

Tick Borne Disease Basics

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Tick borne disease (TBD) recognition, evaluation, treatment and prevention has been controversial for decades. Consequences of unrecognized and inadequately treated tick borne diseases can be devastating. People lives can be dramatically affected by these infections. Careers, intellectual, athletic and musical pursuits, marriages, family relationships, even childhoods can be lost. TBD can create a lifetime of chronic illness.

Tick borne disease is an epidemic throughout all temperate zones as tick populations rise all over the world.

- Climactic change increasing tick habitat
- Changes in land use (suburbanization of previously rural areas)
- Deer population exploding which directly causes explosion in tick population

Ticks are hard to kill

- Active any time of year if temperature over 28°F
- Very high dryer heat for up to 60 minutes required to kill ticks

Jacobs, Steven, *Penn State Agricultural Sciences News* 11/23/05

Ticks appear to be becoming resistant to commonly used insecticides

- 10 years ago 0.5% permethrins killed ticks, now need up to 10%

History of Borrelia infection

- In 1909, Arvid Afzelius presented case history of Erythema chronicum migrans in a patient after *Ixodes reduvius* bite
- In 1920s through 1940s an association between EM rash and neurological symptoms (meningitis, meningoencephalitis, meningopolyneuritis) became apparent.
 - Dr. Sven Hellerstrom, Chair and Professor of Dermatology at Karolinska Institute in Sweden, was the first to suggest that the EM rash from tick bites caused a meningoencephalitis
- In 1969, dermatologist Dr. Rudolph Scrimenti had a 57-year-old physician come to him with headache, muscle pain, low-grade fever, radicular pain, fatigue and malaise in conjunction with an EM rash encircling the entire right side of his torso. The patient had reported removing a small, engorged tick prior to the illness.
- In 1975 Polly Miller brought the New England academic medical community's attention to a cluster of juvenile Rheumatoid Arthritis cases in Lyme, Connecticut.

Dammin, G.J. Erythema Migran: A Chronicle. *Reviews of Infectious Diseases* 1989; Vol 2 No1:142-151.

Scrimenti R.J. and Scrimenti, M. Lyme disease redux: the legacy of Sven Hellerstrom. *Wisconsin Medical Journal* January 1993; p.20-21.

Ticks are cesspools of disease

Many species of ticks carry disease, most notably members of the *Ixodes* genus. The three species we have on the east coast:

Ixodes scapularis deer tick

Dermacentor variabilis dog tick

Amblyomma americana lone star tick

Tick pathogens that infect humans:

- *Borrelia burgdorferi* (Bb), over 300 strains world wide, 100 in US
- Other *Borrelia* species (*garinii*, *afzelii*, others)
- *Babesia microti*, many *Babesia* sp. WA1, MO1, *B divergens*
- *Ehrlichia chaffeensis* or Human Monocytic Ehrlichia (HME)
- *Anaplasma phagocytophilum* or Human Granulocytic Anaplasmosis (HGA)
- *Bartonella henselae* (cat scratch fever) and other *Bartonella*-like organisms
- *Mycoplasma fermentans* (Gulf War Syndrome)
- *Rickettsia rickettsia* or Rocky Mountain Spotted Fever (RMSF)
- *Francisella tularensis*, or Tularemia
- Viruses (HHV-6) and ???

Tick Pathogens

- *Mycoplasma fermentans*
 - Ancient tiny intracellular pathogen
 - Contributes to chronic fatigue and neuropsychiatric symptoms
- *Ehrlichia chaffeensis* (Human Monocytic Ehrlichiosis)
 - Intracellular pathogen in monocytes
 - Very difficult to eradicate in TBD patients
- *Anaplasma phagocytophilum* (Human Granulocytic Anaplasmosis)
 - Intracellular pathogen in granulocytes
 - Synergistically suppresses host immune system with Bb infection
- *Bartonella henselae* and *Bartonella*-like organisms
 - Originally known as cat scratch fever, but infection from ticks seems a much more virulent infection that causes significant vasculitis, rashes of all kinds, abdominal pain and serious neuropsychiatric illnesses.
- *Babesia microti* and other *Babesia* species
 - Intra-erythrocytic pathogen similar to malaria
 - First described in US in 1969 in Nantucket, Mass.
 - Major cause of ongoing symptoms in patients with diagnosis of chronic Lyme disease
 - Can cause a chronic, recurring parasitemia which is hard to eradicate
 - Very complex life cycle
 - Can be acquired from blood transfusions as well as tick bites

