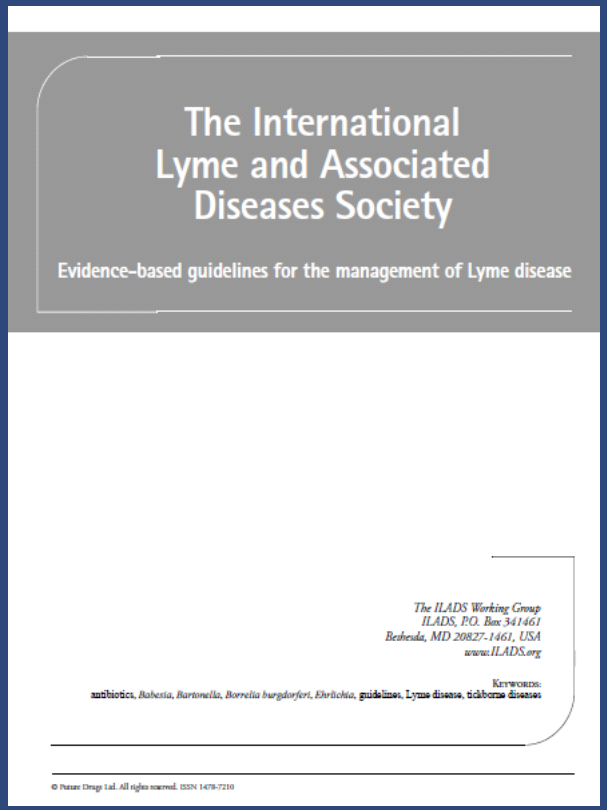
1058-4838/2000/3105I-0001$03.00

Infectious Diseases Society of America

A medical association representing physicians, scientists and other health care professionals who specialize in infectious diseases.

International Lyme and Associated Diseases Society

2004



The International Lyme and Associated Diseases Society

Evidence-based guidelines for the management of Lyme disease

The ILADS Working Group
ILADS, P.O. Box 341461
Bethesda, MD 20827-1461, USA
www.ILADS.org

KEYWORDS:
antibiotics, *Babesia*, *Bartonella*, *Borrelia burgdorferi*, *Ehrlichia*, guidelines, Lyme disease, tickborne diseases

 ISSN 1478-7210

International Lyme and Associated Diseases Society

"An international multidisciplinary medical society dedicated to the diagnosis and appropriate treatment of Lyme and its associated diseases…."

Infectious Diseases Society of America

2006

IDSA GUIDELINES

The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

Gary P. Wormser,[1] Raymond J. Dattwyler,[2] Eugene D. Shapiro,[3,4] John J. Halperin,[3,4] Allen C. Steere,[5] Mark S. Klempner,[6,7] Peter J. Krause,[8] Johan S. Bakken,[9,10] Franc Strle,[11] Gerold Stanek,[12] Linda Bockenstedt,[7] Durland Fish,[8] J. Stephen Dumler,[13] and Robert B. Nadelman[1]

[1]Division of Infectious Diseases and [2]Allergy, Immunology, and Rheumatology, Department of Medicine, New York Medical College, Valhalla, and [3]New York University School of Medicine, New York, New York; [4]Atlantic Neuroscience Institute, Summit, New Jersey; Departments of [5]Medicine and [6]Epidemiology and Public Health and [7]Section of Rheumatology, Department of Medicine, Yale University School of Medicine, New Haven, and [8]Department of Pediatrics, University of Connecticut School of Medicine and Connecticut Children's Medical Center, Hartford; [9]Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, and [10]Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts; [11]Section of Infectious Diseases, St. Luke's Hospital, Duluth, Minnesota; [12]Division of Medical Microbiology, Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland; [13]Department of Infectious Diseases, University Medical Center, Ljubljana, Slovenia; and [14]Medical University of Vienna, Vienna, Austria

Evidence-based guidelines for the management of patients with Lyme disease, human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis), and babesiosis were prepared by an expert panel of the Infectious Diseases Society of America. These updated guidelines replace the previous treatment guidelines published in 2000 (Clin Infect Dis 2000; 31[Suppl 1]:1–14). The guidelines are intended for use by health care providers who care for patients who either have these infections or may be at risk for them. For each of these *Ixodes* tickborne infections, information is provided about prevention, epidemiology, clinical manifestations, diagnosis, and treatment. Tables list the doses and durations of antimicrobial therapy recommended for treatment and prevention of Lyme disease and provide a partial list of therapies to be avoided. A definition of post–Lyme disease syndrome is proposed.

EXECUTIVE SUMMARY

Background

Lyme disease is the most common tickborne infection in both North America and Europe. In the United States, Lyme disease is caused by *Borrelia burgdorferi*, which is transmitted by the bite of the tick species *Ixodes scapularis* and *Ixodes pacificus*. Clinical manifestations most often involve the skin, joints, nervous system, and heart. Extracutaneous manifestations are less commonly seen than in earlier years. Early cutaneous infection with *B. burgdorferi* is called erythema migrans, which is the most common clinical manifestation of Lyme disease. *I. scapularis* may also be infected with and transmit *Anaplasma phagocytophilum* (previously referred to as *Ehrlichia phagocytophila*) and/or *Babesia microti*, the primary cause of babesiosis. Thus, a bite from an *I. scapularis* tick may lead to the development of Lyme disease, human granulocytic anaplasmosis (HGA, formerly known as human granulocytic ehrlichiosis), or babesiosis as a single infection or, less frequently, as a coinfection. *Clinical findings are sufficient*

Received 21 August 2006; accepted 21 August 2006; electronically published 2 October 2006.

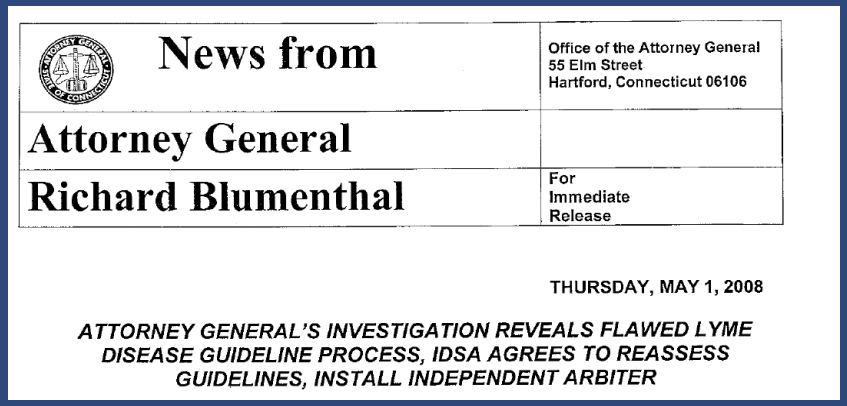
These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Reprints or correspondence: Dr. Gary P. Wormser, Rm. 240, Munger Pavilion, New York Medical College, Valhalla, NY 10595 (Gary_Wormser@nymc.edu).

Clinical Infectious Diseases 2006; 43:1089–134

1058-4838/2006/4308-0001$15.00



News from

Attorney General

Richard Blumenthal

Office of the Attorney General
55 Elm Street
Hartford, Connecticut 06106

For
Immediate
Release

THURSDAY, MAY 1, 2008

ATTORNEY GENERAL'S INVESTIGATION REVEALS FLAWED LYME DISEASE GUIDELINE PROCESS, IDSA AGREES TO REASSESS GUIDELINES, INSTALL INDEPENDENT ARBITER

IDSA

2008

"….The IDSA's guideline panel improperly ignored or minimized consideration of alternative medical opinion **and evidence** regarding chronic Lyme disease, potentially raising serious questions about whether the recommendations reflected all relevant science……"

Institutes of Medicine
Lyme Disease April 2011

Washington, DC – Wednesday, April 20, 2011. Today the Institute of Medicine (IOM) released a report on the critical needs and gaps in Lyme disease research. The chair of the IOM Committee, Dr. Lonnie King stated: "significant gaps in knowledge exist that require new studies and research."

LYME DISEASE
STATE OF ART

Personal interest-chronic fatigue
Historical perspective
Basics
Governor's Task Force on Lyme disease

"State of the Art" the literature:
Diagnostic criteria-concept of seronegativity
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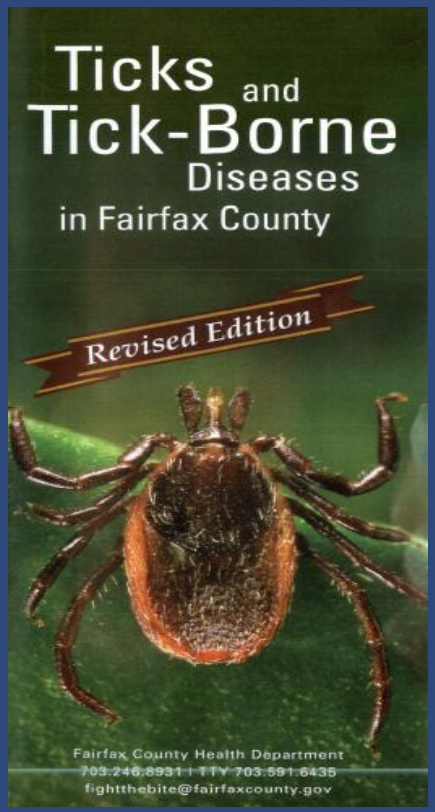
Lyme Disease
Resources



www.fairfaxcounty.gov/fightthebite

Lyme Disease

Infection caused by the spirochetal bacteria

Borrelia burgdorferi

Lyme Disease

"Tick borne illness"

Most common vector borne illness in US

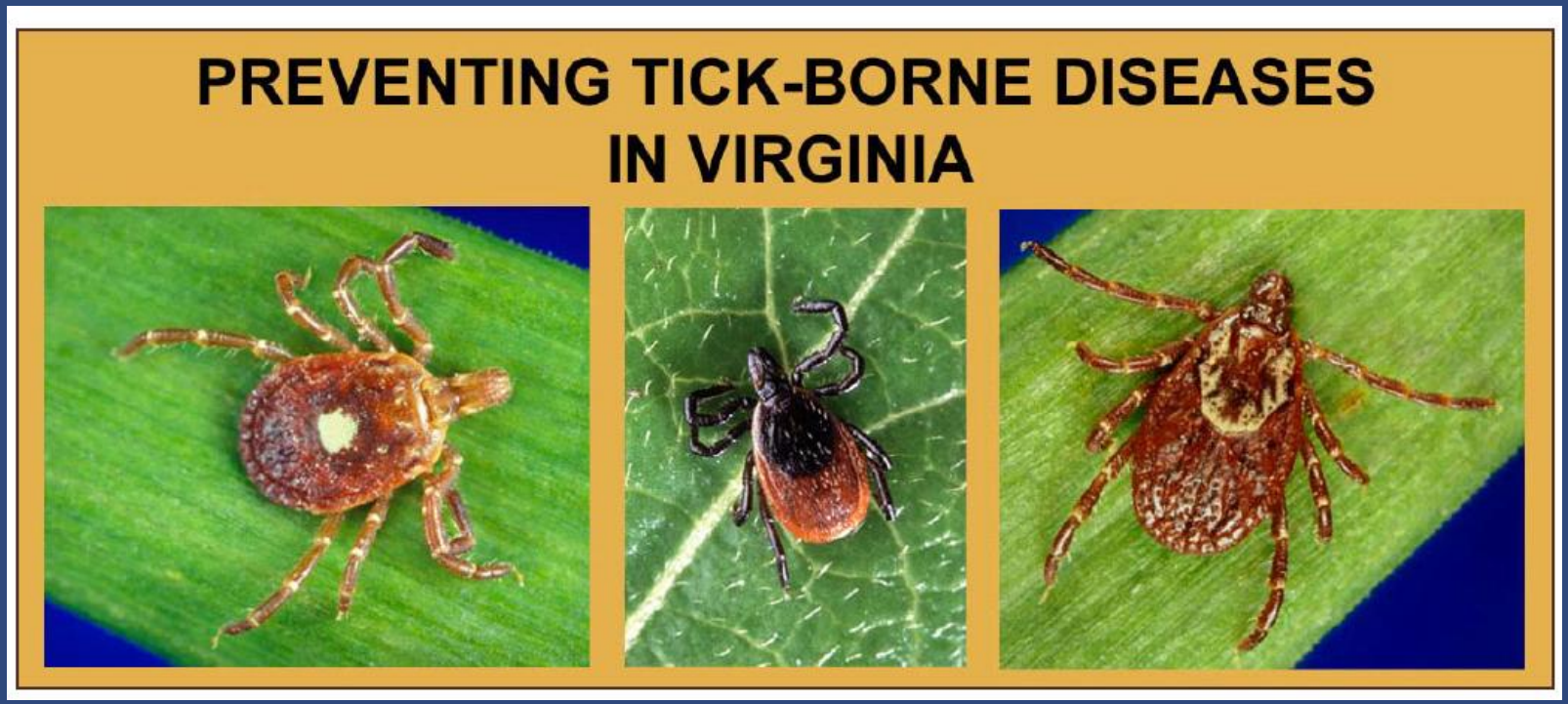
Transmission: Black legged Deer Tick or *Ixodes Scapularis*

[on West Coast: *Ixodes Pacificus*]

The deer tick (*Ixodes scapularis*) adult female

adult female, adult male, nymph, and larva on a centimeter scale

Lyme Disease
Other tick vectors



Lone Star Tick (Amblyomma americancum)

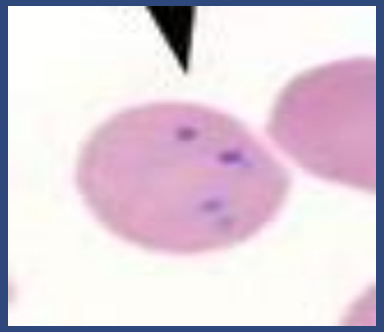
Black legged "deer tick" (*Ixodes scapularis*)

American Dog Tick [Dermacentor Varibalis]

Lyme Disease Co-infections

Other infectious agents may be introduced at the time of the tick bite "blood meal"

Examples:

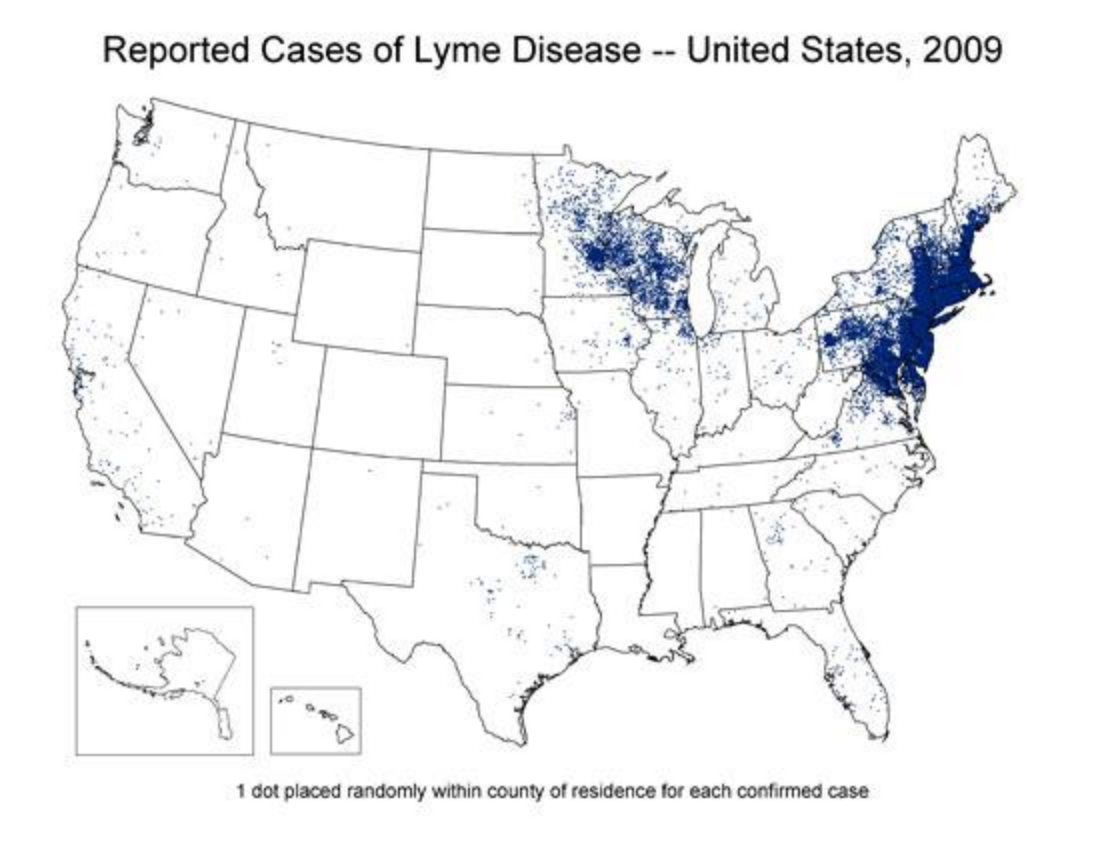


Babesia

Often exacerbating presentation

Lyme Disease
Human case survellance

Centers for Disease Control-CDC



Per CDC: Under reporting estimated by at least a power of 10

LYME DISEASE
LOCAL EPIDEMIOLOGY

Caveat:
The Washington DC metropolitan region is endemic for Lyme disease [1,2]

1.Arias, J Disease Carrying Insects Program Supervisor Fairfax County health department May 2009 personal communication, including "Lyme disease activity in humans 2007"

2.Goodriend, D "Lyme Disease in Loudoun County-Results from a Survey of Reported Cases 2003-2006" presented to the Loudoun County Board of Supervisors 4,19 2006 http://www.loudoun.gov/controls/speerio/resources/RenderContent.aspx?data=cf2dbbdba83e4acf98f8e3ea9cecace4&tabid=340

LYME DISEASE
EPIDEMIOLOGY
HIGH RISK EXPOSURE

"wooded and bushy areas with high grass and leaf litter" [1]
"most patients become infected around the home" [2]

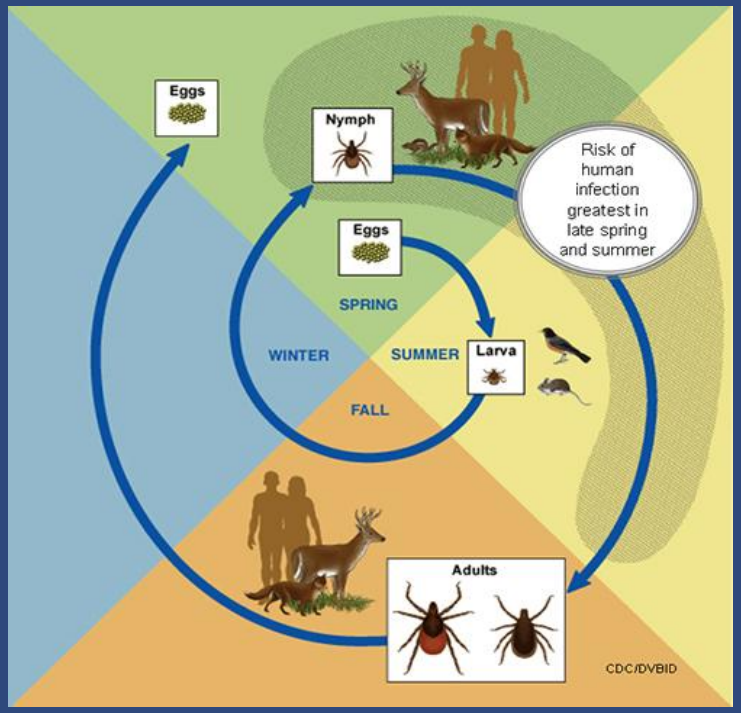
Examples

- gardening
- cutting the grass
- managing leaves

1. http://www.cdc.gov/lyme/prev/on_people.html
2. Stafford II, KC State of Connecticut entomologist Tick Management Handbook

Lyme disease
Local Epidemiology

Lifecycle of deer tick-Incidence Lyme
Peak: Nymph feeding: May-August

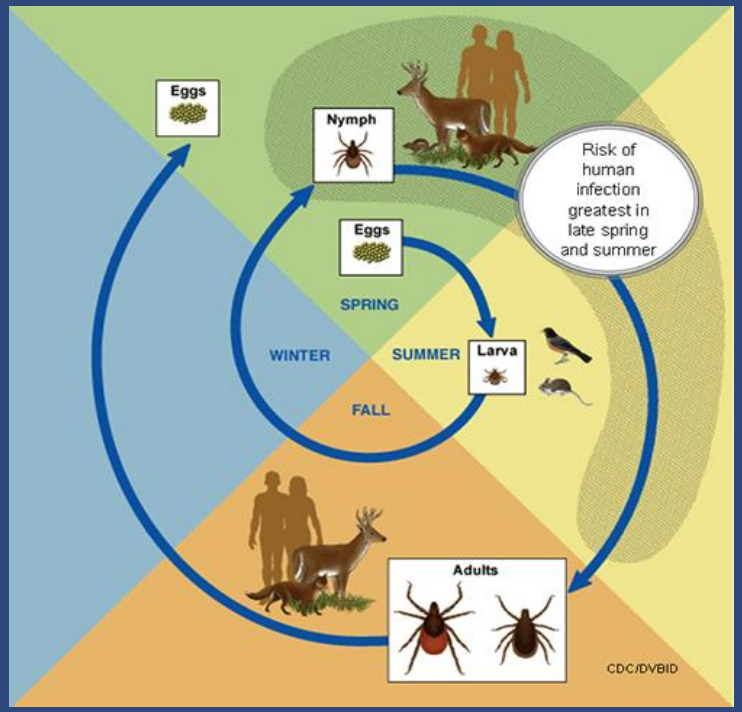


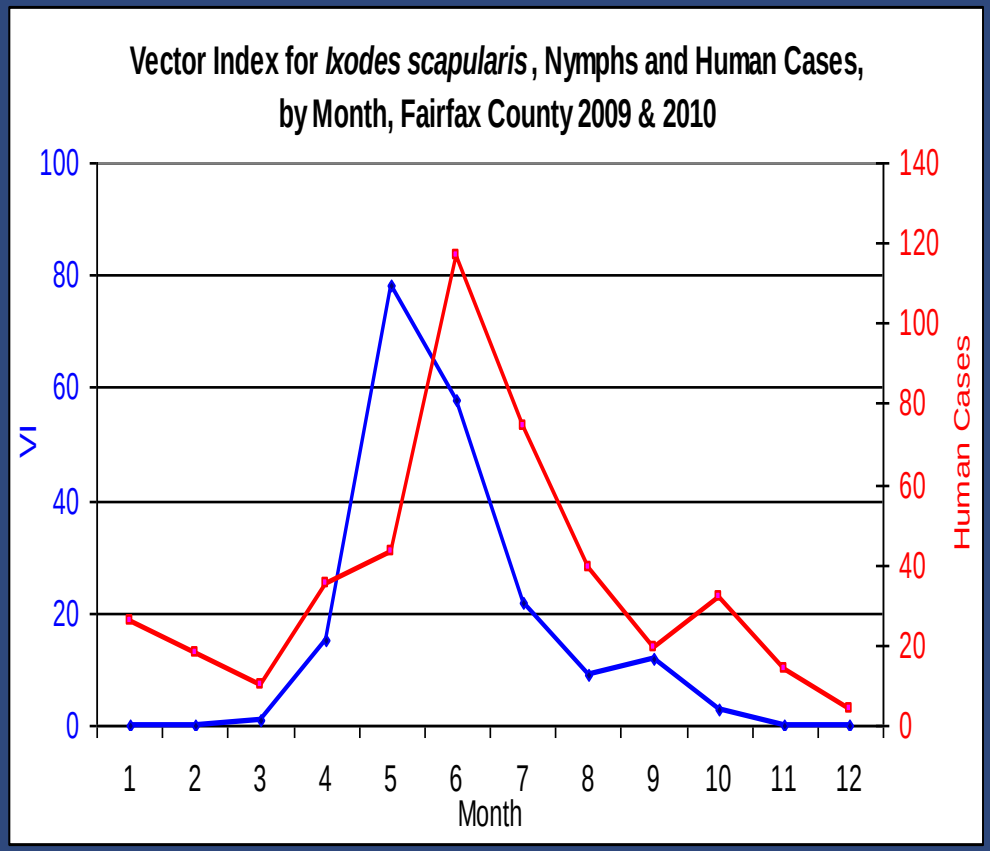
- Adult female ticks lay eggs early spring/summer, eggs hatch into larvae "seed ticks"
  [blood meal #1 sterile]
- dormant (inactive) until the next spring molt into nymphs, Peak: May-Aug
  [blood meal #2*]
- molt into adults in the fall
  [blood meal #3*]

*potential to be infective

Lyme disease
Local Epidemiology

Ix. scapularis Nymphs, Vector Index for *B. burgdorferi* per Month, Fairfax Virginia, 2009-2010





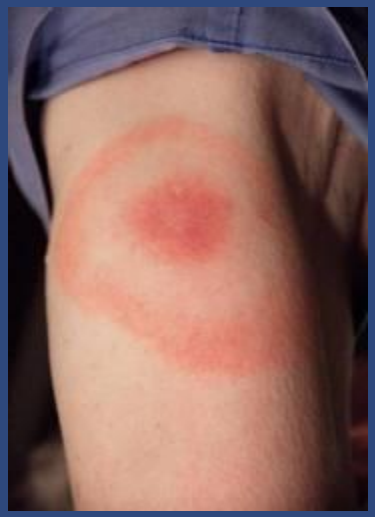
Lyme Disease
Acute Presentation

"Classic" Rash: EM or Erythema Migrans

Usually the site of the tick bite

Generally within 7-14 days of bite [reported range 3-32days]

Published incidence range from 80%, down to <50% [1]



1.Reik L Jr, Burgdorfer W, Donaldson JO Neurologic abnormalities in Lyme disease without erythema chronicum migrans Am J Med 1986; 81: 73-8BJ

Lyme Disease
Acute Presentation

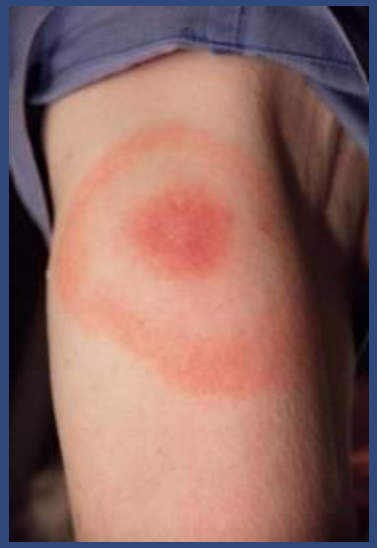
"Classic" Rash: EM or Erythema Migrans

Begins as a small, erythematous macule or papule

expands slowly over days to weeks.

Must achieve a diameter of at least 5cm to qualify for "typical" EM

If occurs: may have atypical characteristics



may not be easily located

Lyme Disease
Typical Acute Presentation

usually within weeks of exposure:

Fever

Headache

Joint pain

Fatigue

Lyme Disease
Acute Presentation
Without EM

"The existence of a flu like illness without erythema migrans of early Lyme Disease has been clearly established"

5 patients: Lyme Endemic Connecticut

- fever and fatigue, resolved spontaneously in 5 to 21
- No EM
- Positive serologies

Feder, H.M., Jr., et al., *Early Lyme disease: a flu-like illness without erythema migrans*. Pediatrics, 1993. **91**(2): p. 456-9.

Lyme Disease
Acute Presentation
Without EM

"… patients from LD endemic areas who have fever and fatigue, especially within a month following a deer tick bite, should be considered for empiric antibiotic therapy for early localized Lyme disease"

i.e. do not delay treatment for tests,

even without a rash

Feder, H.M., Jr., et al., *Early Lyme disease: a flu-like illness without erythema migrans*. Pediatrics, 1993. **91**(2): p. 456-9.

Lyme Disease
Presentation-if left untreated

- Nervous system
  - Pain
    - Peripheral neuropathies-
      - pain, numbness, strange sensations
    - Headaches
  - Facial or Bell's palsy
- Arthritis or Arthralgias
  - often in different joints and "migratory"

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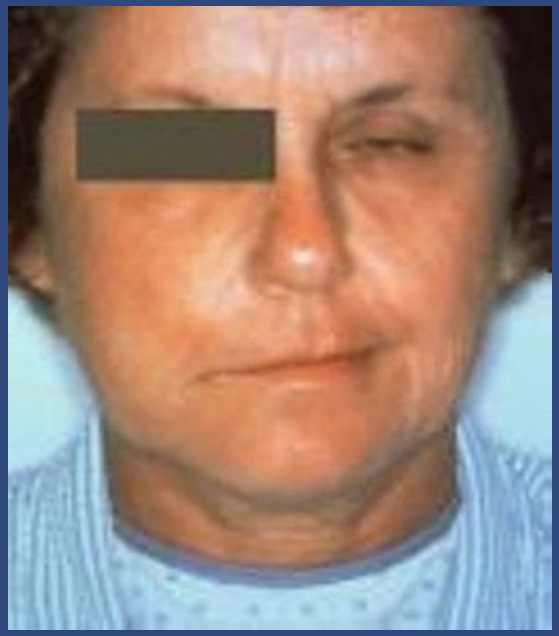
Lyme Disease

Presentation-if left untreated

Nervous system-Facial or Bell's palsy

Peripheral VIIth nerve palsy

Latency- 3 months to 5 years



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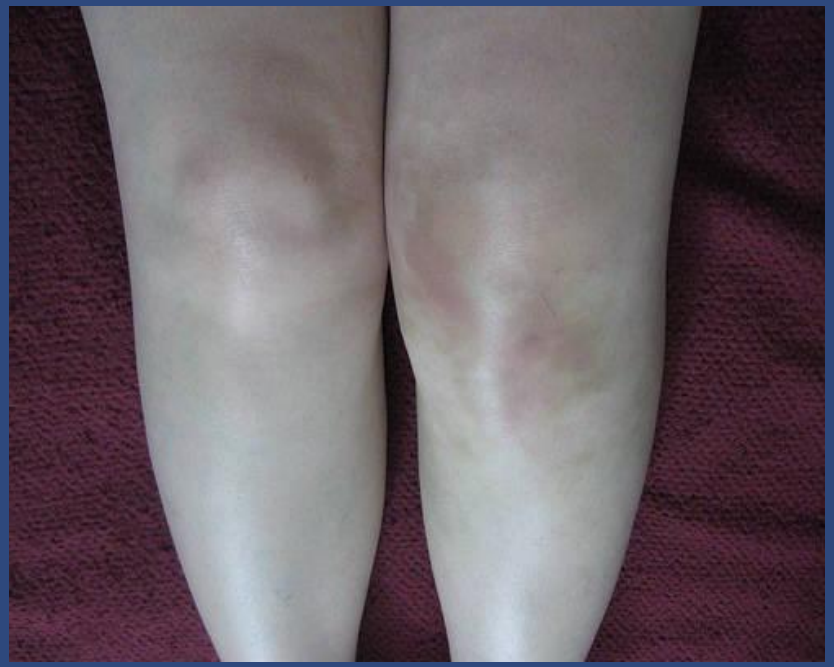
  - Pain
    - Peripheral neuropathies
    - Headaches
  - Facial or Bell's palsy
- Arthritis or Arthralgias
  - often in different joints and "migratory"

Lyme Disease

Presentation-if left untreated

Arthritis-often different joints "migratory"

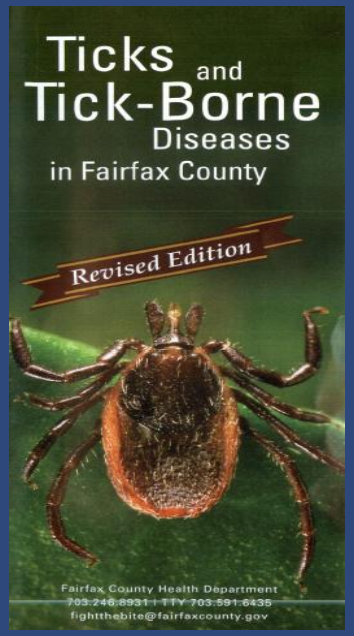
Latency-weeks to years



Albert S, Schulze J, Riegel H, Brade V Lyme arthritis in a 12-year-old patient after a latency period of 5 years. Infection1999;27(4-5):286-8.

Lyme Disease
Prevention

Avoidance
Acaracides-Permethrin
Repellents-Deet
Tick checks



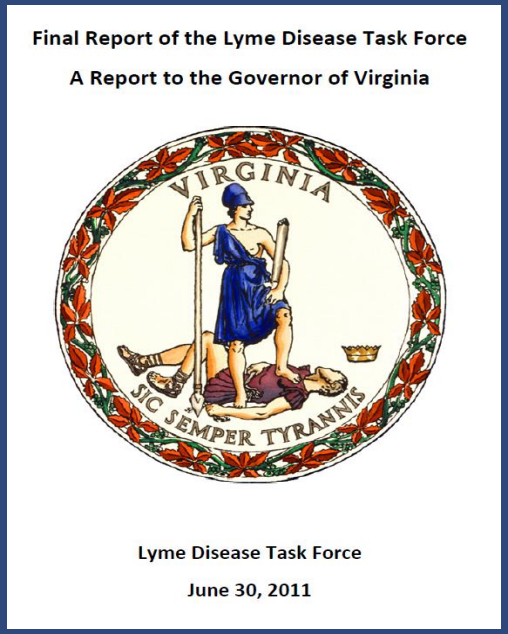
www.fairfaxcounty.gov/fightthebite

LYME DISEASE
EVIDENCE BASED-STATE OF ART

Personal interest-chronic fatigue
Historical perspective
Basics
Governor's Task Force on Lyme disease

"State of the Art" the literature:
Diagnostic criteria-concept of seronegativity
Clinical presentations-additional/Chronic Lyme
Treatment issues

Commonwealth of Virginia
The Governor's Task Force on Lyme Disease



http://wolf.house.gov/uploads/Report_of_the_Virginia_Task_Force_on_Lyme_Disease_Final.pdf

Commonwealth of Virginia The Governor's Task Force on Lyme Disease

Commonwealth of Virginia

The Governor's Task Force on Lyme Disease

FINAL REPORT

Adopted **Unanimously** on June 30, 2011

Introduction

In response to reports of the growing number of cases of Lyme disease and other tick-borne illnesses and out of a sense of concern for the significant number of Virginians infected with these diseases, Governor Bob McDonnell and Secretary William Hazel convened this task force to study and make recommendations in the following areas:

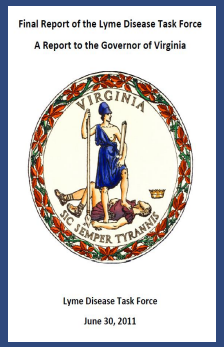
- Diagnosis
- Treatment
- Prevention
- Impact on Children
- Public Education

Commonwealth of Virginia
The Governor's Task Force on Lyme Disease

DIRECTIVE:

- Medical personnel need accurate, fact-based information about prevalence, diagnosis, treatment, and prevention of tick-borne diseases. It is critical to raise awareness in the medical community about Lyme and other tick-borne diseases.

Commonwealth of Virginia
The Governor's Task Force on Lyme Disease



- The CDC case definition for Lyme disease is for epidemiological purposes only and is not now and never has been the singular valid basis for a diagnosis of Lyme disease.

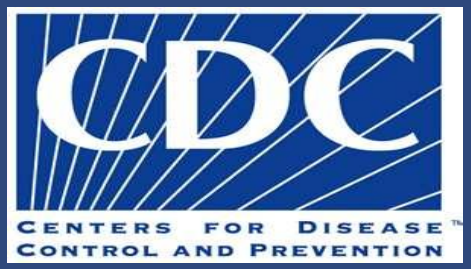
i.e. DON'T NEED "CDC criteria" to be met
in order to make a diagnosis of Lyme Disease

Commonwealth of Virginia
The Governor's Task Force on Lyme Disease

There is no serological test that can "rule out" Lyme disease.

LYME DISEASE
PRESENCE OF EM RASH
DON'T NEED SEROLOGIC CONFIRMATION FOR DX

"Lyme disease is diagnosed on the basis of physician-observed clinical manifestations and a history of probable exposure to infected ticks. **Laboratory tests are neither suggested nor required** to confirm diagnosis for patients with recent onset of a characteristic EM rash. "



Bacon RM, Kugeler JK, Mead, PS MMWR Surveillance for Lyme Disease United States, 1992-2006 October 3, 2008/57(SS10);1-9

Lyme Disease
Evidence Based recommendations:
EM Rash

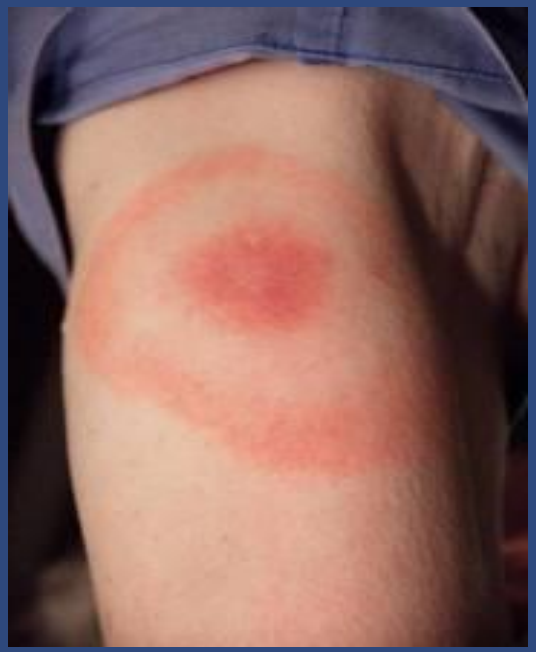
Don't REQUIRE an EM rash for diagnosis

Clinical diagnosis is not limited to the observation of an EM rash. A significant proportion of patients with Lyme disease may never develop or observe such a rash.

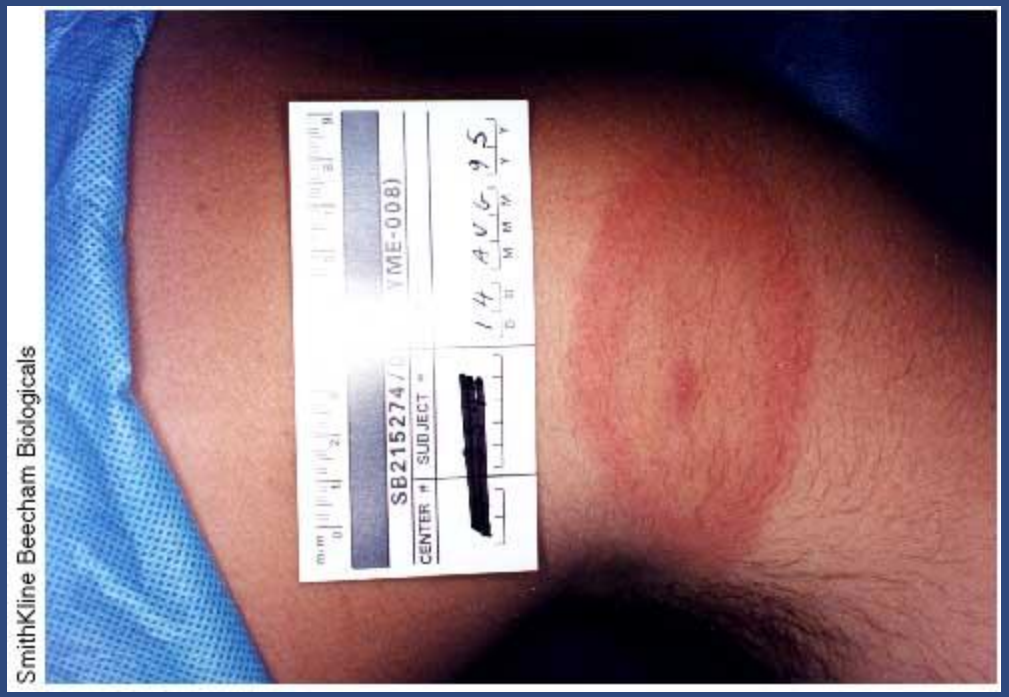
Lyme Disease
EM Rash Directive: Tutorial

Moreover, the EM rash can manifest in non-traditional patterns. The medical community needs a more comprehensive set of visual illustrations so that non-traditional patterns may be properly recognized.

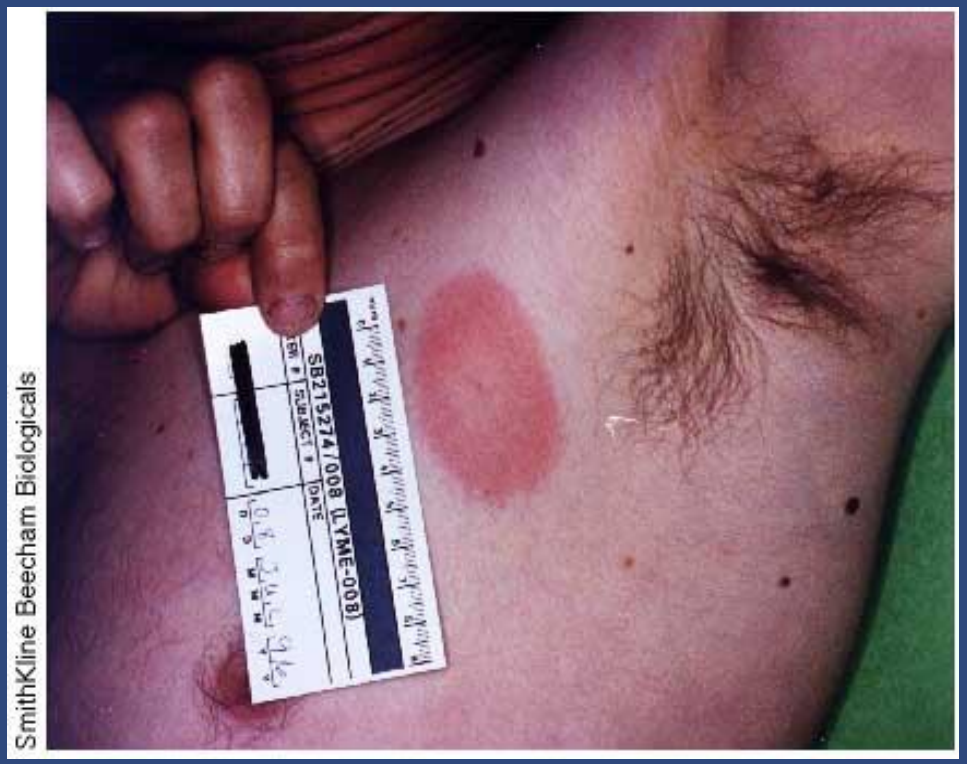
Lyme Disease Task Force Directive: EM Rash Tutorial "Classic"



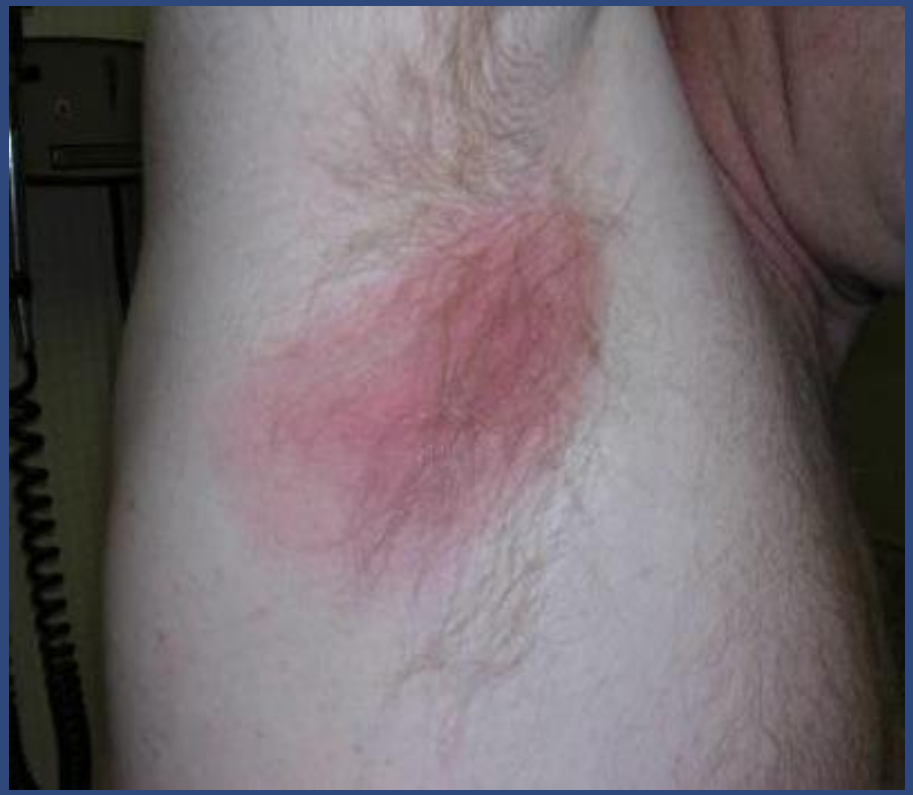
Lyme Disease
EM Rash Tutorial
"Classic"



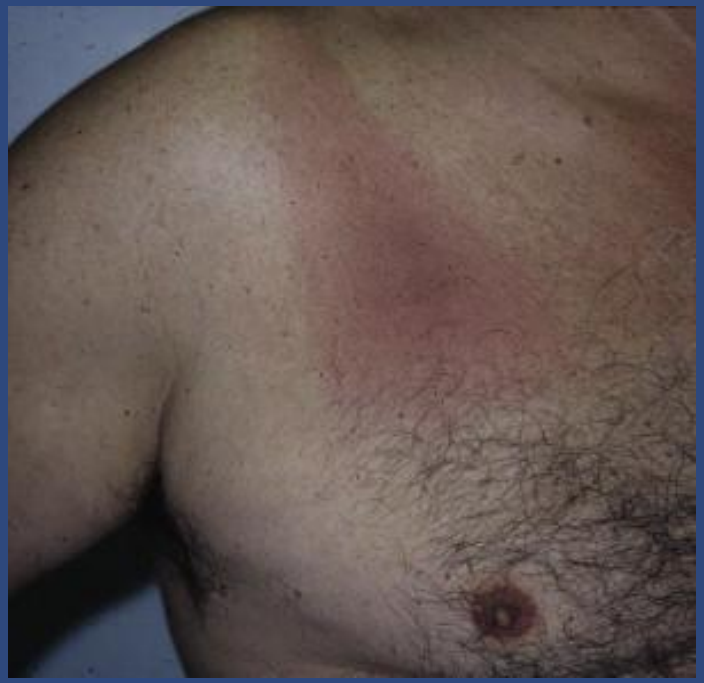
Lyme Disease
EM Rash Tutorial
"Classic"