- *Borrelia burgdorferi* (over 300 strains Bb world wide, 100 in US alone), as well as *B. afzelii* and *B. garinii* in Europe.
 - Spirochete which is the most complex bacterium known to man
 - Complex life cycle requiring multiple hosts
 - Mice, chipmunks and squirrels act as natural reservoir which transmit *Borrelia* sp. to larval ticks. Nymphal or adult ticks infect other species of small mammals, migrating birds, reptiles, deer, domestic animals and humans
 - Remarkably adapted to
 - Live in widely different hosts (arthropods, mammals, birds, and reptiles)
 - Defend against widely divergent host immune systems
 - Survive long periods of dormancy (starvation) inside tick guts (for years) waiting for tick to take a blood meal
 - Basic biology
 - Long life cycle with slow, microaerophilic growth
 - Over 1500 gene sequences that make up
 - 132 functioning genes (*Treponema pallidum* has only 22) with 21 plasmids (three times more than any other known bacteria) and 1 linear chromosome
 - Pathology
 - Disseminates very rapidly in the body
 - Enters all tissues of the body
 - Rapidly crosses the blood brain barrier
 - Can be cultured from spinal fluid within 24 hours of a tick bite
 - Can live inside neurons and glial cells in vitro
 - Crosses the placental barrier and can infect the fetus at any stage of pregnancy
 - Implicated in the round plaques of all neurodegenerative diseases
 - Bb DNA has been found in the pathognomonic granulo-vesicular bodies, fibrillary tangles and plaques of Alzheimer Disease brain tissue from the Harvard brain bank

Immune system evasion by *Borrelia burgdorferi*

- Begins at level of skin with tick saliva. Tick saliva has anti-inflammatory, anti-histaminic and analgesic properties as well as chemical signals to short circuit host innate immune responses.
- Morphological changes: from the spirochetal cell wall form to straightened non-coiled bacillary (or L) forms, cell wall deficient forms, granular and cystic forms
Mursic, et al., *Infection* 1996; 24: 218-26
 - Cystic forms are metabolically active and can be infective.
 - Cystic forms of Bb can revert back to motile spirochetes in vitro and in vivo (infecting mice) after freeze-thawing and being held in distilled water up to one month) Gruntar, et al., *APMIS* 2001; 109: 383-8
Brorson and Brorson *APMIS* 1998; 106:1131-41
 - Incubation of Bb from infected human cerebrospinal fluid in antibiotic solution transformed spirochetes into cysts that then were re-converted back into motile spirochetes in vitro
Brorson and Brorson *Infection* 1998; 26(3): 144-50
- Bb successfully infects immuno-privileged tissues
 - Extracellular sites: often immunologically privileged sites such as the CNS, iris, ligaments and joints. Bb can also cloak itself with host proteins.
Coleman and Benach, *Infect Immun* 2003; 71:5558-64
Coburn et al. *Mol Microbiol* 2005; 57:1182-95
 - Intracellular sites: Bb penetrates B lymphocytes, NK cells, synovial cells, endothelial cells, fibroblasts, macrophages, glial cells and neurons.

Study demonstrating Bb traverses human brain micro-vascular endothelial cells in vitro. Bb may be using the host fibrinolytic system to degrade tight junctions and facilitate penetration in to the CNS as it induces expression of plasminogen activators, plasminogen activator receptors and matrix metalloproteinases.

Grab, DJ et al., *Borrelia burgdorferi*, Host-Derived Proteases, and the Blood-Brain Barriers. *Infections and Immunity* Feb 2005; 73(2): 1014-1022

Very important recent study from the CDC:

“..demonstrated an intracellular localization of *B burgdorferi*. Cytopathic effects were not observed following infection of these cell lines with *B burgdorferi*, and internalized spirochetes were found to be viable.”

“..there were no observable adverse effects under microscopic observation of the infected cells. No cytopathic effects were apparent following 7 day incubation on any of the (infected) cell lines tested..”

Livengood, J. and Gilmore, R. Invasion of human neuronal and glial cells by an infectious strain of *Borrelia burgdorferi*. *Microbes and Infection* 2006; 8:2832-40

- Evades both innate and cell mediated immune systems defending itself from a wide array of host immune responses
 - Innate immune system
 - Bb inhibits the alternative complement pathway to avoid opsonization

- Binds factor H (a host complement inhibitory protein)
- Bb may produce protein that mimics CD59 or protectin
- Cell mediated immune system
 - Bb induces production of IL-10, key inhibitory regulator inflammatory cytokines (e.g. TNF-alpha, INF-gamma), by lymphocytes and macrophages
 - Bb may induce tolerization of mononuclear cells
 - Bb may tie up host antibodies by releasing soluble antigens (in blebs) allowing for the formation of antigen:antibody immune complexes
 - Phase variation: switching between two phenotypes, turning gene expression on or off, which can be random, programmed or modulated by environmental cues
 - Antigenic variation: programmed changes in protein structure that lead to variation in protein antigenicity of those proteins that are targets of host protective immune responses as well as sequential expression of multiple different forms of antigenic surface proteins, permitting the organism to keep one step ahead of host immune response

Very important study showing that anti TNF-alpha treatment allows Bb to persist in mice despite treatment with IV ceftriaxone.

Vrjanainen, H. et al. Anti-Tumor Necrosis Factor-alpha Treatment Activates *Borrelia burgdorferi* Spirochetes 4 Weeks after Ceftriaxone Treatment in C3H/He Mice. *Journal of Infectious Diseases* 2007; 189(5):1489-96

“In Lyme disease *Borrelia*, antigenic variation involves segmental gene conversion...The recombination events have been detected as early as 4 days after infection of mice and appear to occur continuously during infections. As a result, mammals could harbour thousands of different variants at any one time, resulting in altered epitopes and confounding efforts by the immune response to keep up with the sequence variation.”

Norris, Steven J. Antigenic variation with a twist - the *Borrelia* story. *Molecular Microbiology* 2006;60(6);1319-1322

“Individual strains of Bb have been found to contain large arrays of prophage-encoded outer surface proteins that differentially bind complement control factors of a wide range of vertebrate species, preventing the bacteria from being killed by innate immunity.”

Seinost, et al., Infection With Multiple Strains of *Borrelia burgdorferi* Sensu Stricto in Patients With Lyme Disease *Arch Dermatol* 1999; 135

(In this study, white footed mice in Connecticut contained 8 different genotypes of Bb and transmitted all 8 to ticks.)

“Continual genomic change in its gene repertoire, differential expression of gene families and the diversity introduced by lateral transfer of plasmids could provide the Lyme disease spirochetes with sufficient genetic and antigenic diversity to be able to react to the host’s immune attack and thus maintain chronic infection.”

“The Lyme spirochete *B burgdorferi* challenges the host immune system through a broad variety of molecular mechanisms that include complex regulation of differential gene

expression. Strategies in the treatment of chronic, antibiotic resistant Lyme disease might evolve based on future research in this respect.”

Singh and Girschick. Molecular survival strategies of the Lyme disease spirochete. *Lancet Infect Dis* 2004; 4:575-83

Co-infections make disease much more severe

Polymicrobial infections increase disease severity and contribute to the persistence of infection. The bulk of the world wide scientific literature regarding the basic biology, life cycle, morphology and survival strategies for many of these tick borne pathogens supports what we, as health care professionals are seeing in our practices. We see patients that present with chronic multisystem illnesses unresponsive to many different therapies. Patients suffer from polymicrobial infections that synergistically suppress the immune system, often resulting in disabling illnesses.

“Tick borne coinfections such as babesiosis, ehrlichiosis, anaplasmosis, and *B henselae* along with *Bb* infection may lead to more severe symptoms of Lyme disease, including debilitating neuropsychiatric symptoms.”