Lyme Disease
EM Rash Tutorial

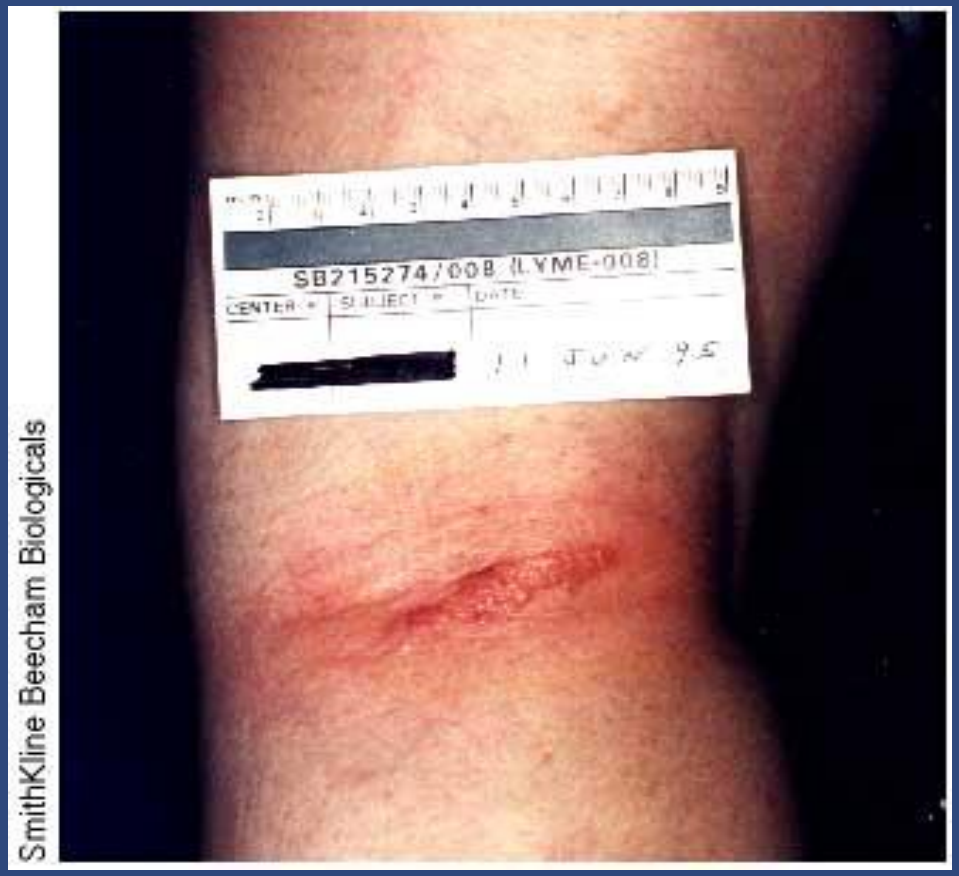


Lyme Disease
EM Rash Tutorial

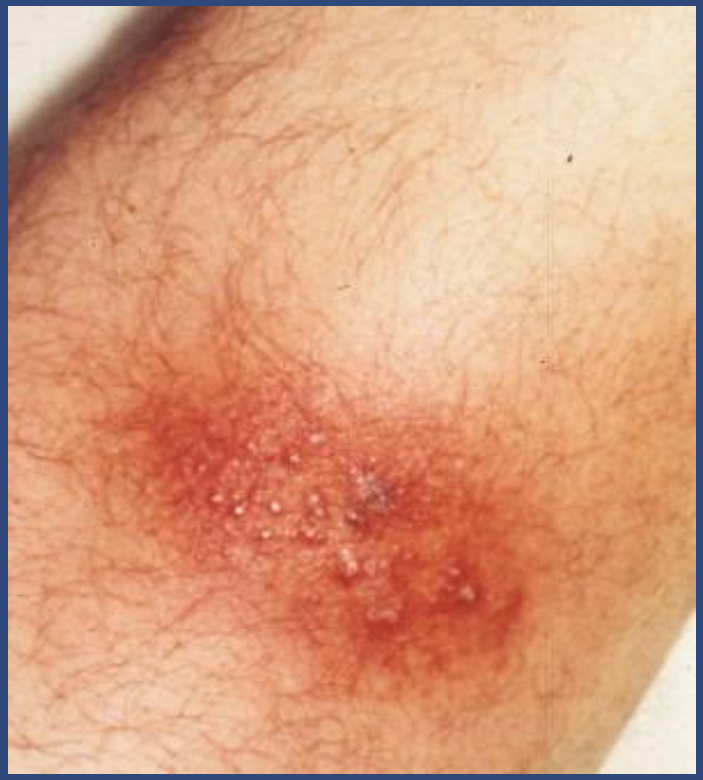


Triangular EM lesion. . (*From* Nadelman RB, Wormser GP. Erythema migrans and early Lyme disease. Am J Med 1995;98(4A):16S

Lyme Disease
EM Rash Tutorial

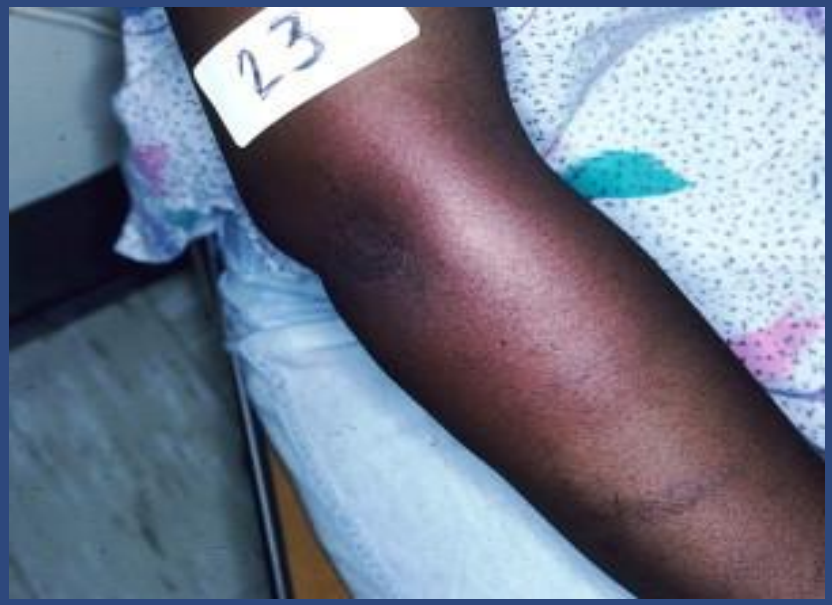


Lyme Disease
EM Rash Tutorial



Vesicular EM lesion. (*From* Nadelman RB, Wormser GP. Erythema migrans and early Lyme disease. Am J Med 1995;98(4A):16S

Lyme Disease
EM Rash Tutorial



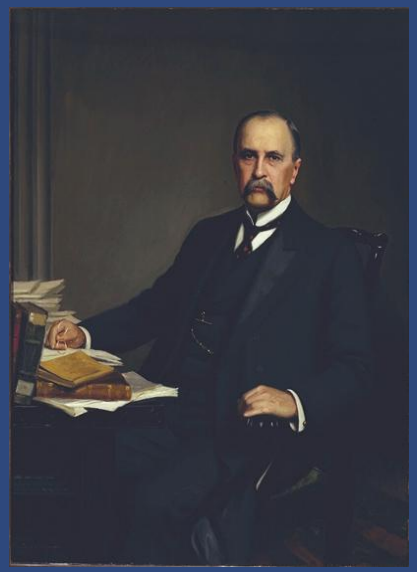
EM lesion in a patient from the Caribbean who acquired infection in Westchester County, New York (*From* Nadelman RB, Wormser GP. Erythema migrans and early Lyme disease. Am J Med 1995;98(4A):16S

LYME DISEASE
EVIDENCE BASED-STATE OF THE ART

Personal interest-chronic fatigue
Historical perspective
Basics
Governor's Task Force on Lyme disease

"State of the Art" the literature:
Diagnostic criteria-concept of seronegativity
Clinical presentations-additional/Chronic Lyme
Treatment issues

LYME
SET THE STAGE: SYPHILIS
COMPLEX: SPIROCHETAL COUSIN



"Father of Modern Medicine"
WILLIAM OSLER, MD

"To know syphilis is to know medicine"

SYPHILIS COMPLEX: EVOLUTIONARY CHARACTERISTICS

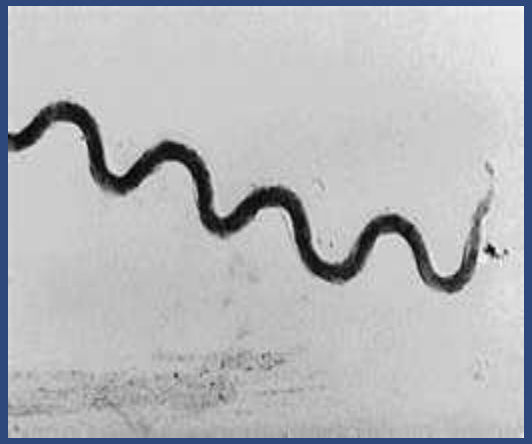
"unlike almost all other infectious disease, it is rarely (if ever!) diagnosed by isolation and characterization of the organsim

Can affect practically any organ system

Variable clinical presentations have resulted in syphilis being labeled "the great impostor"

http://www.columbia.edu/itc/hs/medical/pathophys/id/2005/MID-BrustSyphilisBW.pdf

LYME DISEASE
SYPHILIS
COMPLEX SPIROCHETAL COUSIN



Treponema pallidum

Borrelia burgdorferi

LYME DISEASE
B. BORGDERFERI
GENETIC COMPLEXITY

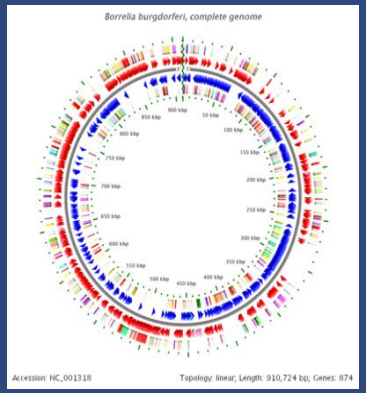
Functioning genes

Borrelia burgdorferi 161

Treponema pallidum 22

~7 times the number of genes

By extension, greater theoretical ability to accommodate to environmental pressures



LYME DISEASE
EVIDENCE BASED-STATE OF ART OVERVIEW

Personal interest-chronic fatigue
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"State of the Art" the literature:
Diagnostic criteria-concept of seronegativity
Insensitivity of testing
Clinical presentations-additional/Chronic Lyme
Treatment issues

LYME DISEASE
DIAGNOSIS
INSENSITIVITY OF TESTING

The testimony that came before the Task Force relayed the highly questionable nature of the ELISA test for early localized disease. We encourage the use of clinical judgment at all stages due to the significant limitations of current serology.

TESTING "TWO TIERED PARADIGM"

HIV Testing

ELISA screening
sensitivity 100% [1]
specificity 99.7%
"confirmatory" western blot

1. Centers for Disease Control and Prevention. *HIV Incidence Surveillance:Estimating National and Local HIV Incidence Using a Population-based Serologic Method to Detect Recent HIV-1 Infection*. Atlanta,Ga: CDC; 2005 Mar 30:1-60.

TESTING "TWO TIERED PARADIGM"

Borrelia burgdorferi

ELISA screening

~50-60% sensitivity [1,2]

"confirmatory" western blot

[not including several highly specific bands]

potentially <50% sensitive

1. Wojciechowska-Koszko I et al Seroidiagnosis of Borreliosis: Indirect Immunofluorescence Assay, Enzyme-Linked Immunosorbent Assay and Immunoblotting Arch. Immunol. Ther. Exp. (2011) 59:69–77
2. Chmielewska-Badora J, Cisak E, Wo´jcik-Fatla A et al Correlation of tests for detection of Borrelia burgdorferi sensu lato infection in patients with diagnosed borreliosis. Ann Agric Environ Med (2006) 13:307–311

INSENSITIVITY OF TESTING I.E. SERONEGATIVITY REALLY/WHY?

Contributing factors

- Multiple strains
- Bb evading immune detection
  - Immune dysfunction
  - Intracellular [sanctuaries]
  - Change in physical characteristics
  - Biofilm
- Potential incomplete use of Western Blot

INSENSITIVITY OF TESTING I.E. SERONEGATIVITY REALLY/WHY?

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Insensitivity of Testing
Seronegativity
Evading Immune Detection

Most diagnostic tools evaluate the immune response-IgM/IgG

Decreased sensitivities of this technology, if immune function is:

1. Impaired
2. Obstructed [sanctuaries]
3. Deceived

INSENSITIVITY OF TESTING I.E. SERONEGATIVITY REALLY/WHY?

Contributing factors

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  - Change in physical characteristics
  - Biofilm
- Potential incomplete use of Western Blot

Insensitivity of Testing
Seronegativity
Impaired Immune Function

- Decreased CD57 subset of NK cells [1]
- Produce chemicals to disable antibodies [2]

1. Stricker RB, Winger EE Decreased CD57 Lymphocyte subset in patients with chronic Lyme disease *Immunology Letters* 76 2001 43-48
2. Schutzer SE, Coyle PK, Belman AL et al Sequestration of antibody to *Borrelia burgdorferi* in immune complexes in sero-negative Lyme disease. *Lancet* 1990; 335(8685): 312-315

Insensitivity of Testing
Seronegativity

Contributing factors

- Multiple strains
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  - Immune dysfunction
  - Intracellular [sanctuaries]
  - Change in physical characteristics
  - Biofilm

Insensitivity of Testing Seronegativity Protected Sanctuaries

Intracellular location

protective effect of skin fibroblasts [1-3]

1. Klempner MS, Noring R, Rogers RA. Invasion of human skin fibroblasts by the Lyme disease spirochete, Borrelia burgdorferi. J Infect Dis. 1993 May;167(5):1074- 81.
2. Georgilis K, Peacocke M, Klempner MS. Fibroblasts protect the Lyme disease spirochete, Borrelia burgdorferi, from ceftriaxone in vitro. J Infect Dis. 1992 Aug;166(2):440- 4.
3. Chmielewski T, Tylewska-Wierzhanowska S Inhibition of fibroblast apoptosis by Borrelia afzelii, Coxiella burnetii and Bartonella henselae. Poll Microbiol 2011;60(3):269-72.

Insensitivity of Testing Seronegativity Protected Sanctuaries

in vitro evidence of *Bb* within endothelial cells, myocardium, ligamentous tissue, synovial cells, keratinocytes, lymphocytes, neurons and glial cells

1. Haupl, T., et al., *Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis.* Arthritis Rheum, 1993. 36(11): p. 1621-6.
2. Ma, Y., A. Sturrock, and J.J. Weis, *Intracellular localization of Borrelia burgdorferi within human endothelial cells.* Infect Immun, 1991. 59(2): p. 671-8
3. Stanek, G., et al., *Isolation of Borrelia burgdorferi from the myocardium of a patient with longstanding cardiomyopathy.* N Engl J Med, 1990. **322**(4): p. 249-52
4. Duray, P.H., et al., *Invasion of human tissue ex vivo by Borrelia burgdorferi.* J Infect Dis, 2005. 191(10): p. 1747-54.
5. Aberer, E., et al., *Heterogeneity of Borrelia burgdorferi in the skin.* Am J Dermatopathol, 1996. 18(6): p. 571-9.

Insensitivity of Testing Seronegativity Protected Sanctuaries

in vitro evidence of *Bb* within endothelial cells, myocardium, ligamentous tissue, synovial cells, keratinocytes, lymphocytes, neurons and glial cells

1. Livengood, J.A. and R.D. Gilmore, Jr., *Invasion of human neuronal and glial cells by an infectious strain of Borrelia burgdorferi.* Microbes Infect, 2006. 8(14-15): p. 2832-40
2. Girschick, H.J., et al., *Intracellular persistence of Borrelia burgdorferi in human synovial cells.* Rheumatol Int, 1996. 16(3): p. 125-32.
3. Dorward, D.W., E.R. Fischer, and D.M. Brooks, *Invasion and cytopathic killing of human lymphocytes by spirochetes causing Lyme disease.* Clin Infect Dis, 1997. 25 Suppl 1: p. S2-8
4. Valesova, M., et al., *Detection of Borrelia in the synovial tissue from a patient with Lyme borreliosis by electron microscopy.* J Rheumatol, 1989. **16**(11): p. 1502-5.
5. Priem, S., et al., *Detection of Borrelia burgdorferi by polymerase chain reaction in synovial membrane, but not in synovial fluid from patients with persisting Lyme arthritis after antibiotic therapy.* Ann Rheum Dis, 1998. **57**(2): p. 118-21
6. de Koning, J., et al., *Demonstration of spirochetes in cardiac biopsies of patients with Lyme disease.* J Infect Dis, 1989. **160**(1): p. 150-3
7. Nanagara, R., P.H. Duray, and H.R. Schumacher, Jr., *Ultrastructural demonstration of spirochetal antigens in synovial fluid and synovial membrane in chronic Lyme disease: possible factors contributing to persistence of organisms.* Hum Pathol, 1996. **27**(10): p. 1025-34.

Insensitivity of Testing Seronegativity

Contributing factors

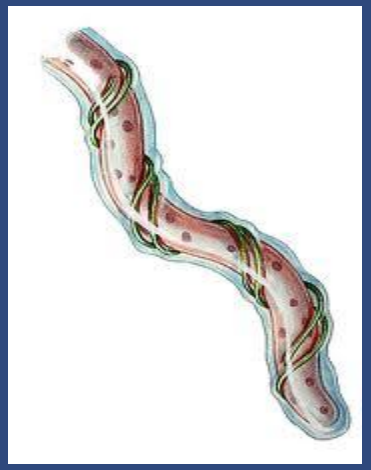
- Multiple strains
- Bb evading immune detection
  - Immune dysfunction [impaired]
  - Intracellular [protected sanctuaries]
  - Change physical characteristics [deceived]
  - Biofilm [protected sanctuaries]

Insensitivity of Testing Seronegativity

Change in physical characteristics (deceived)

Change in outer protein coat

i.e. altering immunogenicity



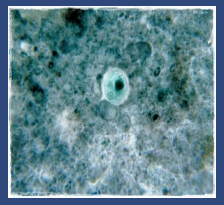
Schwann TG, Piesman J, Golde WT, Dolan MC, Ros PA Induction of an outer surface protein on *Bburgdorferi* during tick feeding. *Proc Natl Acad Sci USA*1995; 92: 2909-2913

Seronegativity
Change in physical characteristics (deceived)

Atypical, pleomorphic, spheroplast cell wall deficient L-forms, also known as "cyst forms" 1-3

Associated with changing environmental pressures:

- Heat exposure
- Antimicrobials



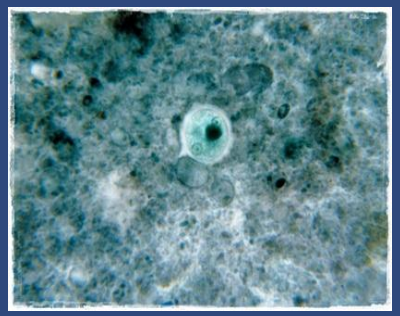
Altered immunogenicity

"Form of resistance to adverse conditions" 3

1. Brorson O, Brorson SH Transformation of cystic forms of *Borrelia burgdorferi* to normal mobile spirochetes. *Infection* 1997; 25: 240-246
2. Gruntar I et al; Conversion of *Borrelia garinii* cystic forms to motile spirochetes in vivo. *APMIS* 2001; 109(5); 383-388
3. Judith Miklossy, Sandor Kasas, Anne D Zurn, Sherman McCall, Sheng Yu and Patrick L McGeer Persisting atypical and cystic forms of *Borrelia burgdorferi* and local inflammation in Lyme neuroborreliosis *Journal of Neuroinflammation* 2008, 5:40; 1-18

Seronegativity
Different forms

"can occur in the absence of the typical spiral *Borrelia* form"



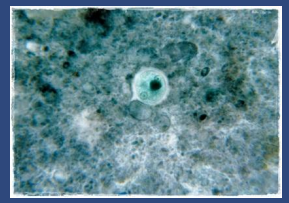
Cell wall deficient "L" or cyst form

Judith Miklossy, Sandor Kasas, Anne D Zurn, Sherman McCall, Sheng Yu and Patrick L McGeer Persisting atypical and cystic forms of *Borrelia burgdorferi* and local inflammation in Lyme neuroborreliosis *Journal of Neuroinflammation* 2008, 5:40; 1-18

Seronegativity
Different forms

Reconversion of cystic *Borrelia* into the typical spiral form has been demonstrated *in vitro* and *in vivo*

Replicating spiral form



Cell wall deficient "L" or cyst form

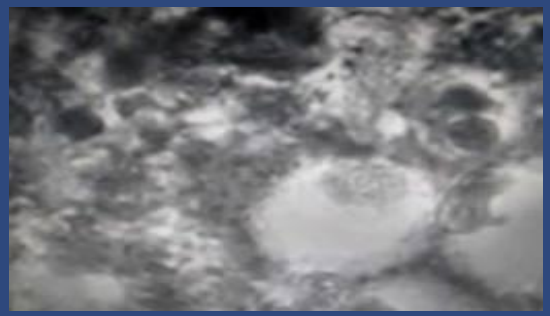
1. Brorson O, Brorson S: In vitro conversion of Borrelia burgdorferi to cystic forms in spinal fluid, and transformation to mobile spirochetes by incubation in BSK-H medium. *Infection* 1998, 26:144-150.
2. Gruntar I, Malovrh T, Murgia R, Cinco M: Conversion of Borrelia garinii cystic forms to motile spirochetes in vivo. *APMIS* 2001, 109:383-838.
3. Mattman LH: Cell wall deficient forms: stealth pathogens. 2nd edition. CRC Press, Inc, Boca Raton, Fla; 1993.

Insensitivity of Testing
Seronegativity

Contributing factors

- Multiple strains
- Bb evading immune detection
  - Immune dysfunction [impaired]
  - Intracellular [protected sanctuaries]
  - Change physical characteristics [deceived]
  - Biofilm [protected sanctuaries]

Seronegativity
Sanctuaries:
Biofilm



"Adherent polysaccharide-based matrices protect bacteria from the hostile host environment and facilitate persistent infection."

Seronegativity Sanctuaries: Biofilm

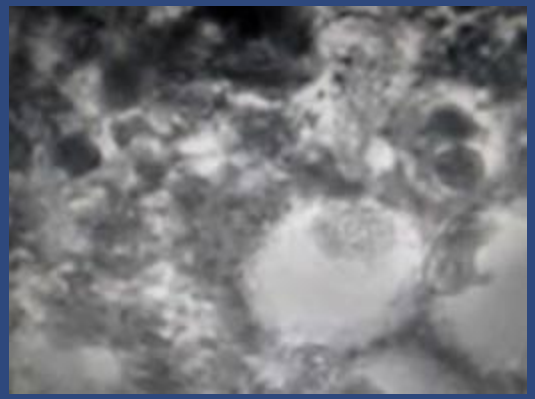
Responsible for a number of chronic infections:

- Periodontitis
- chronic otitis media
- Endocarditis
- gastrointestinal infection
- chronic lung infection

1. Davey ME, O'Toole GA. Microbial biofilms: from ecology to molecular genetics. *Microbiol Mol Biol Rev*. 2000;64:847–867.
2. Stoodley P, Sauer K, Davies DG, Costerton JW. Biofilms as complex differentiated communities. *Annu Rev Microbiol*. 2002;56:187–209.
3. Hoa M, Syamal M, Schaeffer MA, Sachdeva L, Berk R, Coticchia J.Biofilms and chronic otitis media: an initial exploration into the role of biofilms in the pathogenesis of chronic otitis media. *Am J Otolaryngol*. 2010;31:241–245.
4. Trautner BW, Darouiche RO. Role of biofilm in catheter-associated urinary tract infection. *Am J Infect Control*. 2004;32:177–183.
5. de Paz LE, Bergenholtz G, Svensäter G. The effects of antimicrobials on endodontic biofilm bacteria. *J Endod*. 2010;36:70–77.
6. Hamilton S, Bongaerts RJ, Mulholland F, et al. The transcriptional programme of *Salmonella enterica* serovar *Typhimurium* reveals a key role for tryptophan metabolism in biofilms. *BMC Genomics*. 2009;10:599.
7. Ramage G, Mowat E, Jones B, Williams C, Lopez-Ribot J. Our current understanding of fungal biofilms. *Crit Rev Microbiol*. 2009; 35:340–355.

Seronegativity
Sanctuaries:
Biofilm

Borrelia burgdorferi [1-4]



"…these spirochetal formations have been found in culture and in the tick gut…."

1. Sapi E, Kaur N, Anyanwu S, Luecke DF, Datar A, Patel S, Rossi M, Stricker RB. Evaluation of in-vitro antibiotic susceptibility of different morphologic forms of Borrelia burgdorferi Infect Drug Resist. 2011;4:97-113. Epub 2011 May 3.
2. StrickerRB, Johnson, L Lyme disease: the next decade. InfectDrugResist 2011;4:1-9. Epub 2011 Jan 7.
3. Sapi E, MacDonald A. Biofilms of *Borrelia burgdorferi* in chronic cutaneous borreliosis. *Am J Clin Pathol*. 2008;129:988–989.
4. Dunham-Ems SM, Caimano MJ, Pal U, et al. Live imaging reveals a biphasic mode of dissemination of *Borrelia burgdorferi* within ticks.*J Clin Invest*. 2009;119:3652–3665.

Insensitivity of Testing
Seronegativity

- Mechanisms supporting concept of seronegativity
  - Multiple strains
  - Bb evading immune detection
    - Immune dysfunction [impaired]
    - Intracellular [protected sanctuaries]
    - Change physical characteristics [deceived]
    - Biofilm [protected sanctuaries]
- Guideline issues
  - Potential incomplete use of Western Blot

INSENSITIVITY OF TESTING SERONEGATIVITY ?INCOMPLETE USE OF WESTERN BLOT

Protein separation technique
characteristic markers

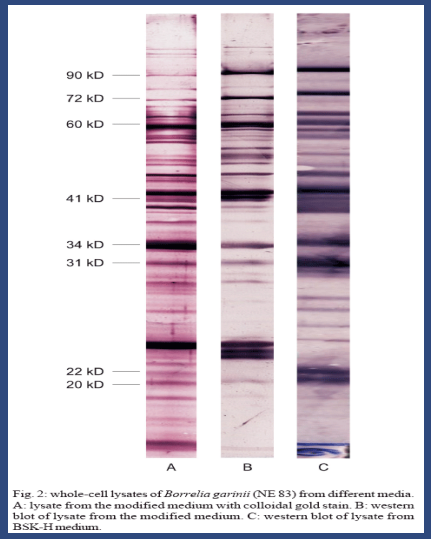


Fig. 2: whole-cell lysates of *Borrelia garinii* (NE 83) from different media. A: lysate from the modified medium with colloidal gold stain. B: western blot of lysate from the modified medium. C: western blot of lysate from BSK-H medium.

WESTERN BLOT
STANDARD BORRELIA BANDS IN COMMERCIAL LABS

Band:	23-25	31	34	39	83-93
Bands generally tested [eg Labcorp/Quest]:					
IgM	X			X	
IgG	X			X	X

Is this enough?

WESTERN BLOT
"HIGHLY SPECIFIC" BANDS

Proteins SPECIFIC to a particular organism:
In this setting: *Borrelia species*

Band:	23-25	31	34	39	83-93
"Highly Specific" [1-6]	X	X	X	X	X

1. H ilton E, Devoti J, Sood S Recommendation To Include *OspA and OspB in th*e New Immunoblotting Criteria for Serodiagnosis of Lyme Disease *JClinMicrobiology* June 1996 Vol34 No6 p1353-1354
2. Tilly K, Krum JG et al *Borrelia burgdorferi* OspC Prote*in Required Exclus*ively in a Crucial Early Stage of Mammalian Infection *Infect Immun* June 2006 74; 6; 3354-3564
3. Ma, B, Chrsten B, Leung D, Vigo-Pelfrey C Serodiagnosis of Lyme Borreliosis by Western Immunoblot: Reacitivity of Various Signficant antibodies against *Borrelia burgdorferi JClinMicrobiology* Feb 1992 30;2; 370-376
4. Fikrig E, Barthold SW, Marcantonio N, et al. Roles of OspA, OspB, and flagellin in protective immunity to Lyme *borreliosis in the laboratory mouse. Infect Immun. 1992; 60: 657-661*
5. Steere, et al. Vaccination against Lyme Disease with Recombinant Borrelia burgdorferi Outer-Surface Lipoprotein A with Adjuvant N Engl
6. Shor, S An analysis of internationally cased defined CFS patients who may have "seronegative" persistent Lyme infection WIRB Study # 1096088

WESTERN BLOT
"HIGHLY SPECIFIC" BANDS 31 AND 34

Use of **antigenic stimulus** of Osp A or band 31 [Osp B or band 34] used to generate **Lyme vaccine**

Band:	23-25	31	34	39	83-93
"Highly Specific"	X	**X**	**X**	X	X

Steere, et al. Vaccination against Lyme Disease with Recombinant Borrelia burgdorferi Outer-Surface Lipoprotein A with Adjuvant N Engl

WESTERN BLOT "HIGHLY SPECIFIC" BANDS

Yet neither bands 31 or 34 are included in the standard kits from most general reference labs such as Labcorp or Quest

Band:	23-25	31	34	39	83-93
"Highly Specific"	X	**X**	**X**	X	X
Bands generally tested [eg Labcorp/Quest]:					
IgM	X			X	
IgG	X			X	X

WESTERN BLOT
"HIGHLY SPECIFIC" BANDS 31 AND 34

"our concern is that the exclusion of the 31- and 34-kDa protein bands from the diagnostic criteria may result in the underdiagnosis of Lyme disease by those who would rely too heavily on serological confirmation."

Band:	23-25	31	34	39	83-93
"Highly Specific"	X	**X**	**X**	X	X

H ilton E, Devoti J, Sood S Recommendation To Include *OspA and OspB in the* New Immunoblotting Criteria for Serodiagnosis of Lyme Disease *JClinMicrobiology* June 1996 Vol34 No6 p1353-1354

LYME DISEASE
PLAUSIBILITY OF SERONEGATIVITY

- Evolutionary mechanisms supporting seronegativity
  - Multiple strains
  - Bb evading immune detection
    - Immune dysfunction [impaired]
    - Intracellular [protected sanctuaries]
    - Change physical characteristics [deceived]
    - Biofilm [protected sanctuaries]
- Guideline issues
  - Potential incomplete use of Western Blot

Lyme Disease
Insensitivity of testing-"seronegativity"
Theory to reality

- 17 patients who all suffered from either neurological or arthritic signs frequently attributed to chronic *borrelia* infection.
  - pathognomonic erythema migrans (EM) rash
  - all had T cell blastogenic responses consistent with exposure to borrelia
  - "curiously, **all lacked detectable antibodies** against *borrelia."*

Dattwyler RJ, Volkman DJ, Luft BJ, Halperin JJ, Thomas J, Golightly MG. Seronegative late Lyme borreliosis: dissociation of Borrelia burgdorferi specific T and B lymphocyte responses following early antibiotic therapy. N Engl J Med 1988;319:1441–6

Lyme Disease
Insensitivity of testing-"seronegativity"
Theory to reality

"diagnosed based on the detection of *Borrelia burgdorfe*ri DNA in synovial fluid. No humoral immune response to *Borrelia burgdorferi* was detectable before, at the time of diagnosis and up to 3 years."

Holl-Wieden A, Suerbaum S, Girschick HJ. Seronegative Lyme arthritis Rheumatol Int. 2007 ;27:1091-3

Lyme Disease
Insensitivity of testing-"seronegativity"

Paradoxically, sicker patients are more likely to be seronegative, because of more impaired immune response

1. Luft BJ, Dattwyler RJ et al Azithromycin Compared with Amoxicillin in the Treatment of Erythema Migrans A Double-Blind, Randomized, Controlled Trial *Ann Intern Med.* 1996;124:785-791.
2. **Mouritsen CL, Wittwer CT, Litwin CM, Yang L, Weis JJ, Martins TB, Jaskowski TD, Hill HR.** Polymerase chain reaction detection of Lyme disease: correlation with clinical manifestations and serologic responses.Am. J. Clin. Pathol. 1996 May;105(5):647-54.
3. **Keller TL, Halperin JJ, Whitman M.** PCR detection of Borrelia burgdorferi DNA in cerebrospinal fluid of Lyme neuroborreliosis patients. Neurology. 1992 Jan;42(1):32-42.

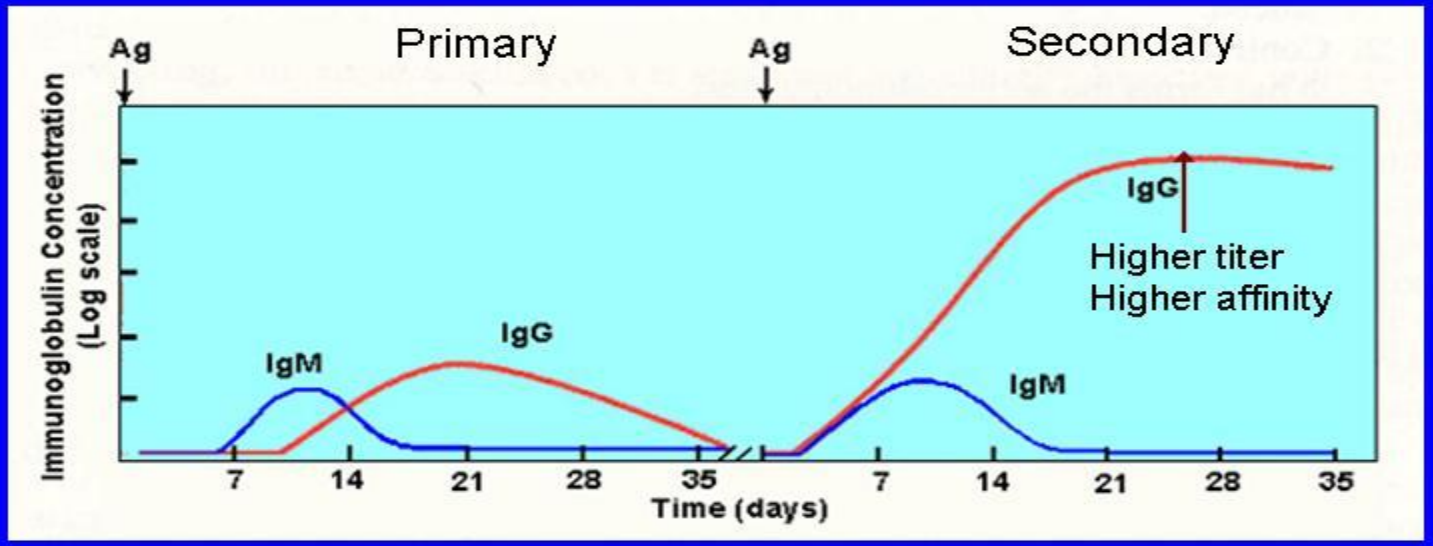
LYME DISEASE
EVIDENCE BASED-STATE OF ART OVERVIEW

Personal interest-chronic fatigue
Historical perspective
Basics
Governor's Task Force on Lyme disease

"State of the Art" the literature:
Diagnostic criteria-concept of seronegativity
?IgM positivity in chronic disease
Clinical presentations-additional/Chronic Lyme
Treatment issues

Lyme Disease Controversy-IgM interpretation

The Antibody Response



Lyme Disease Controversy
?signficance of positive *Bb* IgM
OPINION

"…IgM criteria are only applicable in the first month or so of disease…After this, patients **should** have developed a measurable IgG response and an isolated positive IgM antibody more than 1 month into the course of symptoms is most suggestive of a false-positive result"

Halperin JJ Neurologic Manifestations of Lyme Disease
Curr Infect Dis Rep 2011 Apr 12

Lyme Disease Controversy

?signficance of positive *Bb* IgM

EVIDENCE

Precedence for IgM in Chronic Infection

In this study, we demonstrate that chronic infection with the intracellular bacterium Ehrlichia muris elicits a protective, **long-term IgM response**

Rachael Racine, Maura McLaughlin,Derek D. Jones, Susan T. Wittmer, Katherine C. MacNamara,David L. Woodland, and Gary M. Winslow, IgM Production by Bone Marrow Plasmablasts Contributes to Long-Term Protection against Intracellular Bacterial Infection The Journal of Immunology, 2011, 186: 1011–1021

Lyme Disease Controversy
?signficance of positive *Bb* IgM
EVIDENCE

Specific to *Borrelia*

"The amount of IgM…generally rose during exacerbations and fell during remissions…. Thus, IgM was an important correlate of clinical disease activity…."

Steere, A.C., et al., *Lyme arthritis: correlation of serum and cryoglobulin IgM with activity, and serum IgG with remission.* Arthritis Rheum, 1979. **22**(5): p. 471-83.

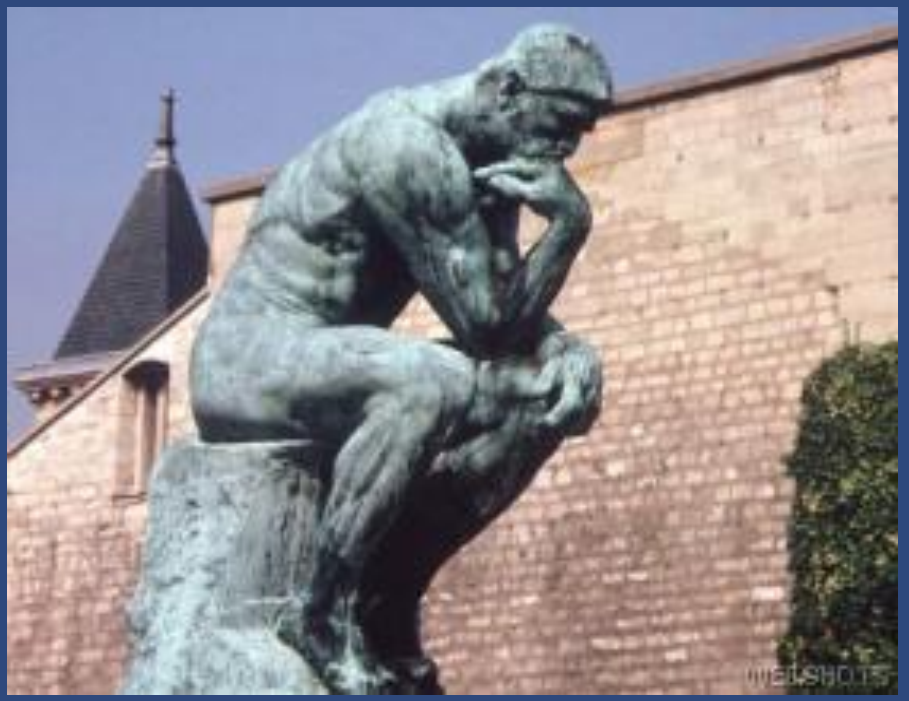
Lyme Disease Controversy
?signficance of positive *Bb* IgM
EVIDENCE

Specific to *Borrelia*

"Antigens of Borrella burgdorferi: recognized during Lyme Disease appearance of a **new** Immunoglobulin M response and expansion of the immunoglobulin G response **late** in the illness" [1,2]

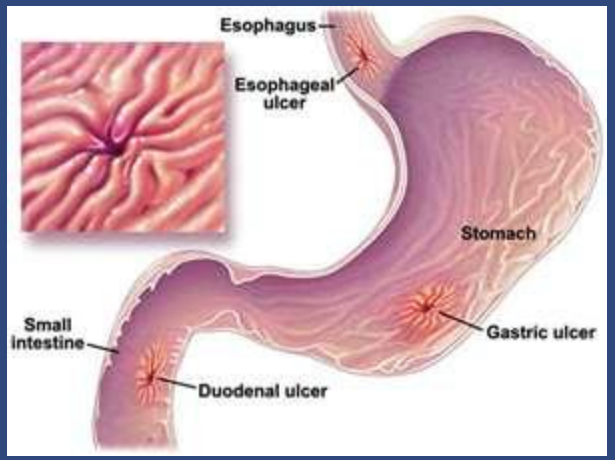
Craft J, Fischer DK, Shimamoto GT, Steere AC. 1986. J. Clin.Invest.1978: 934-939

"THINK OUT OF THE BOX"



PRECEDENCE: *HELICOBACTER PYLORI*

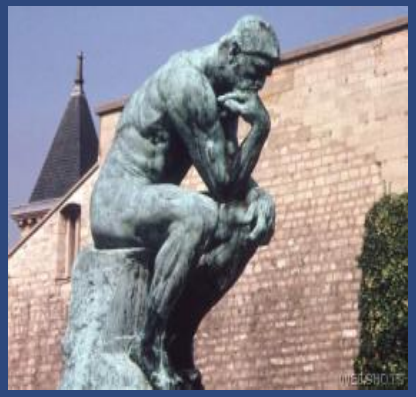
"no organism could survive in the low gastric pH"

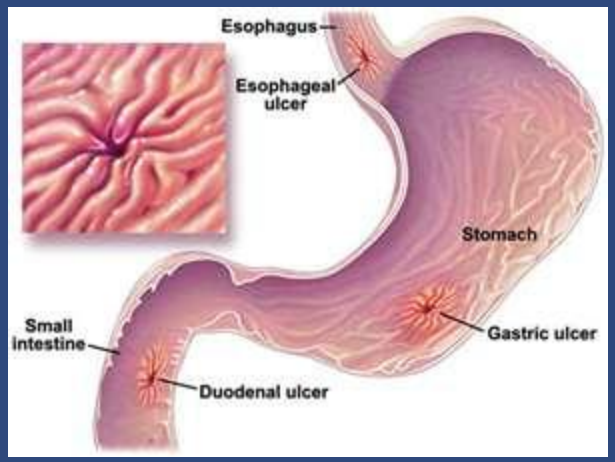


HELICOBACTER PYLORI

http://www.cdc.gov/ulcer/keytocure.htm

"we now know that most ulcers are caused by *H. pylori*…."





LYME DISEASE
EVIDENCE BASED-STATE OF THE ART

Personal interest-chronic fatigue
Historical perspective
Basics
Governor's Task Force on Lyme disease

"State of the Art" the literature:
Diagnostic criteria-concept of seronegativity-summary:
Clinical presentations-additional/Chronic Lyme
Treatment issues

Reiterating: Commonwealth of Virginia The Governor's Task Force on Lyme Disease 2010-2011

As acknowledged by the CDC, Lyme disease and many related tick-borne illnesses cannot be adequately diagnosed by serology alone in many cases. There is no serological test that can "rule out" Lyme disease.

CONSIDER: FURTHER ASSESSMENT OF "SERONEGATIVE LYME"

Implications of highly specific band analysis:

1. IF any are present this is a HIGHLY suspect finding
2. IF the western blot analysis is not in keeping with your clinical impressions of Lyme disease, consider sending to a reference lab that performs testing of bands 31 and 34

Stonybrook Lyme Reference Lab
Stony Brook, New York 11794-7300
(631) 444-3744

Medical Diagnostic Labs
2439 Kuser Road Hamilton, NJ 08690
877 269-0090 www.mdlab.com

Clongen Laboratories, LLC
12321 Middlebrook Road, Suite 120
Germantown, MD 20874 USA
Phone: 301-916-0173 www.clongen.com

Igenex Palo Alto, California 94303
1 800 832-3200 [650 424-1191]
http://www.igenex.com/

CONSIDER: FURTHER ASSESSMENT OF "SERONEGATIVE LYME" CO-INFECTIONS

Consider obtaining screening labs for the most common potential coinfections [1,2]

Lyme disease is the most common tick borne disease in the US [3] the presence of any of the following would suggest a tick bite exposure:

- *Babesia*: *B microti* and *B duncani* species
- *Bartonella* profile: *B hense*lae and *B quint*ana species
- *Ehrlichia* profile:
  - *E chaffeensis* human monocytic ehrlichiosis (HME)
  - *Anaplasma phagocytophilum* [previously known as human granulocytic ehrlichiosis (HGE)]

1. Swanson SJ, Neitzel D, Reed KD, Belengia EA Coinfections acquired from ixodes ticks. Clin Microbiol Rev. 2006 Oct;19(4):708-27.
2. OwenDC Is Lyme disease always poly microbial?--The jigsaw hypothesis.Med Hypotheses. 2006;67(4):860-4. Epub 2006 Jun 30.
3. Bacon RM, Kugeler JK, Mead, PS MMWR Surveillance for Lyme Disease United States, 1992-2006 October 3, 2008/57(SS10);1-9

LYME DISEASE
EVIDENCE BASED-STATE OF ART

Personal interest-chronic fatigue
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"State of the Art" the literature:

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Clinical presentations-additional
Chronic Lyme Disease
Treatment issues

Lyme Disease Controversies

"Chronic Lyme Disease"

[i.e. active infection perpetuating chronic sxs]

IDSA

"There is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease*"

i.e. Chronic Lyme Disease does not exist

IDSA GUIDELINES

The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

Gary P. Wormser,[1] Raymond J. Dattwyler,[2] Eugene D. Shapiro,[3] John J. Halperin,[4] Allen C. Steere,[5] Mark S. Klempner,[6] Peter J. Krause,[7] Johan S. Bakken,[8] Franc Strle,[9] Gerold Stanek,[10] Linda Bockenstedt,[11] Durland Fish,[12] J. Stephen Dumler,[13] and Robert B. Nadelman[1]

Wormser PG et al The Clinical Assessment, Treatment and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babebiosis: Clinical Practice Guidelines by the Infectious Disease Society of America *CID* 2006:43 (1 November) 1089-1134

Chronic Lyme Disease [i.e. ongoing infection] Proposed ILADS "Working Group" Definition

1. A tick bite or exposure [may be occult]
2. Once having evidence of LD by the CDC's epidemiologic case definition, a positive serologic test for LD, and/or a clinical diagnosis
3. Persistent or relapsing multi-systemic presentations including fatigue, neuro-cognitive impairment, neuro-psychiatric and/or musculoskeletal symptoms for 3 months

Chronic Lyme Disease
Proposed ILADS"Working Group" Definition

4. Symptoms are moderate to severe and/or lead to significant compromise of an individual's occupational, education, social or personal activities
5. Symptoms persist despite an assessment for other conditions (i.e. rule out "other conditions)
6. Documentation of a pre-existing, comorbid condition, or a condition caused by or associated LD cannot be used to "rule out" LD (eg. Depression).