Stricker et al., Lyme disease: point/counterpoint. *Expert Rev Anti Infect Ther* 2005; 3:155-65

Babesia coinfection makes Lyme Disease more severe:

Moro, M. “*Babesia microti* Causes Down Regulation of Cytokines and Increased Severity of Lyme Arthritis” Presentation at Lyme Disease Association Medical Conference 2006 Phila, PA

Moro et al., Increased arthritis severity in mice coinfecting with *Borrelia burgdorferi* and *Babesia microti*. *J Infect Dis* 2002; 186: 428-431

Krause et al., Concurrent Lyme disease and babesiosis. Evidence for increased severity and duration of illness. *JAMA* 1996; 275: 1657-1660

Krause, et al., Persistent parasitemia after acute babesiosis. *N Engl J Med* 1998; 339: 160-165

Alfred, D. Babesiosis: persistence in the face of adversity. *Trends Parasitol* 2003; 19: 51-55

Oleson et al., Transverse myelitis secondary to coexistent Lyme disease and babesiosis. *J Spinal Cord Med* 2003; 26: 168-171

Anaplasma phagocytophilum coinfection makes Lyme disease more severe:

When sero-positive for *Anaplasma phagocytophilum* (Ap), patients with Bb have impaired ability to mount a strong Th-1 response (reducing Il-12 secreting cells)

Jarefors, S. et al., Reduced number of interleukin-12 secreting cells in patients with Lyme borreliosis previously exposed to *Anaplasma phagocytophilum*. *Clin Exp Immunol*. Feb 2006;143(2):322-8

“..co-infection with *A phagocytophilum* contributes to increased spirochetal loads and severity of Lyme disease”

“More *B burgdorferi* crossed human cells in the presence of *A phagocytophilum*-infected neutrophils without affecting endothelial cell integrity.”

Nyarko et al., *Anaplasma phagocytophilum*-infected neutrophils enhance transmigration of *Borrelia burgdorferi* across the human blood brain barrier in vitro. *Int J Parasitol*. 2006 Mar 6 (Epub ahead of print)

Thomas, et al., Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis alters murine immune responses, pathogen burden, and severity of Lyme arthritis. *Infect Immun* 2001; 69: 3359-3371

Zeidner, et al., Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis suppresses IL-2 and IFN gamma production and promotes an IL-4 response in C3H/HeJ mice. *Parasite Immunol* 2000; 22: 581-588

Dumler and Bakken. Human granulocytic ehrlichiosis in Wisconsin and Minnesota: a frequent infection with the potential for persistence. *J Infect Dis* 1996; 173: 1027-1030

Bartonella henselae coinfection makes Lyme disease more severe:

Eskow E; Rao RV; Mordechai E. Concurrent infection of the central nervous system by *Borrelia burgdorferi* and *Bartonella henselae*: evidence for a novel tick-borne disease complex. *Archives of Neurology* 2001; 58(9): 1357-1363

Chomel et al., Clinical impact of persistent *Bartonella* bacteremia in humans and animals. *Ann N Y Acad Sci* 2003; 990: 267-278

Dogs are multiply coinfectd and suffer from persistent infection as well:

Dogs with *Bartonella*, *Ehrlichia*, *Babesia* and *Rickettsia* species.

Kordick, S. et al., Coinfection with Multiple Tick-Borne Pathogens in a Walker Hound Kennel in North Carolina *Journal of Clinical Microbiology* August 1999; 37(8):2631-38

Harrus et al., Amplification of ehrlichial DNA from dogs 34 months after infection with *Ehrlichia canis*. *J Clin Microbiol* 1998; 36: 73-76

Persistent infections present as chronic illness

Persistence of Bb infection in animals and humans despite antibiotic therapy has been repeatedly documented in peer-reviewed literature since 1989.

www.lymeinfo.net/medical/LDPersist.pdf

“...antibiotic treatment for 30 consecutive days failed to eliminate the bacterium from infected dogs. The spirochete survives antibiotic treatment.”

Staubinger et al., *Wien Klin Wochenschr*, 1998;110(24):874-81

“It is clear that bacterial diversity provides bacterial populations, as a whole, the ability to persist in the face of a multi-faceted host response.”