Lyme Disease
Clinical Presentation

If left untreated-as already discussed

[or IF inadequately treated]

- Nervous system
  - Pain
    - peripheral neuropathies
    - Headaches
  - Facial or Bell's palsy
- Arthritis
  - often in different joints and "migratory"

Lyme Disease Clinical Presentation

If left untreated/inadequately treated:

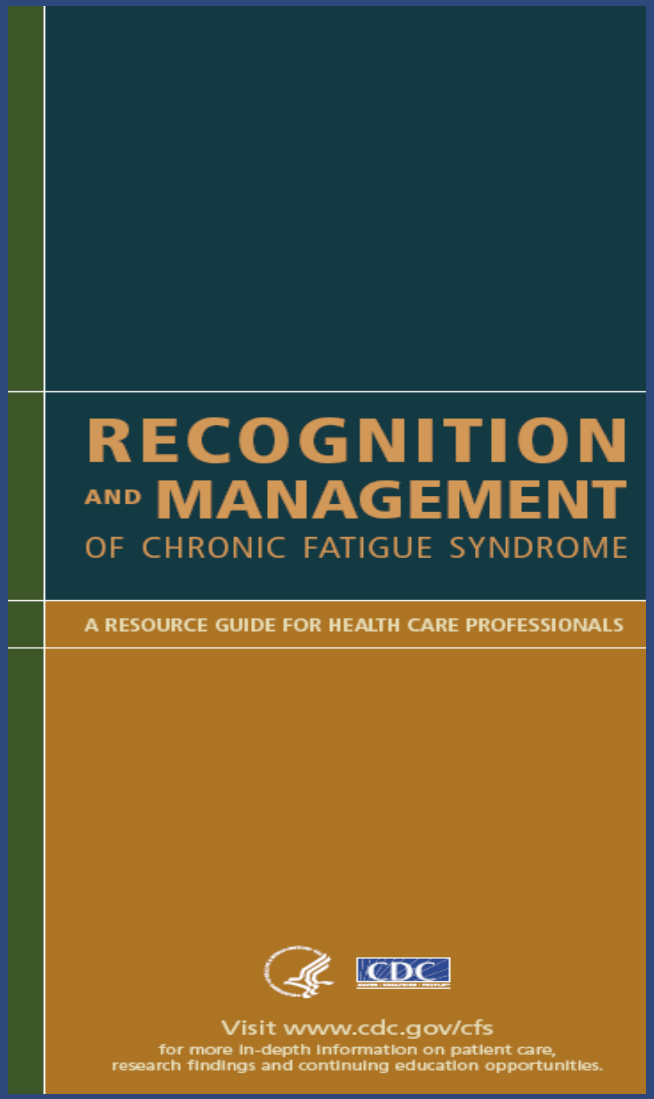
- Chronic Lyme Disease
- Chronic fatigue "CFS like"
- Nervous system
  - Pain
    - peripheral neuropathies
    - Headaches
  - Facial or Bell's palsy
  - Autonomic dysfunction [eg. POTS]
  - Fractured Sleep
  - Neuropsychiatric-bipolar, depression, panic
  - Cognitive impairment
  - Potentially Parkinsons, ALS and MS "like"
- Arthritis/Arthralgias
  - often in different joints and "migratory"

Lyme Disease Clinical Presentation

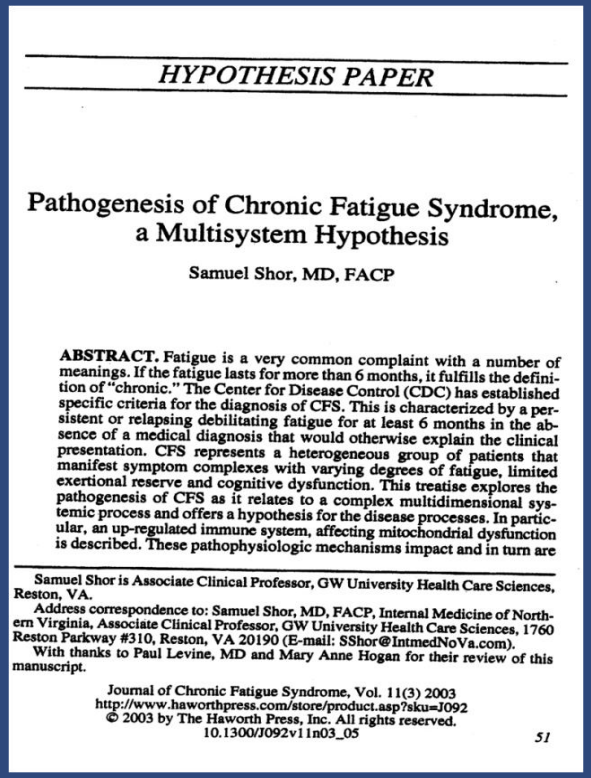
- If left untreated-expanding literature supported:
- Chronic Lyme Disease
- Chronic fatigue "CFS like"
- Nervous system
  - Pain
    - peripheral neuropathies
    - Headaches
  - Facial or Bell's palsy
  - Autonomic dysfunction [eg. POTS]
  - Fractured Nonrestorative Sleep
  - Neuropsychiatric-bipolar, depression, panic
  - Cognitive impairment
  - Potentially Parkinsons, ALS and MS "like"
- Arthritis/Arthralgias
  - often in different joints and "migratory"

Chronic Fatigue Syndrome

- Definition-
  - chronically fatiguing illness of unclear cause
  - lasting > 6 months
  - functional capacity < 50%
  - Other "causes of fatigue have been ruled out"
- Diagnosis of exclusion. There are no "markers" to define this condition.



Chronic Fatigue
Personal interest



HYPOTHESIS PAPER

Pathogenesis of Chronic Fatigue Syndrome, a Multisystem Hypothesis

Samuel Shor, MD, FACP

ABSTRACT. Fatigue is a very common complaint with a number of meanings. If the fatigue lasts for more than 6 months, it fulfills the definition of "chronic." The Center for Disease Control (CDC) has established specific criteria for the diagnosis of CFS. This is characterized by a persistent or relapsing debilitating fatigue for at least 6 months in the absence of a medical diagnosis that would otherwise explain the clinical presentation. CFS represents a heterogeneous group of patients that manifest symptom complexes with varying degrees of fatigue, limited exertional reserve and cognitive dysfunction. This treatise explores the pathogenesis of CFS as it relates to a complex multidimensional systemic process and offers a hypothesis for the disease processes. In particular, an up-regulated immune system, affecting mitochondrial dysfunction is described. These pathophysiologic mechanisms impact and in turn are

Samuel Shor is Associate Clinical Professor, GW University Health Care Sciences, Reston, VA.

Address correspondence to: Samuel Shor, MD, FACP, Internal Medicine of Northern Virginia, Associate Clinical Professor, GW University Health Care Sciences, 1760 Reston Parkway #310, Reston, VA 20190 (E-mail: SShor@IntmedNoVa.com).

With thanks to Paul Levine, MD and Mary Anne Hogan for their review of this manuscript.

Journal of Chronic Fatigue Syndrome, Vol. 11(3) 2003
http://www.haworthpress.com/store/product.asp?sku=J092

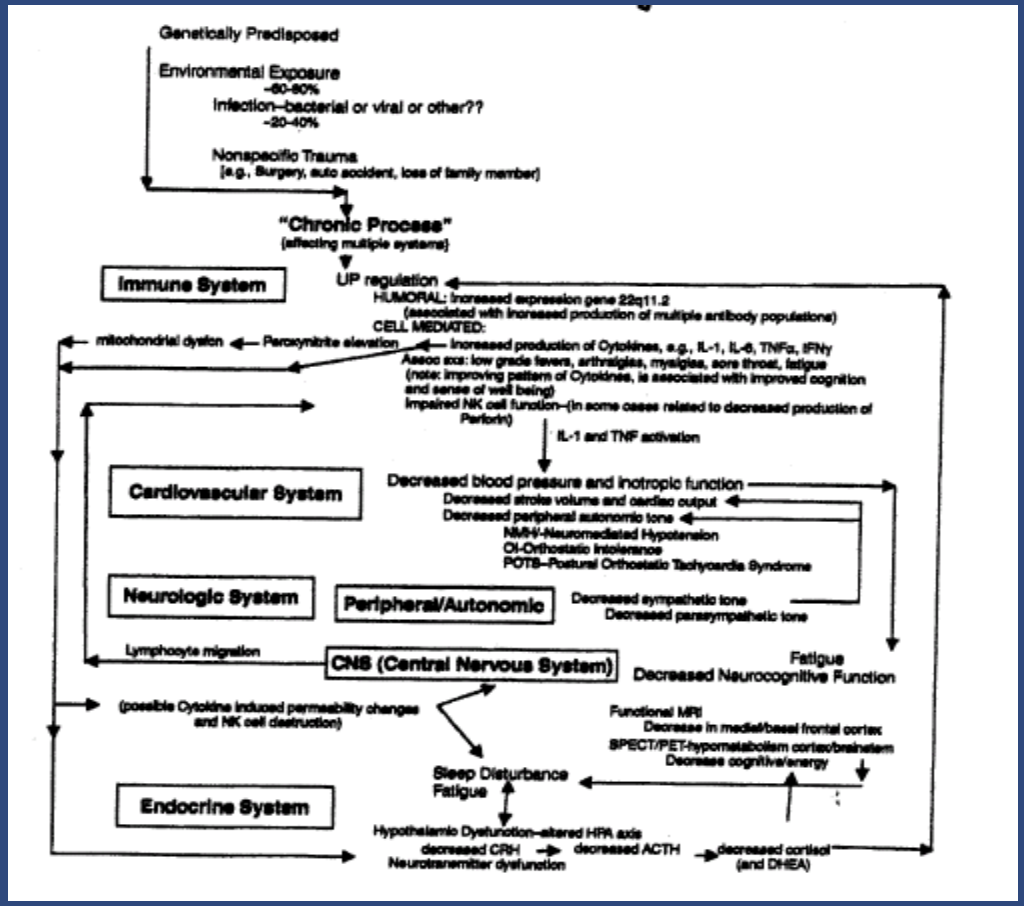
10.1300/J092v11n03_05

2003

Shor S Pathogenesis of Chronic Fatigue Syndrome, A Multisystem Hypothesis *Journal of Chronic Fatigue Syndrome* Vol. 11(3) 2003: 51-68

Chronic Fatigue Syndrome

Pathogenesis-A Multisystem Hypothesis



Shor S Pathogenesis of Chronic Fatigue Syndrome, A Multisystem Hypothesis *Journal of Chronic Fatigue Syndrome* Vol. 11(3) 2003: 51-68

CFS/?Lyme Clinically suggestive:

Chronic Fatigue Syndrome

Associated symptoms:

- Fatigue-lack of energy reserves and "post exertional malaise"
- Sleep disorders-nonrefreshing, fractured
- Fibromyalgia and pain
- Cognitive "fog"
- Hormone problems
  - adrenal dysfunction-"adrenal fatigue" low cortisol, often low DHEA, testosterone, etc
- Blood pressure - particularly upon standing with drops in blood pressure: "dysautonomias"
- Mood issues

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Chronic Lyme

Lyme Disease Clinical Presentation

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Lyme Disease
Clinical Presenation

Postural orthostatic tachycardia syndrome following Lyme disease

VIA MEDICA — ORIGINAL ARTICLE

Cardiology Journal 2011, Vol. 18, No. X, pp. 1–x
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ISSN 1897–5593

Postural orthostatic tachycardia syndrome following Lyme disease

Khalil Kanjwal, Beverly Karabin, Yousuf Kanjwal, Blair P. Grubb

Section of Electrophysiology, Division of Cardiology, Department of Medicine, The University of Toledo Medical Center, Toledo, USA

Abstract

Background: *A subgroup of patients suffering from Lyme disease (LD) may initially respond to antibiotics only to later develop a syndrome of fatigue, joint pain and cognitive dysfunction referred to as 'post treatment LD syndrome'. We report on a series of patients who developed autonomic dysfunction in the form of postural orthostatic tachycardia syndrome (POTS).*

Methods: *All of the patients in this report had suffered from LD in the past and were successfully treated with antibiotics. All patients were apparently well, until years later when they presented with fatigue, cognitive dysfunction and orthostatic intolerance. These patients were diagnosed with POTS on the basis of clinical features and results of the tilt table (HUTT) testing.*

Results: *Five patients (all women), aged 22–44 years, were identified for inclusion in this study. These patients developed symptoms of fatigue, cognitive dysfunction, orthostatic palpitations and either near syncope or frank syncope. The debilitating nature of these symptoms had resulted in lost of the employment or inability to attend school. Three patients were also suffering from migraine, two from anxiety and depression and one from hypertension. All patients demonstrated a good response to the employed treatment. Four of the five were able to engage in their activities of daily living and either resumed employment or returned to school.*

Conclusions: *In an appropriate clinical setting, evaluation for POTS in patients suffering from post LD syndrome may lead to early recognition and treatment, with subsequent improvement in symptoms of orthostatic intolerance.* (Cardiol J 2011; 18, x: xx–xx)

Key words: postural tachycardia, orthostatic intolerance, Lyme disease

Introduction

Lyme disease (LD), a tick-borne illness caused by the spirochete borellia burgdorferi, is the multi-system disorder that begins with erythema migrans and may later be followed by widespread complications which may involve the nervous system, cardiovascular system and musculoskeletal system [1, 2]. While most of these manifestations usually respond to antibiotic treatment, there is a subgroup of patients who later develop a syndrome of fatigue, joint pains and cognitive dysfunction known as 'post treatment LD syndrome' [3–5]. The post treatment LD syndrome has been reported to result in a substantial decline in the quality of life in affected patients [5]. We present a series of patients who suffered from LD and were successfully treated initially with antibiotics, but who later developed a syndrome of fatigue, cognitive dysfunction and symptoms of orthostatic intolerance (OI). Further investigation revealed that each of these patients was suffering from postural orthostatic tachycardia syndrome (POTS).

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Received: 16.06.2010 Accepted: 29.09.2010

2010

Khalil Kanjwal, Beverly Karabin, Yousuf Kanjwal, Blair P. Grubb Postural orthostatic tachycardia syndrome following Lyme disease Cardiology Journal 2011, Vol. 18, No. X pages 1-4

Lyme Disease Clinical Presentation

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  - Cognitive impairment
  - Potentially Parkinsons, ALS and MS "like"
- Arthritis/Arthralgias
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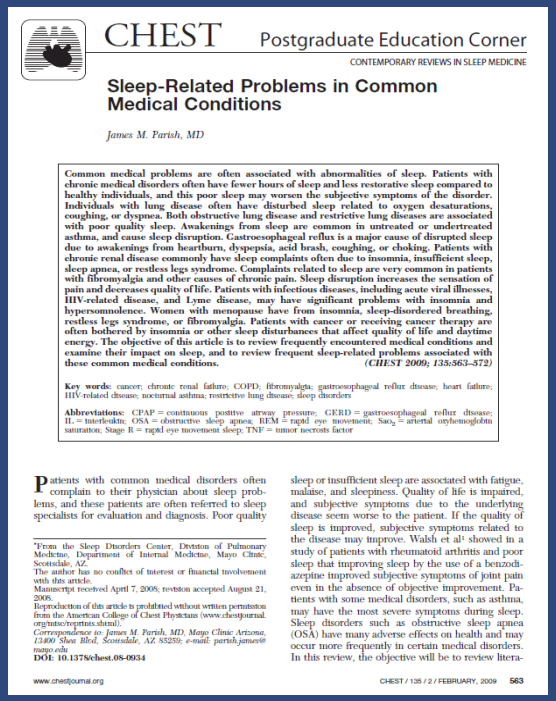
Lyme Disease
Clinical Presentation

"Patients with infectious diseases, including …Lyme disease, may have significant problems with insomnia and hypersomnolence."



CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN SLEEP MEDICINE

Sleep-Related Problems in Common Medical Conditions

James M. Parish, MD

Common medical problems are often associated with abnormalities of sleep. Patients with chronic medical disorders often have fewer hours of sleep and less restorative sleep compared to healthy individuals, and this poor sleep may worsen the subjective symptoms of the disorder. Individuals with lung disease often have disturbed sleep related to oxygen desaturations, coughing, or dyspnea. Both obstructive lung disease and restrictive lung diseases are associated with poor quality sleep. Awakenings from sleep are common in untreated or undertreated asthma, and cause sleep disruption. Gastroesophageal reflux is a major cause of disrupted sleep due to awakenings from heartburn, dyspepsia, acid brash, coughing, or choking. Patients with chronic renal disease commonly have sleep complaints often due to insomnia, insufficient sleep, sleep apnea, or restless legs syndrome. Complaints related to sleep are very common in patients with fibromyalgia and other causes of chronic pain. Sleep disruption increases the sensation of pain and decreases quality of life. Patients with infectious diseases, including acute viral illnesses, HIV-related disease, and Lyme disease, may have significant problems with insomnia and hypersomnolence. Women with menopause have from insomnia, sleep-disordered breathing, restless legs syndrome, or fibromyalgia. Patients with cancer or receiving cancer therapy are often bothered by insomnia or other sleep disturbances that affect quality of life and daytime energy. The objective of this article is to review frequently encountered medical conditions and examine their impact on sleep, and to review frequent sleep-related problems associated with these common medical conditions. ***(CHEST 2009; 135:563–572)***

Key words: cancer; chronic renal failure; COPD; fibromyalgia; gastroesophageal reflux disease; heart failure; HIV-related disease; nocturnal asthma; restrictive lung disease; sleep disorders

Abbreviations: CPAP = continuous positive airway pressure; GERD = gastroesophageal reflux disease; IL = interleukin; OSA = obstructive sleep apnea; REM = rapid eye movement; Sao_2 = arterial oxyhemoglobin saturation; Stage R = rapid eye movement sleep; TNF = tumor necrosis factor

Patients with common medical disorders often complain to their physician about sleep problems, and these patients are often referred to sleep specialists for evaluation and diagnosis. Poor quality sleep or insufficient sleep are associated with fatigue, malaise, and sleepiness. Quality of life is impaired, and subjective symptoms due to the underlying disease seem worse to the patient. If the quality of sleep is improved, subjective symptoms related to the disease may improve. Walsh et al[1] showed in a study of patients with rheumatoid arthritis and poor sleep that improving sleep by the use of a benzodiazepine improved subjective symptoms of joint pain even in the absence of objective improvement. Patients with some medical disorders, such as asthma, may have the most severe symptoms during sleep. Sleep disorders such as obstructive sleep apnea (OSA) have many adverse effects on health and may occur more frequently in certain medical disorders. In this review, the objective will be to review litera-

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Parish JM Sleep-related problems in common medical conditions. Chest. 2009 Feb;135(2):563-72.

Lyme Disease Clinical Presentation

If left untreated/inadequately treated:

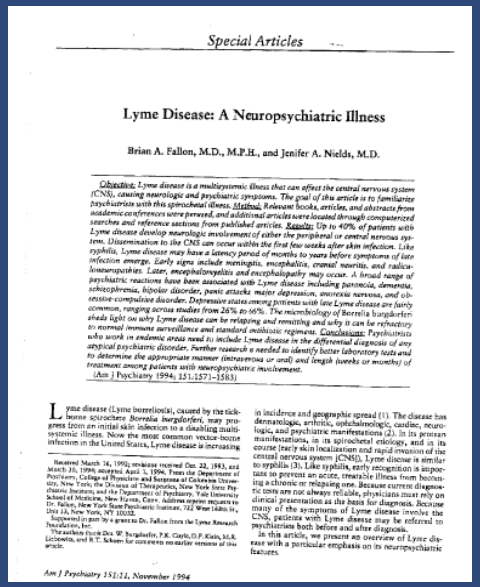
- Chronic Lyme Disease
- Chronic fatigue "CFS like"
- Nervous system
  - Pain
    - peripheral neuropathies
    - Headaches
  - Facial or Bell's palsy
  - Autonomic dysfunction [eg. POTS]
  - Fractured Sleep
  - Neuropsychiatric-bipolar, depression, panic
  - Cognitive impairment
  - Potentially Parkinsons, ALS and MS "like"
- Arthritis/Arthralgias
  - often in different joints and "migratory"

Lyme Disease

Presentation-if left untreated

Lyme Disease: A Neuropsychiatric Illness

"…psychiatric reactions have been associated with Lyme Disease including paranoia, dementia, schizophrenia, bipolar disorder, panic attacks, major depression, anorexia nervosa and obssessive-compulsive disorder….."



Special Articles

Lyme Disease: A Neuropsychiatric Illness

Brian A. Fallon, M.D., M.P.H., and Jenifer A. Nields, M.D.

Objective: Lyme disease is a multisystemic illness that can affect the central nervous system (CNS), causing neurologic and psychiatric symptoms. The goal of this article is to familiarize psychiatrists with this spirochetal illness. *Method:* Relevant books, articles, and abstracts from academic conferences were perused, and additional articles were located through computerized searches and reference sections from published articles. *Results:* Up to 40% of patients with Lyme disease develop neurologic involvement of either the peripheral or central nervous system. Dissemination to the CNS can occur within the first few weeks after skin infection. Like syphilis, Lyme disease may have a latency period of months to years before symptoms of late infection emerge. Early signs include meningitis, encephalitis, cranial neuritis, and radiculoneuropathies. Later, encephalomyelitis and encephalopathy may occur. A broad range of psychiatric reactions have been associated with Lyme disease including paranoia, dementia, schizophrenia, bipolar disorder, panic attacks, major depression, anorexia nervosa, and obsessive-compulsive disorder. Depressive states among patients with late Lyme disease are fairly common, ranging across studies from 26% to 66%. The microbiology of Borrelia burgdorferi sheds light on why Lyme disease can be relapsing and remitting and why it can be refractory to normal immune surveillance and standard antibiotic regimens. *Conclusions:* Psychiatrists who work in endemic areas need to include Lyme disease in the differential diagnosis of any atypical psychiatric disorder. Further research is needed to identify better laboratory tests and to determine the appropriate manner (intravenous or oral) and length (weeks or months) of treatment among patients with neuropsychiatric involvement.
(Am J Psychiatry 1994; 151:1571–1583)

Lyme disease (Lyme borreliosis), caused by the tick-borne spirochete *Borrelia burgdorferi*, may progress from an initial skin infection to a disabling multisystemic illness. Now the most common vector-borne infection in the United States, Lyme disease is increasing in incidence and geographic spread (1). The disease has dermatologic, arthritic, ophthalmologic, cardiac, neurologic, and psychiatric manifestations (2). In its protean manifestations, in its spirochetal etiology, and in its course (early skin localization and rapid invasion of the central nervous system [CNS]), Lyme disease is similar to syphilis (3). Like syphilis, early recognition is important to prevent an acute, treatable illness from becoming a chronic or relapsing one. Because current diagnostic tests are not always reliable, physicians must rely on clinical presentation as the basis for diagnosis. Because many of the symptoms of Lyme disease involve the CNS, patients with Lyme disease may be referred to psychiatrists both before and after diagnosis.