Ehlich et al., Bacterial plurality as a general mechanism driving persistence in chronic infections. *Clin Orthop Relat Res*. 2005 Aug; 437:20-4

“...infectious agents likely determine more cancers, immune-mediated syndromes, neurodevelopmental disorders, and other chronic conditions than currently appreciated.”

O’Conner et al., Emerging Infectious Determinants of Chronic Diseases *Emerg Infect Dis* 2006;12(7):1051-1057

“A considerable body of experimental and clinical evidence supports the concept that cell wall-deficient forms (L-forms) may be agents of disease...in recent years, many once idiopathic, chronic, debilitating disorders have been discovered to be caused by microbial agents...”

Domingue, G. and Woody, H., Bacterial Persistence and Expression of Disease. April 1997 *Clinical Microbiology Reviews*: pages 320-344.

***Borrelia burgdorferi* is a congenitally transmitted disease**

“The aim of treatment of early Lyme disease during pregnancy is not only to treat the infection and prevent long-term sequelae but to eliminate the infections as quickly as possible so as to prevent congenital transmission to the fetus.”

Luft, BJ, Halpern, JJ, Datwyler, RJ et al., A perspective on the Treatment of Lyme Borreliosis *Reviews of Infectious Diseases* 1989 2(6): S1518-S1525

- Lyme can pass through the placenta and infect a growing baby at any stage of pregnancy
- By birth, the baby can die, be anywhere from severely to mildly ill or appear completely well
- Maternal antibiotic treatment during pregnancy does not guarantee that the fetus will be free of infection
- Mothers with Lyme disease should be treated throughout pregnancy
- Breast feeding, unclear risks
- Bb has been cultured out of breast milk

Schlessinger, PA, Duray, PH, Steere, AC, et al., Maternal-fetal transmission of the Lyme disease spirochete. **1985** *Annals of Internal Medicine*; 103: 67-8

Markowitz, L., Steere, AC, et al., Lyme disease during pregnancy. *JAMA* **1986**; 255: 3394-6

MacDonald, A. and Burgdorfer, W. **1987**: Stillbirth following maternal Lyme disease. *NY State J Med*; 87(616).

Weber, K., Duray, PH., et al. **1988**: *Borrelia burgdorferi* in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. *Pediatric Infectious Disease Journal*; April; 7(4):286-289.

MacDonald, A. **1989**: Gestational Lyme Borreliosis Implications for the Fetus. *Rheumatic Disease Clinics of North America* November 1989; 15(4): 657-677

- *Borrelia* spirochetes found at autopsy in fetal brain, liver, adrenal glands, spleen, bone marrow, heart and placenta
- None of the infected tissues showed any sign of inflammation

***Borrelia burgdorferi* infection is associated with neurodegenerative diseases**

- Alzheimer's disease
 - Dr. Alan MacDonald's work: www.molecularalzheimer.org
- Dr. MacDonald's work over the last 30 years has been remarkable. Look very carefully at his website and all the pathological evidence of *Borrelia burgdorferi* infection as the source of the lesions seen in neurodegenerative disorders. The immunofluorescent molecular beacon he developed stains only 24 base pairs specific to *Borrelia burgdorferi* DNA.
- Multiple sclerosis
 - Dr. Steven Phillips Lyme symposium lecture "Chronic Lyme Disease: The Connection to MS-The Facts Behind the Controversy" given on May 12, 2006 at The University of New Haven is available on DVD from University of New Haven www.unh-lyme.org
 - Parkinson's disease
 - Amyotrophic Lateral Sclerosis (ALS)

***Borrelia burgdorferi* infection is associated with autoimmunity to thyroid, nerve and skin antigens**

"These studies of Lyme disease have increased the need to consider persistent infection by slow-growing or fastidious bacterial pathogens as an etiology for idiopathic diseases with autoimmune features."

"The idea that microbial species, including bacteria, viruses and parasites, may represent the major environmental factors that initiate and sustain anti-self immune responses

continues to exert a powerful influence on autoimmune disease research. The ideas arises naturally from the obvious fact that the immune system has evolved mainly to recognize and respond to microbial pathogens.”