In this article, we present an overview of Lyme disease with a particular emphasis on its neuropsychiatric features.

Received March 16, 1994; revision received Oct. 22, 1993, and March 10, 1994; accepted April 5, 1994. From the Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York; the Division of Therapeutics, New York State Psychiatric Institute; and the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn. Address reprint requests to Dr. Fallon, New York State Psychiatric Institute, 722 West 168th St., Unit 24, New York, NY 10032.

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The authors thank Drs. W. Burgdorfer, P.K. Coyle, D.P. Klein, M.S. Liebowitz, and R.T. Schoen for comments on earlier versions of this article.

1994

Fallon BA, Nields JA Lyme Disease A Neuropsychiatric Illness *Am J Psychiatry* 151:11, Nov 1994 1571-1583

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  - Potentially Parkinsons, ALS and MS "like"
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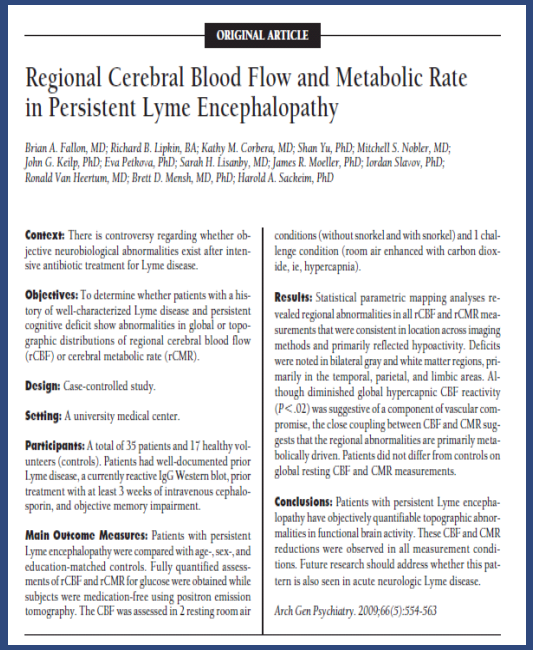
  - often in different joints and "migratory"

Lyme Disease
Clinical Presentation
Cognitive impairment



ORIGINAL ARTICLE

Regional Cerebral Blood Flow and Metabolic Rate in Persistent Lyme Encephalopathy

Brian A. Fallon, MD; Richard B. Lipkin, BA; Kathy M. Corbera, MD; Shan Yu, PhD; Mitchell S. Nobler, MD; John G. Keilp, PhD; Eva Petkova, PhD; Sarah H. Lisanby, MD; James R. Moeller, PhD; Iordan Slavov, PhD; Ronald Van Heertum, MD; Brett D. Mensh, MD, PhD; Harold A. Sackeim, PhD

Context: There is controversy regarding whether objective neurobiological abnormalities exist after intensive antibiotic treatment for Lyme disease.

Objectives: To determine whether patients with a history of well-characterized Lyme disease and persistent cognitive deficit show abnormalities in global or topographic distributions of regional cerebral blood flow (rCBF) or cerebral metabolic rate (rCMR).

Design: Case-controlled study.

Setting: A university medical center.

Participants: A total of 35 patients and 17 healthy volunteers (controls). Patients had well-documented prior Lyme disease, a currently reactive IgG Western blot, prior treatment with at least 3 weeks of intravenous cephalosporin, and objective memory impairment.

Main Outcome Measures: Patients with persistent Lyme encephalopathy were compared with age-, sex-, and education-matched controls. Fully quantified assessments of rCBF and rCMR for glucose were obtained while subjects were medication-free using positron emission tomography. The CBF was assessed in 2 resting room air conditions (without snorkel and with snorkel) and 1 challenge condition (room air enhanced with carbon dioxide, ie, hypercapnia).

Results: Statistical parametric mapping analyses revealed regional abnormalities in all rCBF and rCMR measurements that were consistent in location across imaging methods and primarily reflected hypoactivity. Deficits were noted in bilateral gray and white matter regions, primarily in the temporal, parietal, and limbic areas. Although diminished global hypercapnic CBF reactivity ($P < .02$) was suggestive of a component of vascular compromise, the close coupling between CBF and CMR suggests that the regional abnormalities are primarily metabolically driven. Patients did not differ from controls on global resting CBF and CMR measurements.

Conclusions: Patients with persistent Lyme encephalopathy have objectively quantifiable topographic abnormalities in functional brain activity. These CBF and CMR reductions were observed in all measurement conditions. Future research should address whether this pattern is also seen in acute neurologic Lyme disease.

Arch Gen Psychiatry. 2009;66(5):554-563

Fallon BA, Linkin RB, Corbera KM, Yu S, Nobler MS, Keilp JG, Petkova E, Lisanby SH, Moeller JR, Slavov I, Van Heertum R, Mensh BD, Sackeim HA Regional cerebral blood flow and metabolic rate in persistent Lyme encephalopathy. Arch Gen Psychiatry 2009 May;66(5):554-63.

CFS/?Lyme
CONCEPT: Clinically suggestive:

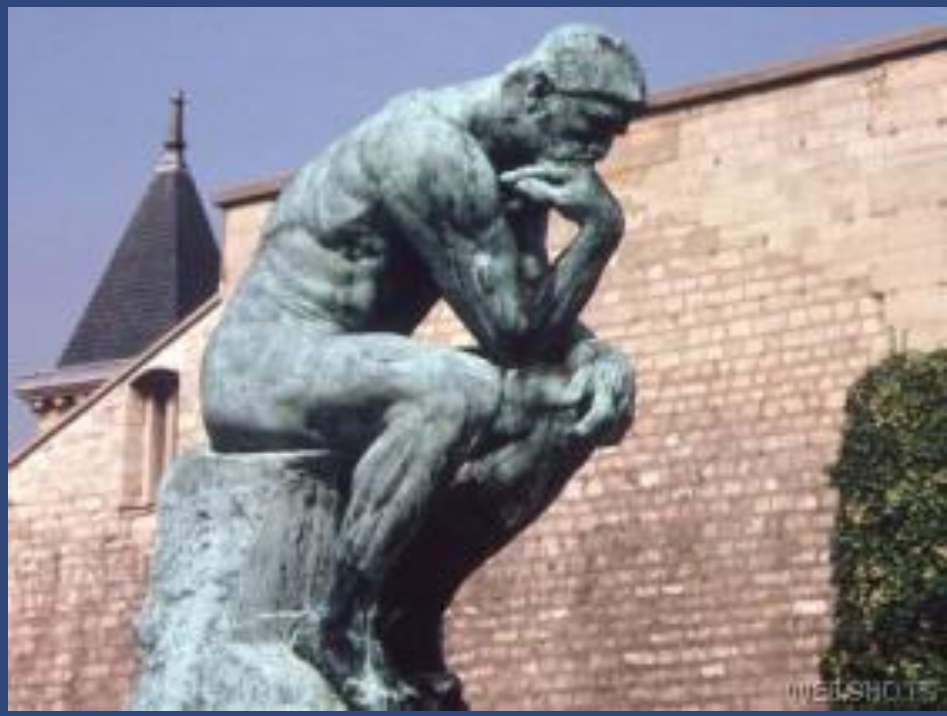
Chronic Fatigue Syndrome

Associated symptoms:

- Fatigue-lack of energy reserves and "post exertional malaise"
- Sleep disorders- nonrefreshing, fractured
- Fibromyalgia and pain
- Cognitive "fog"
- Hormone problems
  - adrenal dysfunction- "adrenal fatigue" low cortisol, often low DHEA, testosterone, etc
- Blood pressure - particularly upon standing with drops in blood pressure: "dysautonomias"
- Mood issues

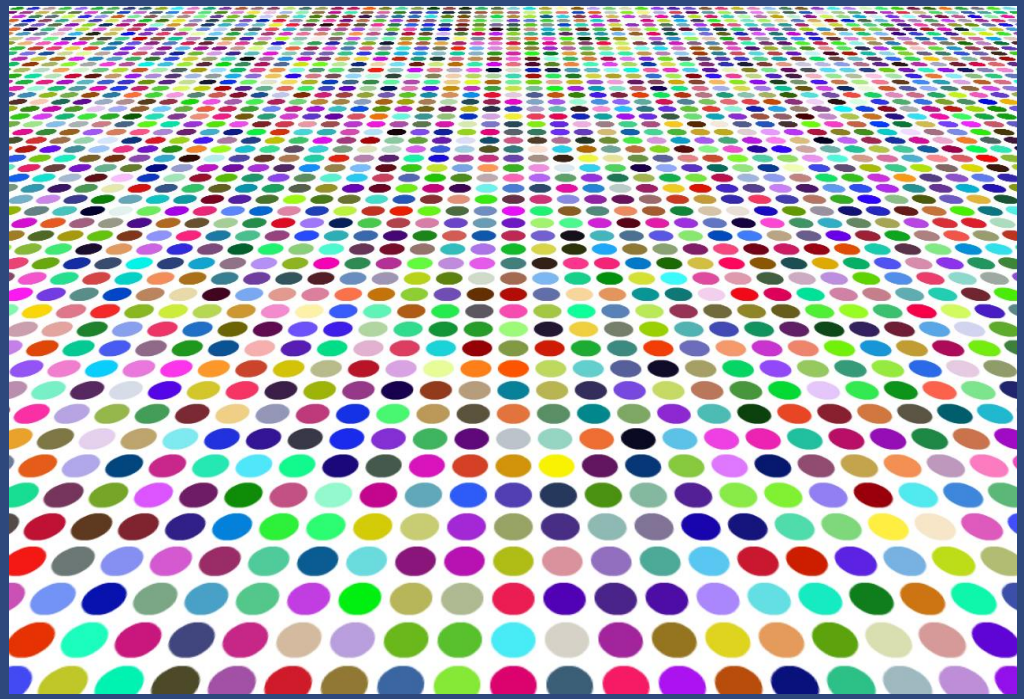
Chronic Lyme

Chronic Fatigue/Lyme disease
challenging complex



Think Outside the Box

Chronic Fatigue Syndrome
Lyme Disease
"Connecting the Dots"



Chronic Fatigue Syndrome
Defined

- Fatiguing illness of unknown etiology
- >6 months
- Functional capacity of <50% premorbid state
- Such that other causes of chronic fatigue have been "ruled out" [including Lyme disease]

Commonwealth of Virginia
The Governor's Task Force on Lyme Disease

There is no serological test that can "rule out" Lyme disease.

LYME DISEASE AND CHRONIC FATIGUE SYNDROME IS THERE A RELATIONSHIP?

Could ACTIVE Lyme disease **CAUSE** some cases of CFS?

Lyme Disease/CFS
Original peer review published data

Test Hypothesis:

- That a cohort of CFS patients actually have perpetuation of symptoms in part due to ongoing occult "seronegative" Lyme disease
- In essence, active "seronegative" Lyme disease

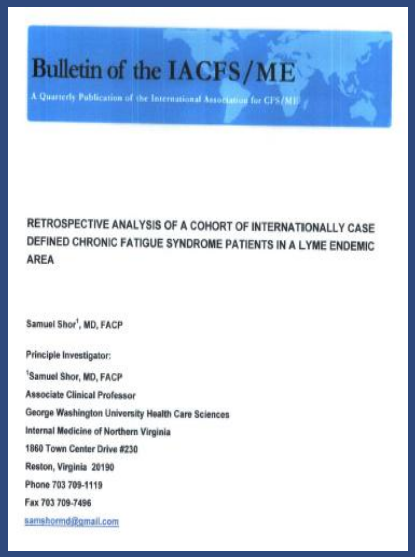
Need to assess this possible relationship

Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123

"Seronegative" Lyme Disease presenting as Chronic Fatigue Syndrome

March 2011

Peer reviewed
Original research



Bulletin of the IACFS/ME

A Quarterly Publication of the International Association for CFS/ME

RETROSPECTIVE ANALYSIS OF A COHORT OF INTERNATIONALLY CASE DEFINED CHRONIC FATIGUE SYNDROME PATIENTS IN A LYME ENDEMIC AREA

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Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123

CFS/Lyme
Retrospective/Observational Study

- Define the study population
  - International Case Defined CFS
    - Including negative Lyme "two tiered" criteria
  - "seronegative" Lyme-
    - POSITIVE alternative criteria

Presence ANY highly specific band 23-25,31,34,39,83-93	Presence of ANY co-infection	Low CD57

- Response to therapeutic intervention

CFS/Lyme
Original peer review published data

Analysis of PI patients	N
International Case Defined CFS	**210**

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- Response to therapeutic intervention

CFS/Lyme
Original peer review published data

Analysis of PI patients	N	% total
International Case Defined CFS	210	100%
"seronegative" Bb screen, **POSITIVE alternative criteria for POSSIBLE Dx**	**209**	**99%**

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CFS/Lyme
Retrospective/Observational Study

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- Response to therapeutic intervention

Chronic Fatigue Syndrome/?Lyme
Due Diligence:

Risk Benefit Analysis

Metric with which to assess response

Chronic Fatigue Syndrome/?Lyme
Due Diligence:
Risk Benefit assessment

- Risks
  - Side effects and drug interactions
  - Potential for drug resistance with wider use of antibiotics
- Benefits
  - Assumptions: that there is an appropriate indication
  - Potential for improved outcomes

Test Hypothesis: Lyme/CFS

METRIC-response to therapeutic intervention

- Initial small test population
- Track clinical response to intervention:
- Symptom questionnaires completed at <u>each</u> office visit, in an attempt to "quantify" subjective symptomotology contemporaneously.
- The more symptoms present, the higher the score.

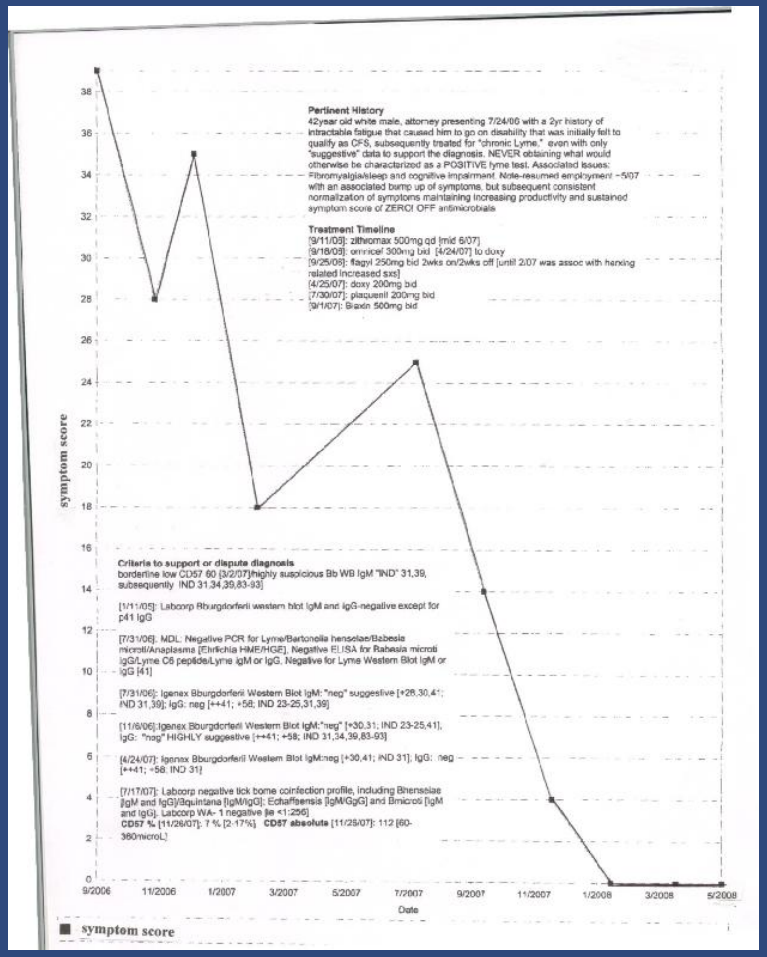
Symptom Severity Score since your last visit, or at the time of this visit if this is your first visit here: 0-none, 1 mild, 2 moderate, 3 severe				
Symptom:	0	1	2	3
unexplained fevers, sweats, chills or flushing				
unexplained weight change [loss or gain]				
fatigue, tiredness, poor stamina				
unexplained hair loss				
swollen glands				
sore throat				
testicular or pelvic pain				
unexplained menstrual irregularity				
irritable bladder or bladder dysfunction				
unexplained milk production or breast pain				
sexual dysfunction or loss of libido [sex drive]				
upset stomach or abdominal pain				
changes in bowel function-constipation and/or diarrhea				
chest pain or rib soreness				
shortness of breath or cough				
heart palpitations or skipping heart				
stiffness of the back				
muscle pain or cramps				
twitching of face or other muscles				
headache				
neck stiffness or pain				
tingling,numbness,shooting pains and/or skin sensitivities				
facial paralysis or Bell's Palsy				
joint pain or swelling				
vision problems-double, blurry, increased floaters and/or light senitivity				
ear or hearing problems-buzzing, ringing, ear pain, sound sensitivity				
motion sickness, vertigo and/or poor balance				
lightheadedness, wooziness, unavoidable need to sit down				
tremor				
confusion and/or difficulty thinking				
difficulty with concentration and/or reading				
forgetfullness,short term memory loss,poor attention and/or problems absorbing information				
disorientation, getting lost and/or going to wrong places				
difficulty with speech, or writing or name blocking				
mood swings, irritability and/or depression				
disturbed sleep-too much,too little,frequent awakening and/or early awakening				
TOTAL [Score]				
present antibiotic regimen:				
miscellaneous comments:				

CFS/Lyme case studies

No evidence of "CDC/IDSA criteria" for diagnosis of Lyme disease

Case study #1: 42 year old lawyer on disability for 2 years

- Dx: CFS, subsequently "chronic Lyme"
- NEVER meeting "CDC criteria" for the diagnosis,
- Directed antibiotics for ~15 months: now working full time and OFF all other "supportive" medication:



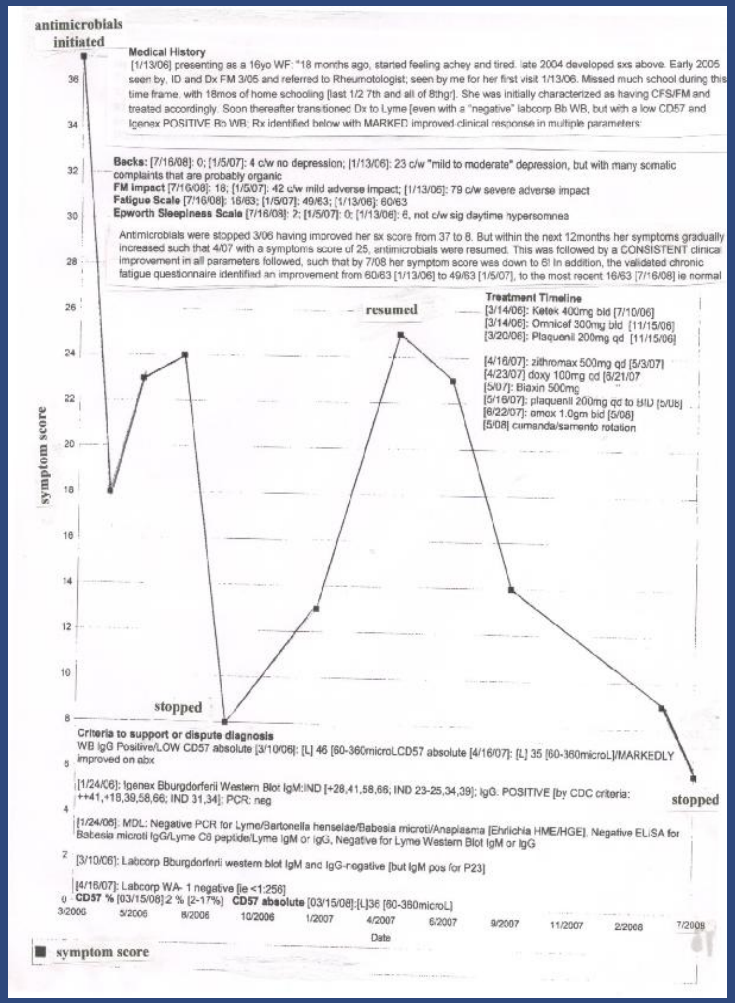
CFS/Lyme case studies

No evidence of "CDC/IDSA criteria" for diagnosis of Lyme disease

Case study #2

16 year female with Dx of CFS/FM preliminary studies "CDC criteria" negative

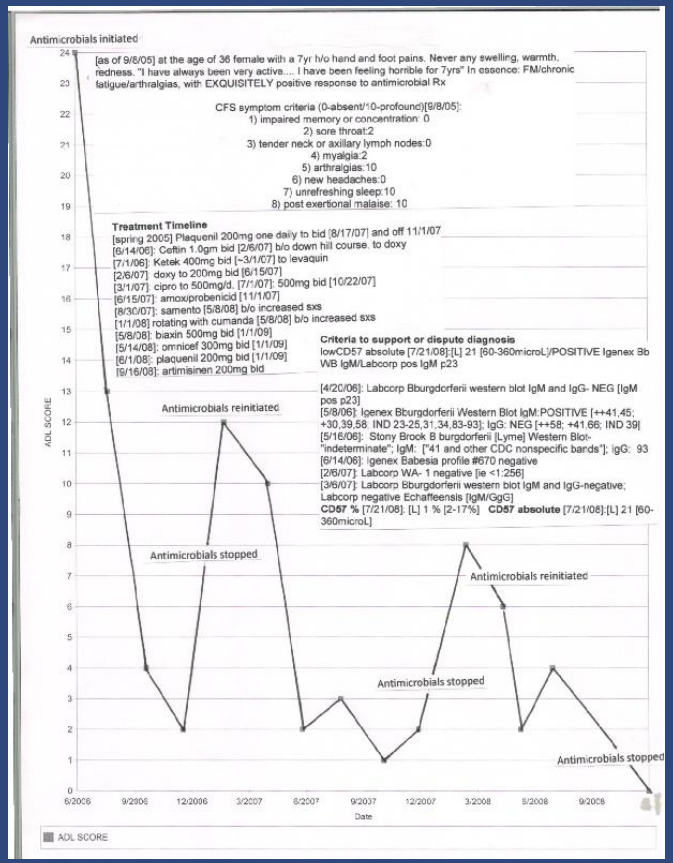
- Subsequently characterized with Lyme disease using "alternative criteria"
- Initial positive response to antimicrobials
- Worsening when antimicrobials were stopped, without known re-exposure.
- Normalization of symptoms when antimicrobials were resumed.



CFS/Lyme case studies

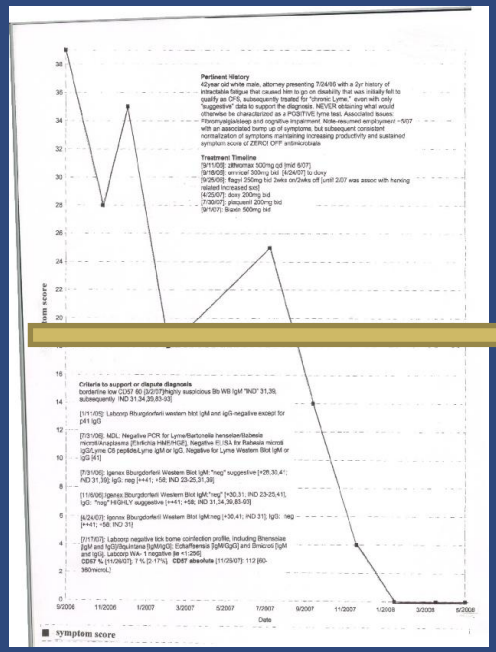
No evidence of "CDC/IDSA criteria" for diagnosis of Lyme disease

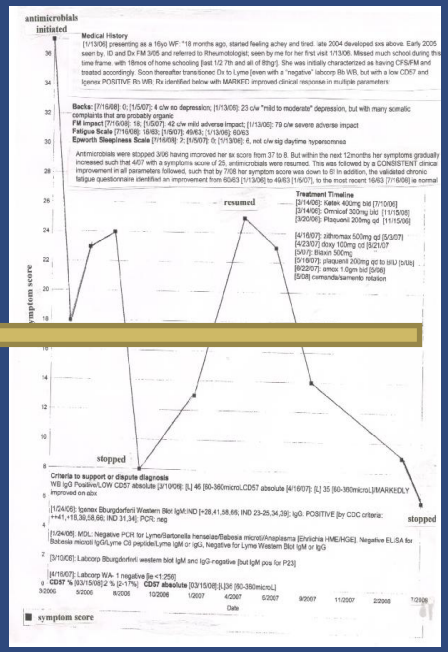
- Case study #3: 36 year female with 7hr h/o hand and foot pain
- Responsive to initial course abx
- Recurrence same symptom complex x 2
- each time
  - without new exposure
  - Responsive to re treatment



"Chronic Fatigue Syndrome"
?Seronegative Lyme
Response to Antibiotics

Goal>50% improvement in symptom score





i.e. ultimate score <50% of high score

CFS/Lyme

Original peer review published data

Analysis of PI patients	N	% total	% seronegative Lyme patients
International Case Defined CFS	210	100%	
"seronegative" Bb screen, POSITIVE alternative criteria	209	99%	100%
equal to or > **50% clinical improvement**	130		**62%**
<50% improvement but still clinically significant	55		26%
Total clinically significant improvement	185		**88%**

Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123

Moving towards validation of Chronic Lyme Disease

Case Series

Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area

S. Shor

George Washington University Health Care Sciences
Reston, Virginia, USA

62%-88% of 209 CFS patients

"…. with what would otherwise be consistent with internationally case defined CFS in a Lyme endemic environment actually have a perpetuation of their symptoms driven by a [sero negative] persistent infection by *Borrelia burgdorferi*…."

Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123

Lyme Disease Presenting as CFS
Potential Limitations

- Possible selection bias
- Retrospective/Observational study
- Placebo effect
- "anti-inflammatory"effect of antibiotics

Lyme Disease Presenting as CFS
Potential Limitations

- Possible selection bias
  - in seeking a clinician known to have expertise in chronic fatigue and Lyme disease
  - Lyme endemic region
    - However:
      - Expanding "endemic" regions
      - Mobile population

Lyme Disease Presenting as CFS
Potential Limitations

- Possible selection bias
- Retrospective/Observational study
- Placebo effect
- "anti-inflammatory" effect of antibiotics

Lyme Disease Presenting as CFS
Potential Limitations

- Observational study
  - Limitations
    - not randomized
    - Or controlling of confounding variables
    - Often include additional intervention to treat other issues such as sleep, pain, etc
  - Value: "….usually DO provide valid information." [1]
  - Helpful to direct "real life" insight
    - but may not be as valid as carefully performed prospective placebo controlled research

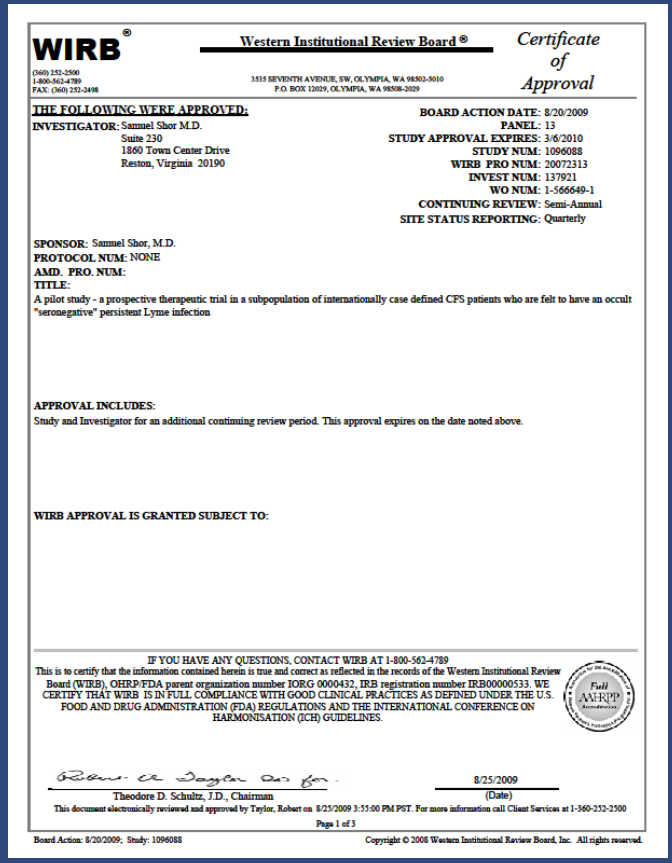
[1] Benson K and Hartz AJ *A Comparison of Observational Studies and Randomized Controlled Trials* N Engl J Med 2000;342:1878-86]

CFS/Lyme

Proposed prospective, placebo controlled interventional trial

Shor, S A pilot study - a prospective therapeutic trial in a subpopulation of internationally case defined CFS patients who are felt to have an occult "seronegative" persistent Lyme infection WIRB Study # 1096088

NIH application pursued- not funded



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FAX: (360) 252-2498

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P.O. BOX 12029, OLYMPIA, WA 98508-2029

Certificate of Approval

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: Samuel Shor M.D.
Suite 230
1860 Town Center Drive
Reston, Virginia 20190

BOARD ACTION DATE: 8/20/2009
PANEL: 13
STUDY APPROVAL EXPIRES: 3/6/2010
STUDY NUM: 1096088
WIRB PRO NUM: 20072313
INVEST NUM: 137921
WO NUM: 1-566649-1
CONTINUING REVIEW: Semi-Annual
SITE STATUS REPORTING: Quarterly

SPONSOR: Samuel Shor, M.D.
PROTOCOL NUM: NONE
AMD. PRO. NUM:
TITLE:
A pilot study - a prospective therapeutic trial in a subpopulation of internationally case defined CFS patients who are felt to have an occult "seronegative" persistent Lyme infection

APPROVAL INCLUDES:
Study and Investigator for an additional continuing review period. This approval expires on the date noted above.

WIRB APPROVAL IS GRANTED SUBJECT TO:

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789
This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB), OHRP/FDA parent organization number IORG 0000432, IRB registration number IRB00000533. WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Full AAHRPP Accreditation

Theodore D. Schultz, J.D., Chairman

8/25/2009
(Date)

This document electronically reviewed and approved by Taylor, Robert on 8/25/2009 3:55:00 PM PST. For more information call Client Services at 1-360-252-2500

Page 1 of 3

Board Action: 8/20/2009; Study: 1096088

Lyme Disease Presenting as CFS
Potential Limitations

- Possible selection bias
- Retrospective/Observational study
- Placebo effect
- "anti-inflammatory" effect of antibiotics

Lyme Disease Presenting as CFS
Potential Limitations

- Placebo effect
  - probably has some effect
  - HOWEVER, how does one reconcile:
    - Normalization of profuse sweating?
    - or an improvement in the hemodynamics of blood pressure and heart rate in a patient with postural orthostatic tachycardic syndrome?

Lyme Disease Presenting as CFS
Potential Limitations

- Possible selection bias
- Retrospective/Observational study
- Placebo effect
- "anti-inflammatory" effect of antibiotics

Lyme Disease Presenting as CFS
Potential Limitations

?Impact of antimicrobial anti-inflammatory effect:

How does one reconcile the frequently associated Jarisch-Herxheimer reaction?

i.e. an associated crescendoing POST antibiotic PRO-inflammatory response

Pound MW, May DB Proposed mechanisms and preventative options of Jarisch-Herxheimer reactions *Journal of Clnical Pharmacy and Therapeutics* (2005) 30,291-295

See S, , Scott EK,, and Levin MW, Penicillin-Induced Jarisch-Herxheimer Reaction Published Online, www.theannals.com *The Annals of Pharmacotherapy*: 15 November 2005 Vol. 39, No. 12, pp. 2128-2130.

Lyme Disease Presenting as CFS
Concern: prolonged antimicrobials

Precedence :

- *Mycobacterium tuberculosis* treated for 6-18 months with multiple agents (1)
- Nontuberculous mycobacteria such as *Mycobacterium marinum* are likely to require at least 6months of treatment (2)
  - disseminated *Mycobacterium chelona* treatment may involve a combination of oral and intravenous antibiotics administered for 6 to 12 months (3)
- Hansen's Disease [Leprosy] protocols are for up to 2 years (4-6)

1. Small PM, Fujiwara PI Management of tuberculosis in the USA N. Engl. J. Med. 345, 189-200 (2001)
2. Cummins DL, Delacerda D, Tausk FA. Mycobacterium marinum with different responses to second-generation tetracyclines. Int J Dermatol 2005;44:518-20. Int J Dermatol. 2005 Jun;44(6):518-20.
3. Wallace RJ Jr, Tanner D, Brennan PJ., Brown BA. Clinical trial of clarithromycin for cutaneous (disseminated) infection due to *Mycobacterium chelona*. *Ann. Intern. Med* (1993) 119, 482-486
4. Shaw IN, Natrajan MM, Rao GS, Jesudasan K, Christain M, Kavitha M Long-term follow up of multibacillary leprosy patients with high BI treated with WHO/MDT regimen for a fixed duration of 2yrs. Int. J. Lepr. Other Mycobact. Dis. 2000, 68, 405-409
5. Goto M, Nogami R, Hatano K, Okano Y, , Gidoh M, Ishida Y, Ozaki M; ad hoc committee on treatment guideline and judgment of cure, Japanese Leprosy. Guideline for the treatment of Hansen's disease in Japan (Second edition). Nihon Hansenbyo Gakkai Zasshi. 2006 Sep;75(3):191-226.
6. Goto M. Chemotherapy of leprosy: theoretical basis of new guideline in Japan. Nihon Hansenbyo Gakkai Zasshi (2001)70, 151-155

Lyme Disease Presenting as CFS Precautions

Prolonged antimicrobial therapy

- Risk of resistance
- Side effects of drugs
  - Including Cdiff colitis

Lyme Disease Presenting as CFS Precautions

Prolonged antimicrobial therapy

A careful risk/benefit analysis needs to be performed at the point of care

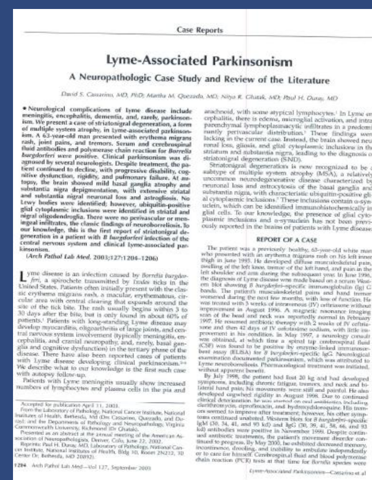
NEED to avoid indiscriminant use of antimicrobials

Lyme Disease
Clinical Presentation

- If left untreated-expanding literature supported:
- Chronic Lyme disease
- Chronic fatigue "CFS like"
- Nervous system
  - Pain
    - peripheral neuropathies
    - Headaches
  - Facial or Bell's palsy
  - Autonomic dysfunction [eg. POTS]
  - Fractured Nonrestorative Sleep
  - Neuropsychiatric-bipolar, depression, panic
  - Cognitive impairment
  - Potentially Parkinsons, ALS and MS "like"
- Arthritis
  - often in different joints and "migratory"

Lyme Disease
Clinical Presentation

Lyme-Associated Parkinsonism

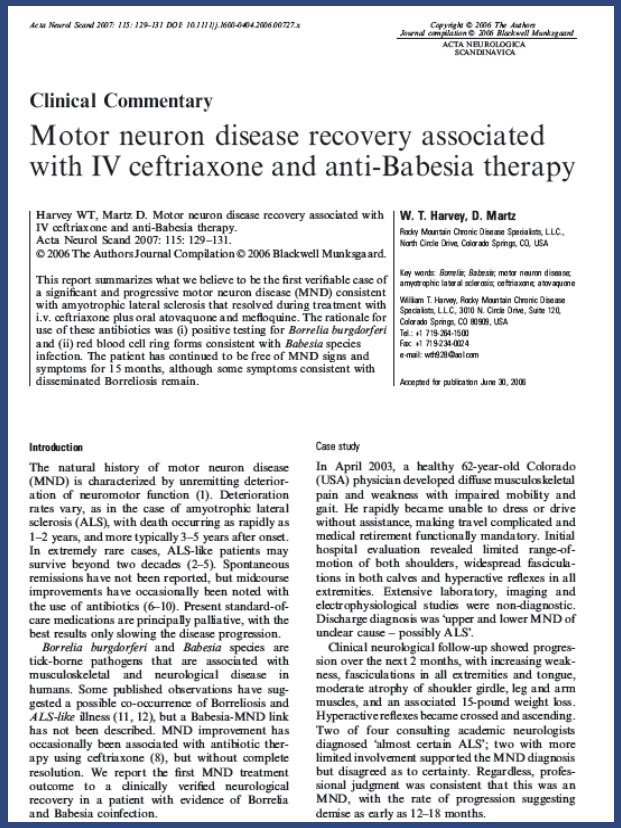

Case Reports

Lyme-Associated Parkinsonism

A Neuropathologic Case Study and Review of the Literature

1. David S. Cassarino, MD, PhD; Martha M. Quezado, MD; Nitya R. Ghatak, MD; Paul H. Duray, MD Lyme-Associated Parkinsonism A Neuropathologic Case Study and Review of the Literature Arch Pathol Lab Med—Vol 127, September 2003
2. Kuntzer T, Bogousslavsky J, Miklossy J, et al Borrelia rhombencephalomyelopathy. *Arch Neurol.* 1991; 48:832-836
3. Kobayashi K, Mizukoshi C, Aok T, et al Borrelia burgdorferi-seropositive chronic encephalomyelopathy: Lyme neruoborreliosis? An autopsied report. Depigment *Geriatr Cogn Disord.* 1997; 8: 384-390
4. Bertrand E, Szpak GM, Pilkowska E, et al. Central nervous system infection caused by Borrelia burgdorfer: clinic-pathological correlation of three post-mortem case. *Folia Neuropathol.* 1999; 37: 43-51
5. Kohlepp W, Kuhn W, Kruger H. Extrapyramidal features in Lyme borreliosis. *Eur Neurol.* 1989; 29: 150-155.
6. Cadavid D, O'Neill T, Schaerfer H, Pachner AR. Localization of Borrelia burgdoerferi in the nervous system and other organs in a nonhuman primate model of Lyme disease. *Lab Invest.* 2000;80:1043-1054

Lyme Disease
Clinical Presentation
ALS-Motor Neuron Disease



Acta Neurol Scand 2007: 115: 129–131 DOI: 10.1111/j.1600-0404.2006.00727.x

ACTA NEUROLOGICA
SCANDINAVICA

Clinical Commentary

Motor neuron disease recovery associated with IV ceftriaxone and anti-Babesia therapy

Harvey WT, Martz D. Motor neuron disease recovery associated with IV ceftriaxone and anti-Babesia therapy.
Acta Neurol Scand 2007: 115: 129–131.

This report summarizes what we believe to be the first verifiable case of a significant and progressive motor neuron disease (MND) consistent with amyotrophic lateral sclerosis that resolved during treatment with i.v. ceftriaxone plus oral atovaquone and mefloquine. The rationale for use of these antibiotics was (i) positive testing for *Borrelia burgdorferi* and (ii) red blood cell ring forms consistent with *Babesia* species infection. The patient has continued to be free of MND signs and symptoms for 15 months, although some symptoms consistent with disseminated Borreliosis remain.

W. T. Harvey, D. Martz
Rocky Mountain Chronic Disease Specialists, L.L.C., North Circle Drive, Colorado Springs, CO, USA

Key words: *Borrelia*; *Babesia*; motor neuron disease; amyotrophic lateral sclerosis; ceftriaxone; atovaquone

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Accepted for publication June 30, 2006

Introduction

The natural history of motor neuron disease (MND) is characterized by unremitting deterioration of neuromotor function (1). Deterioration rates vary, as in the case of amyotrophic lateral sclerosis (ALS), with death occurring as rapidly as 1–2 years, and more typically 3–5 years after onset. In extremely rare cases, ALS-like patients may survive beyond two decades (2–5). Spontaneous remissions have not been reported, but midcourse improvements have occasionally been noted with the use of antibiotics (6–10). Present standard-of-care medications are principally palliative, with the best results only slowing the disease progression.

Borrelia burgdorferi and *Babesia* species are tick-borne pathogens that are associated with musculoskeletal and neurological disease in humans. Some published observations have suggested a possible co-occurrence of Borreliosis and *ALS-like* illness (11, 12), but a Babesia-MND link has not been described. MND improvement has occasionally been associated with antibiotic therapy using ceftriaxone (8), but without complete resolution. We report the first MND treatment outcome to a clinically verified neurological recovery in a patient with evidence of Borrelia and Babesia coinfection.

Case study

In April 2003, a healthy 62-year-old Colorado (USA) physician developed diffuse musculoskeletal pain and weakness with impaired mobility and gait. He rapidly became unable to dress or drive without assistance, making travel complicated and medical retirement functionally mandatory. Initial hospital evaluation revealed limited range-of-motion of both shoulders, widespread fasciculations in both calves and hyperactive reflexes in all extremities. Extensive laboratory, imaging and electrophysiological studies were non-diagnostic. Discharge diagnosis was 'upper and lower MND of unclear cause – possibly ALS'.

Clinical neurological follow-up showed progression over the next 2 months, with increasing weakness, fasciculations in all extremities and tongue, moderate atrophy of shoulder girdle, leg and arm muscles, and an associated 15-pound weight loss. Hyperactive reflexes became crossed and ascending. Two of four consulting academic neurologists diagnosed 'almost certain ALS'; two with more limited involvement supported the MND diagnosis but disagreed as to certainty. Regardless, professional judgment was consistent that this was an MND, with the rate of progression suggesting demise as early as 12–18 months.

Harvey WT, Martz DMotor neuron disease recovery associated with IV ceftriaxone and anti-Babesia therapy. Acta Neurol Sand. 2007 Feb;115(2):129-31.

LYME DISEASE
EVIDENCE BASED-STATE OF ART

Personal interest-chronic fatigue
Historical perspective
Basics
Governor's Task Force on Lyme disease

"State of the Art" the literature:
Diagnostic criteria-concept of seronegativity
Clinical presentations-additional/Chronic Lyme
Treatment issues

LYME DISEASE
TREATMENT

Lyme disease is treatable if detected early

Lyme Disease Treatment

What is adequate?

Controversies

IDSA

"There is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease*"

*the longest duration of recommended treatment: 28days

IDSA GUIDELINES

The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

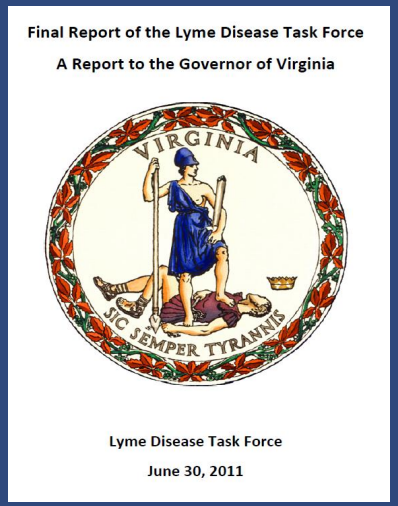
EXECUTIVE SUMMARY

Background

Wormser PG et al The Clinical Assessment, Treatment and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babebiosis: Clinical Practice Guidelines by the Infectious Disease Society of America *CID* 2006:43 (1 November) 1089-1134

Commonwealth of Virginia
The Governor's Task Force on Lyme Disease
Treatment

We received substantial testimony from lay witnesses that they had been successfully treated with long-term antibiotics.



Lyme Disease Treatment
What is the Evidence?
"There is no benefit to the use of long term antibiotics"

Based upon 3 NIH funded prospective trials:

- **Klempner MS, et al** Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001 Jul 12;345(2):85-92
- **Krupp LB, et al** Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30
- **Fallon BA et al**A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2007 Oct 10;

Lyme Disease Treatment

"There is no benefit to the use of long term antibiotics"

Statement based on 3 prospective placebo controlled studies, for a total of 221 patients

- **Klempner MS et al:**
  - **seropositive to Bb IgG** **78**
  - **Seronegative to Bb IgG** **51**
  - **Total in this study** **129**
- **Krupp LB et al:** **55**
- **Fallon BA et al:** **37**

total: **221**

1. Klempner MS, et al Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001 Jul 12;345(2):85-92
2. Krupp LB, et al Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30
3. Fallon BA et alA randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2007 Oct 10;

Lyme Disease Treatment

"it is unlikely that prolonged antibiotic treatment will offer any major benefit to symptomatic patients who are no longer infectious"

Klempner MS et al

Design:

seropositive to Bb IgG 78

seronegative toBb IgG 51

[h/o validated EM]

Total in this study 129

4 wks ceftriaxone then 2 months doxycycline vs placebo

ANTIBIOTIC TREATMENT IN PATIENTS WITH PERSISTENT SYMPTOMS AND A HISTORY OF LYME DISEASE

TWO CONTROLLED TRIALS OF ANTIBIOTIC TREATMENT IN PATIENTS WITH PERSISTENT SYMPTOMS AND A HISTORY OF LYME DISEASE

MARK S. KLEMPNER, M.D., LINDEN T. HU, M.D., JANINE EVANS, M.D., CHRISTOPHER H. SCHMID, PH.D., GARY M. JOHNSON, RICHARD P. TREVINO, B.S., DELONA NORTON, M.P.H., LOIS LEVY, M.S.W., DIANE WALL, R.N., JOHN MCCALL, MARK KOSINSKI, M.A., AND ARTHUR WEINSTEIN, M.D.

ABSTRACT

Background It is controversial whether prolonged antibiotic treatment is effective for patients in whom symptoms persist after the recommended antibiotic treatment for acute Lyme disease.