Behar, S. and Porcelli, S. MECHANISMS OF AUTOIMMUNE DISEASE INDUCTION, the Role of the Immune Response to Microbial Pathogens. *Arthritis and Rheumatism* 1995 38(4): 458-476

- **Thyroid:** 16 *Borrelia* proteins are homologous to the segments of thyroid autoantigens that are known to be autoantigenic.
Santarpia, *Thyroid* 2006; 16(3): 225-236
- **Nerve tissue:**
Alaedini and Latov. Antibodies against OspA epitopes of *Borrelia Burgdorferi* cross-react with neural tissue., *J Neuroimmunology* 2005; 159: 192-5
- **Skin:** “The cause of lichen sclerosus is unknown, but genetic, autoimmune and traumatic etiologies have been suggested. The condition has also been linked to infection, particularly with human papillomavirus and borrelia spirochetes.”
Walling, A. *American Family Physician* 1999; 60(5) quoting Powell JJ, Wojnarowska F. Lichen sclerosus. *Lancet* May 22, 1999; 353:1777-83.
Dramatic improvement of lichen sclerosus with treatment with antiborrelial antibiotics (ceftriaxone, IM benzathine penicillin and oral PCNs).
Shelly et al. *Int J Dermatol.* 2006 Sep; 45(9):1104-6

Infection and Autoimmunity Yehuda Shoenfeld and Noel R. Rose, Editors Elsevier, Amsterdam, the Netherlands, 2004 ISBN:0-444-51271-3

Signs and Symptoms of TBD

Constitutional symptoms

- Flu-like illness at any time of the year
- Fatigue, often unrelieved by rest
- Unexplained fevers, often cyclical
- Headaches of all kinds
- Abdominal pain of all kinds
- Migratory, intermittent joint pains
- Muscle aches and pains, deep bone pain
- Aerobic exercise intolerance
- Frequent infections; either viral, bacterial or fungal
- Recurrent sore throats and swollen glands
- Sleep disturbances
- Palpitations, chest pains, shortness of breath, dry cough
- Urinary urgency and frequency, painful urination, incontinence
- Rashes of all kinds that come and go
- Dark circles under the eyes
- Intermittent red, hot ears

Neuropsychiatric symptoms

- Headaches of all kinds
- Sensory hypersensitivities (sound, light, odor, touch, taste)
- Poor balance and coordination
- Peripheral neuropathies – numbness and tingling, bug crawling feelings, severely painful neuralgias
- Movement disorders – spasticity, ataxia, motor or vocal tics, loss of previously acquired motor skills, muscle weakness, spasms, twitches, tremors
- Cranial neuropathies, e.g. Bell’s palsy, optic neuritis which can result in visual loss, ear pain and hearing abnormalities, swallowing difficulties
- Partial complex seizures
- Neurodegenerative diseases of the brain and spinal cord (AD, MS, PD, ALS)
- Pseudo tumor cerebri (increased intracranial pressure with papilledema)
- Mood disturbances, irritability, emotional lability
- Social withdrawal, decreased participation in activities
- Depression (suicidal ideation and, unfortunately, even successful suicide)
- Rage attacks and anger-management disorders
- Anxiety, panic attacks and phobias
- Oppositional behaviors
- Obsessive compulsive disorders
- Hallucinations of all kinds
- Psychosis
- Personality changes
- Self-mutilating behaviors
- Cognitive dysfunction or “brain fog”
- Difficulty with concentration and attention, easy distractibility (children often labeled with a learning disability or ADD)
 - 90% of infected children have a deterioration in school performance
- Slow verbal fluency with word and name finding problems
- Short term memory difficulties
- Defects in auditory and visual sequential processing (slower processing speeds)

Congenitally infected infants (as well as those infected from breast milk or in early infancy can show):

- Floppiness with poor muscle tone
- Irritability
- Frequent fevers and illnesses early in life
- Joint and skin sensitivities with somatic body pain
- Gastroesophageal reflux
- Up regulated allergic responsiveness
- Developmental delays of fine and/or gross motor skills
- Abnormal cognitive development manifesting as learning disabilities and psychiatric syndromes of all kinds

Evaluation of patients with TBD

- Risk factors:
 - Known tick attachment (less than 50% remember tick bite)
 - Deer in home, work, or school environments
 - Outdoor activities
 - Travel history
- History of erythema migrans or EM rash
 - Only about 60% patients bitten by ticks develop EM rash
 - Extreme variability of clinical presentation of EM rash underappreciated
- Full medical history and physical examination

Testing of Tick Borne Disease patients

- Tick Borne Disease is a clinical diagnosis
- Serologies (antibody testing)
 - Two tiered CDC testing ELISA / WB misses half of infected patients
 - Western Blot is the most useful serologic test, but tests varies considerably from lab to lab
 - WB only needs to show one species-specific band to demonstrate exposure to Bb thereby confirming a diagnosis of Lyme disease. These species-specific bands include 18, 23-25, 31, 34, 37, 39, 83, and 93 kDa.
- PCR (urine, serum, whole blood, tissues)
 - Is more accurate testing method because it detects Bb DNA

Tick Borne Disease testing laboratories:

- Igenex www.igenex.com
- Medical Diagnostic Laboratories www.mdlab.com
- Lab Corp for CD 57 HNK Panel: test number 505026

- Pathology
 - Silver staining, acrine orange staining
 - Dark field microscopy
 - Focus floating microscopy

Eisendle K. et al. Focus floating microscopy: "gold standard" for cutaneous borreliosis?
Am J Clin Pathol. 2007 Feb;127(2):1-10

- Immunofluorescent molecular beacon – not commercially available
- Also, a complete laboratory work up is performed for:
 - Biotoxin illness
 - Basic organ function
 - Systemic inflammation
 - Autoimmunity
 - Leaky gut

- Hypercoagulability
- Hormones
- Other infectious agents
- Heavy metal evaluation
- SPECT scanning
 - Amen clinic, CA and VA

Complexity of TBD patient presentations

- Biotoxin illness in susceptible HLA types (about 25% of the population). Toxins:
 - Are water and lipid-soluble inonophores from indoor toxic mold, Bb, Bm and *Pfiesteria sp.*
 - Alter DNA expression of fat cells turning on production of inflammatory cytokines
 - up regulated inflammatory cytokines up regulate systemic inflammation, increase insulin resistance, increase bad lipid level, alter levels of VEGF and PAI-1.
 - Bind to and damage leptin receptors in the hippocampus and hypothalamus leading to breakdown of the proopiomelanocortin system with resultant deficiencies in two very important master regulating hormones: MSH (melanocyte stimulating hormone) and VIP (vasoactive intestinal peptide)
 - Ongoing damage of hippocampus, hypothalamus and both anterior and posterior pituitary affect all hormonal systems
 - Immune system dysregulation allows the overgrowth of MARCoNS (multiple antibiotic resistant coagulase negative *Staphylococcus epidermidis*) and other bacteria which grow in the nose and sinus cavities. These biofilm forming organisms elaborate toxins which cause ongoing damage to the brain and can be very hard to eradicate.

Biotoxin illness or Sick Building Syndrome is the life work of Ritchie Shoemaker, MD:

- website is www.chronicneurotoxins.com
- book: “The Mold Warriors” can be purchased on amazon.com
- double blind placebo controlled study in *Neurotoxicology and Teratology* explains his theories nicely:

Shoemaker, R.C and House, D.E. Sick building syndrome (SBS) and exposure to water-damaged buildings: Time series study, clinical trial and mechanisms. *Neurotoxicology and Teratology* 2006; 28:573-588

- Immune system anergy
 - Need to correct cytokine imbalances and down regulate inflammation while up regulating specific targeted pathogens
- Lipids abnormalities
- Up regulated allergic reactions
- Multiple infections besides the tick borne ones
- Hypercoagulability

- Vasculitis
- Gut dysbiosis
- Autoimmunity
 - Thyroid (TPO, thyroglobulin antibodies)
 - Endothelial lining of blood vessels (anticardiolipin antibodies)
 - Nerve tissue (myelin basic protein antibodies)
 - Skin
 - Lupus (ANA)
 - Rheumatoid Arthritis (RF)
- Liver detoxification abnormalities
- Hormonal dysfunction
 - Insulin and leptin resistance
 - Thyroid insufficiency
 - Sex hormone deficiencies
 - Renin-angiotensin system and antidiuretic hormone abnormalities
 - Adrenal gland stress or resistance or exhaustion
- Heavy metal toxicity
- Bone marrow metabolic dysfunction with persistent
 - Thrombocytopenia
 - Neutropenia, often specifically lymphopenia
 - Anemia
- Patients often have a history of prior physical, emotional, or psychic trauma
- Multisystem organ damage (cellular phases of homotoxicology model) from tick borne disease infections themselves, especially of the nervous system