Methods We conducted two randomized trials: one in 78 patients who were seropositive for IgG antibodies to *Borrelia burgdorferi* at the time of enrollment and the other in 51 patients who were seronegative. The patients received either intravenous ceftriaxone, 2 g daily for 30 days, followed by oral doxycycline, 200 mg daily for 60 days, or matching intravenous and oral placebos. Each patient had well-documented, previously treated Lyme disease but had persistent musculoskeletal pain, neurocognitive symptoms, or dysesthesia, often associated with fatigue. The primary outcome measures were improvement on the physical- and mental-health–component summary scales of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) — a scale measuring the health-related quality of life — on day 180 of the study.

Results After a planned interim analysis, the data and safety monitoring board recommended that the studies be discontinued because data from the first 107 patients indicated that it was highly unlikely that a significant difference in treatment efficacy between the groups would be observed with the planned full enrollment of 260 patients. Base-line assessments documented severe impairment in the patients' health-related quality of life. In intention-to-treat analyses, there were no significant differences in the outcomes with prolonged antibiotic treatment as compared with placebo among either the seropositive or the seronegative patients.

Conclusions There is considerable impairment of health-related quality of life among patients with persistent symptoms despite previous antibiotic treatment for acute Lyme disease. However, in these two trials, treatment with intravenous and oral antibiotics for 90 days did not improve symptoms more than placebo. (N Engl J Med 2001;345:85-92.)

ANTIBIOTIC treatment is highly effective for the acute and late septic manifestations of Lyme disease, which is caused by the tick-borne bacterium *Borrelia burgdorferi*.[1] However, some patients have persistent fatigue, myalgias, arthralgias without arthritis, dysesthesias or paresthesias, or mood and memory disturbances after the standard courses of antibiotics.[2,3] Persistent symptoms have been reported both in patients who are seropositive for antibodies against *B. burgdorferi* and in patients who are seronegative. Although the cause of persistent symptoms has not been determined, their temporal association with *B. burgdorferi* infection has led some physicians to treat patients with prolonged courses of antibiotics. Case reports and uncontrolled trials describe success with prolonged antibiotic therapy, often with a recurrence of the symptoms after the discontinuation of therapy.[4] In view of the substantial morbidity and even death[5] associated with prolonged parenteral antibiotic treatment of Lyme disease, it is important to determine the efficacy of such therapy. We report results from randomized, placebo-controlled, double-blind trials of antibiotic therapy in seropositive and seronegative patients who had chronic symptoms after treatment for Lyme disease.

METHODS

Patients

Patients were recruited by means of advertisements and referrals from physicians. Between July 24, 1997, and November 14, 2000, eligible patients were enrolled in two double-blind, placebo-controlled trials, each conducted at three sites. Patients with a positive Western blot for IgG antibodies against *B. burgdorferi* antigens[6] were enrolled in a study of seropositive patients, and patients who were seronegative were enrolled in a separate study. Seronegative patients were required to have documentation of an erythema migrans skin lesion provided by an experienced physician. We initially planned to enroll 260 patients in the studies (194 seropositive and 66 seronegative patients). Patients were eligible if they were at least 18 years old, had a history of acute Lyme disease acquired in the United States, and had at least one of the following: a history of single or multiple erythema migrans skin lesions, early neurologic or cardiac symptoms attributed to Lyme disease, radiculoneuropathy, or Lyme arthritis. Documentation by a physician of previous treatment of acute Lyme disease with a recommended antibiotic regimen was also required. At the time of enrollment, all patients had one or more of the following symptoms that interfered with their functioning: widespread musculoskeletal pain, cognitive impairment, radicular pain, paresthesias, or dysesthesias. Profound fatigue often accompanied one or more of these symptoms. The chronic symptoms had to have begun within 6 months after the initial infection with *B. burgdorferi* and had to have persisted for at least 6 months but less than 12 years.

From New England Medical Center and Tufts University School of Medicine, Boston (M.S.K., L.T.H., C.H.S., G.M.J., R.P.T., J.M.); Yale–New Haven Hospital, New Haven, Conn. (J.E., D.W.); New York Medical College, Valhalla (D.N., L.L., A.W.); and Quality Metric, Lincoln, R.I. (M.K.). Address reprint requests to Dr. Klempner at the Departments of Medicine, Boston University School of Medicine, 715 Albany St., Boston, MA 02118, or at klempner@bu.edu.

Because of its potential importance in the treatment of Lyme disease, this article was published at www.nejm.org on June 12, 2001.

Lyme Disease Treatment
Persistence of Infection

2012 study:
12 Rhesus monkeys

Treated with equivalent regimen in Klempner human study

Evidence of adequate MICs of ceftriaxone and doxycycline

Embers ME, Barthold SW, Borda JT, Bowers L, Doyle L, Hodzic E, Jacobs MB, Hasenkampf NR, Martin DS, Narasimhan S, Phillippi-Falkenstein KM, Purcell JE, Ratterree MS, Philipp MT. Persistence of *Borrelia burgdorferi* in rhesus macaques following antibiotic treatment of disseminated infection. PLoS One. 2012;7(1):e29914. Epub 2012 Jan 11.

Lyme Disease Treatment
Persistence of Infection

12/12 POSITIVE skin CULTURE 4wks after treatment

"These results demonstrate that *B. burgdorferi* can withstand antibiotic treatment, administered post dissemination, in a primate host."

Embers ME, Barthold SW, Borda JT, Bowers L, Doyle L, Hodzic E, Jacobs MB, Hasenkampf NR, Martin DS, Narasimhan S, Phillippi-Falkenstein KM, Purcell JE, Ratterree MS, Philipp MT. Persistence of *Borrelia burgdorferi* in rhesus macaques following antibiotic treatment of disseminated infection. PLoS One. 2012;7(1):e29914. Epub 2012 Jan 11.

Lyme Disease Treatment
Klempner MS et al

Flaws in design and interpretation
?selection bias ?Study generalizability

- Patients had been ill for an average of 4.7 years
- Previously failed an average of 3 courses of abx
  - often including the protocol employed

1. Cameron DJ. Generalizability in two clinical trials of Lyme disease. Epidemiol Perspect Innov. 2006 Oct 17;3:12.
2. Bransfield R, Brand S, Sherr V. Treatment of patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001 Nov 8;345(19):1424-5.
3. Donta ST. Treatment of patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001 Nov 8;345(19):1424.
4. McCaulley ME. Treatment of patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001 Nov 8;345(19):1424

Lyme Disease Treatment
Klempner MS et al

Choice of "prolonged" antibiotic therapy for patients with neurologic disease (1 month of IV Ceftriaxone followed by 2 months of low-dose oral doxycycline)

- May not have been long enough?
- Nor sufficiently bacteriacidal for patients with deep seated neurologic disease?

1. Bransfield R, Brand S, Sherr V. Treatment of patients with persistent symptoms and a history of Lyme disease *N. Engl. J. Med.* 345,1424-1425 (2001)
2. Phillips SE, Bransfield R, Sherr VT et al. Evaluation of antibiotic treatment in patients with persistent symptoms of Lyme disease: an ILADS position paper www.ilads.org March 2005

Lyme Disease Treatment
Implications of restrictive guidelines

- Patients may not be receiving adequate management
- Insurance companies using this to restrict care

> Lay witnesses stated that long term treatment of Lyme disease is often not covered by their insurance carriers and that they can spend thousands of dollars per month for their treatment plan. The extent to which this is occurring is unknown to the Task Force and the Task Force recommends that this issue be evaluated by the Bureau of Insurance.

Lyme disease
Evidence based-State of the Art
In summary

- **Chronic Lyme disease**

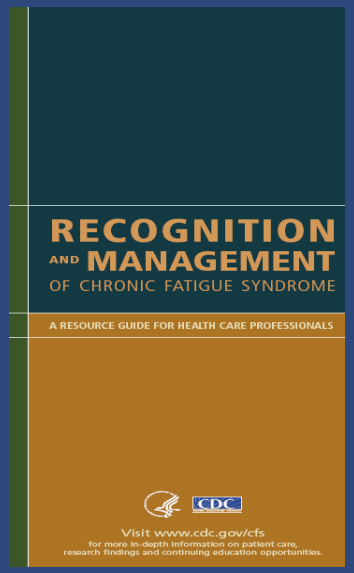
  does this really exist?
- Chronic fatigue "CFS like"
- Nervous system
  - Pain
    - peripheral neuropathies
    - Headaches
  - Facial or Bell's palsy
  - Autonomic dysfunction [eg. POTS]
  - Fractured Nonrestorative Sleep
  - Neuropsychiatric-bipolar, depression, panic
  - Cognitive impairment
  - Potentially Parkinsons, ALS and MS "like"
- Arthritis/Arthralgias
  - often in different joints and "migratory"

Chronic Lyme Disease-does it exist?
Precedence:
Chronic Fatigue Syndrome

Still an unaccepted diagnosis by many

However, now acknowledged by:

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION



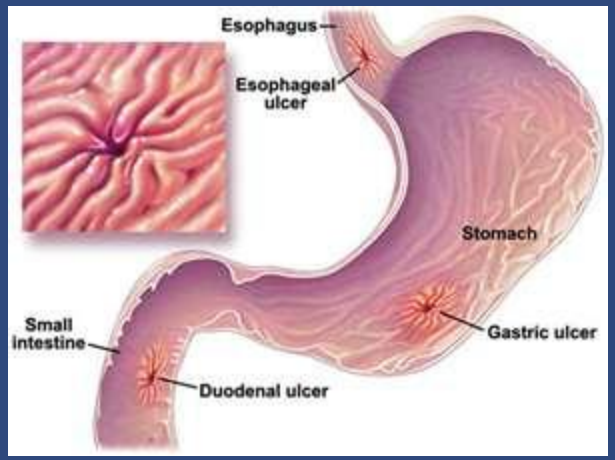
PRECEDENCE: *HELICOBACTER PYLORI*

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

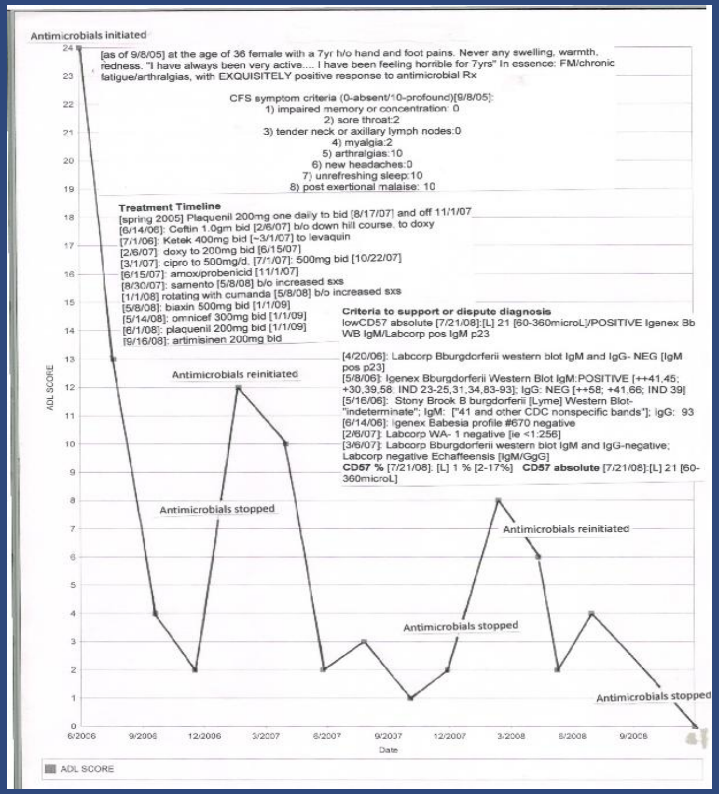
http://www.cdc.gov/ulcer/keytocure.htm

"we now know that most ulcers are caused by *H. pylori*…."

:



Chronic Lyme disease does it exist? Plethora of Anecdotal Evidence:



Chronic Lyme disease
Does it exist?

Lyme disease can CLEARLY be associated with chronic symptoms

Chronic Lyme disease Does it exist?

Associated symptoms:

- Fatigue-lack of energy reserves and "post exertional malaise"
- Sleep disorders- nonrefreshing, fractured
- Fibromyalgia and pain
- Cognitive "fog"
- Hormone problems
  - adrenal dysfunction- "adrenal fatigue" low cortisol, often low DHEA, testosterone, etc
- Blood pressure - particularly upon standing with drops in blood pressure: "dysautonomias"
- Mood issues

Chronic Lyme

Chronic Lyme disease does it exist? Peer reviewed observational study

Case Series

Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area

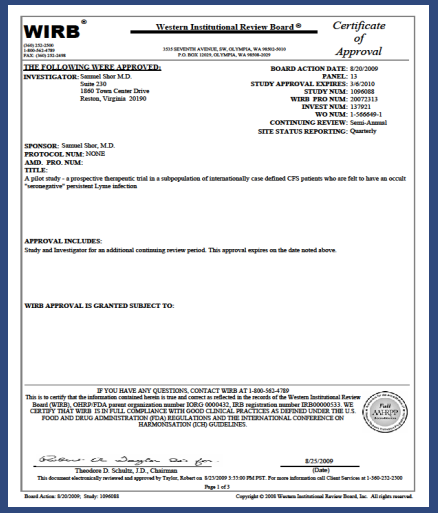
S. Shor

George Washington University Health Care Sciences
Reston, Virginia, USA

Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123

Chronic Lyme disease
Should it be treated?
Clinical Judgment

Do we withhold therapy while trying to obtain prospective, placebo controlled research?



WIRB®

Western Institutional Review Board®

Certificate of Approval

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: Samuel Shor M.D.
Suite 230
1860 Town Center Drive
Reston, Virginia 20190

BOARD ACTION DATE: 8/20/2009
PANEL: 13
STUDY APPROVAL EXPIRES: 3/6/2010
STUDY NUM: 1096088
WIRB PRO NUM: 20072313
INVEST NUM: 137921
WO NUM: 1-566649-1
CONTINUING REVIEW: Semi-Annual
SITE STATUS REPORTING: Quarterly

SPONSOR: Samuel Shor, M.D.
PROTOCOL NUM: NONE
AMD. PRO. NUM:
TITLE:
A pilot study - a prospective therapeutic trial in a subpopulation of internationally case defined CFS patients who are felt to have an occult "seronegative" persistent Lyme infection

APPROVAL INCLUDES:
Study and Investigator for an additional continuing review period. This approval expires on the date noted above.

WIRB APPROVAL IS GRANTED SUBJECT TO:

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789

This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB). OHRP/FDA parameters assigned to IORG 0000843, IRB registration number IRB00000533. WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Theodore D. Schultz, J.D., Chairman — 8/25/2009 (Date)

This document electronically reviewed and approved by Taylor, Robert on 8/25/2009 3:33:00 PM PDT. For more information call Client Services at 1-360-252-2500

Page 1 of 3

Board Action: 8/20/2009; Study: 1096088

Chronic Lyme disease Should it be treated?
Clinical Judgment

The "art of medicine":

Or do we assess each individual at the point of care, weighing the risks/benefits of treating OR NOT

1. Cameron DJ Consequences of treatment delay in Lyme disease Journal of Evaluation in Clinical Practice 13 (2007) 470–472
2. Cameron DJ Insufficient evidence to deny antibiotic treatment to chronic Lyme disease patients Medical Hypotheses 72 (2009) 688–691
3. Cameron DJ Research Article Proof That Chronic Lyme Disease Exists Interdisciplinary Perspectives on Infectious Diseases Volume 2010 1-4

LYME DISEASE
EVIDENCE BASED-STATE OF ART OVERVIEW

Personal interest-chronic fatigue
Historical perspective
Basics
Governor's Task Force on Lyme disease

"State of the Art" the literature:
Diagnostic criteria-concept of seronegativity
Clinical presentations-additional
Treatment issues-SUMMARY

LYME DISEASE
SHOULD AN INDIVIDUAL BE TREATED?

RISKS/BENEFITS:

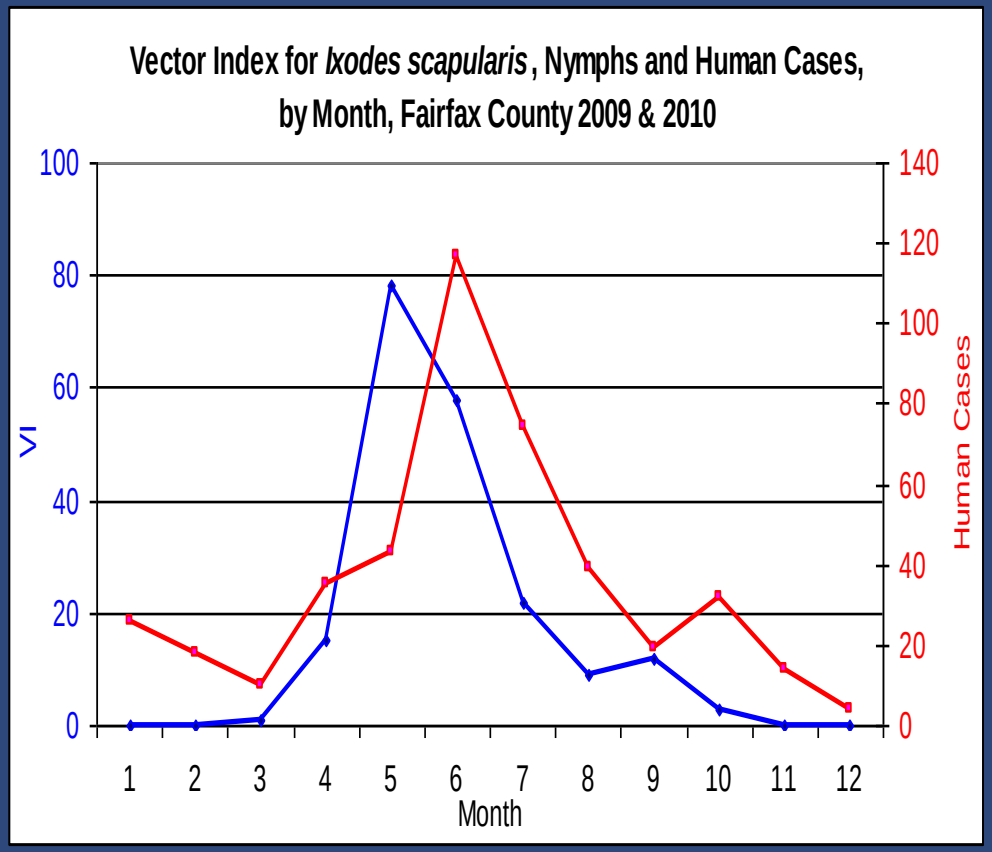
Assess Risks of exposure:

Season

Environmental history

Tick bite [don't need to have seen it]

Lyme disease
Local Epidemiology



LYME DISEASE
SHOULD AN INDIVIDUAL BE TREATED?

RISKS/BENEFITS:

CAVEATS: **If risk is high:**

- Do NOT "wait for a rash" 50% don't ever get
- Do NOT "wait for a positive blood test"
- Potentially ~50% negative, with real disease

- Treat if have high enough index of suspicion

LYME DISEASE
EVIDENCE BASED-STATE OF THE ART

Consider the following "pearls"

Don't be willing to accept a "negative blood test" if your clinical suspicions suggest otherwise

"no serology can rule out Lyme Disease"

Consider alternative testing when appropriate

LYME DISEASE
EVIDENCE BASED-STATE OF ART
UNMET NEEDS

- Reliable **diagnostic biomarkers**
  - Early detection of early disease
  - Identification of chronic disease
  - Determination ACTIVITY of disease
- Reliable, reproducible **treatment strategies**
  - Prophylaxis
  - Treatment of early disease
  - Treatment of late manifestations

LYME DISEASE
EVIDENCE BASED-STATE OF ART

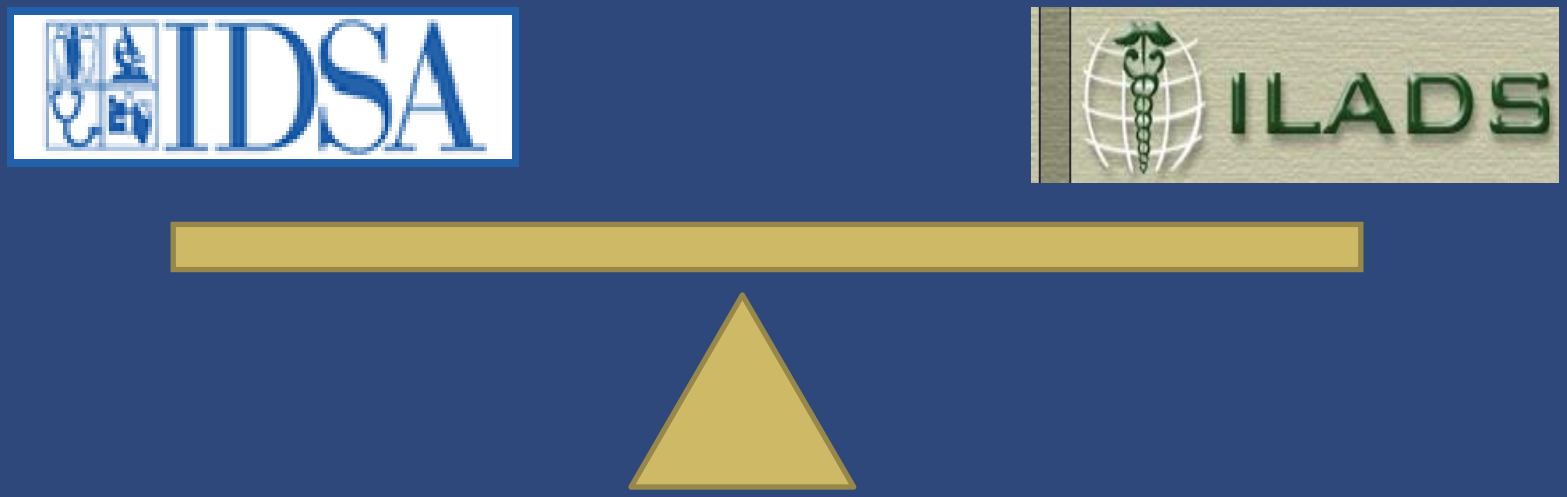
Until this technology/information is available:

Best Clinical Judgment:
Our best interpretation of the literature
Our best assessment at the point of care

In the meantime, guidelines are just that guidelines, NOT mandates

Lyme Disease
Where Does This Leave us?

Assimilate the literature and provide a balanced assessment of guidelines



LYME DISEASE
WHERE DOES THIS LEAVE US?
TWO SCHOOLS OF THOUGHT

Once recommendations are generated:

provide appropriate counseling and consent to the patient

In essence: that there are differing opinions as to interpretation of the literature

LYME DISEASE
EVIDENCE BASED-STATE OF ART OVERVIEW

Personal interest-chronic fatigue
Historical perspective
Basics
Governor's Task Force on Lyme disease
"State of the Art" the literature:
IDSA/ILADS
Diagnostic criteria-seronegativity/IgM
Clinical presentations-Chronic Lyme Disease
Treatment issues

Lyme Disease
Evidence Based-State of the Art
GOALS:

Increased awareness and education of both the medical and lay communities

This is an important step in that process

LYME DISEASE
EVIDENCE BASED-STATE OF THE ART

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