Treatment approach to patients with TBD

Treat using as many healing disciplines as possible:

- Allopathic medicine
- Homeopathic medicine
- Chiropractic medicine
- Cranial osteopathy
- Naturopathic medicine
- Traditional Chinese herbal medicine and acupuncture
- Body work of all kinds
- Energy medicine
- Applied kinesiology
- Many other techniques and treatment modalities (HBO)
- German Biological Medicine

My approach follows German Biological Medicine principles:

- Restore vitality
- Paleolithic diet: low sugar and simple CHO, no processed foods, only grass fed meats, and organic food
- Balance Omega 3:6 ratios, replete nutritional deficiencies
- Treat gut dysbiosis

- Optimize liver detoxification
- Reduce inflammation
- Clean up extracellular matrix
- Reduce infectious burden with antimicrobials
- Attain sound, healthy, restorative sleep
- Try to reverse biotoxin illness damage
- Restore normal immune system function: address Th1:Th2 balance, treat autoimmunity, fight pathogens
- Restore healthy function to the endothelial lining of entire cardiovascular system
- Remove heavy metals and other toxins
- Restore aerobic exercise tolerance and encourage lifelong cardiovascular fitness

Prevention

http://www.lymepa.org/html/protecting_yourself.html

If you learn nothing else from this talk, please learn how to protect yourself and your loved ones from exposure to ticks, tick bites and tick borne disease. Go to the above link and read carefully!

Treatment controversy: two standards of care IDSA vs. ILADS

ILADS:

The International Lyme and Associated Diseases Society (ILADS) Working Group. Evidence-based guidelines for the management of Lyme disease. *Expert Review of Anti-infective Therapy* 2004; 2(1) S1-S13

www.guidelines.gov National Guideline Clearinghouse. Search “lyme” or enter guideline no. 003481

or

www.ilads.org/files/ILADS_Guidelines.pdf

IDSA:

Wormser, Dattwyler, Shapiro, Halpern, Steere, Klemmner, Krause, Bakken, Strie, Stanek, Bockenstedt, Fish, Dumler, Nadelman. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2006; 43(9): 1089-1134

<http://www.journals.uchicago.edu/CID/journal/issues/v43n9/40897/40897.html>

Suggested reading

Johnson, L. and Stricker, R., Treatment of Lyme disease: a medicolegal assessment. 2004; *Expert Rev. Anti-infect. Ther.* 2(4): 533-557

The International Lyme and Associated Diseases Society (ILADS) Working Group. Evidence-based guidelines for the management of Lyme disease. *Expert Review of Anti-infective Therapy* 2004; 2(1) S1-S13 www.ilads.org/files/ILADS_Guidelines.pdf

Stricker, R. and Lautin, A., The Lyme Wars: time to listen *Expert Opin. Investig. Drugs* 2003; 12(10): 1-6

Burrascano, J. *Diagnostic Hints and Treatment Guidelines for Lyme and Other Tick Borne Illnesses* 2005 15th edition www.ilads.org/burrascano_0905.html

Websites of interest

www.ilads.org the website of ILADS, The International Lyme and Associated Diseases Society

www.lymepa.org the Lyme Disease Association of Southeastern Pennsylvania's website, an incredibly useful and accurate resource

www.lymediseaseassociation.org the national organization that does tremendous work for TBD patients; also full of important, accurate information

www.thehumansideoflyme.net Dr. Virginia Sherr's site, a Lyme literate psychiatrist and founding board member of ILADS

www.lymeinfo.net/lymefiles.html incredibly useful files cataloguing and summarizing hundreds of peer-reviewed medical literature about spirochetal infection over the last hundred years (compiled by Joanne Rubel from Thomas Jefferson Medical School library's collection of medical journals)

www.lymeinfo.net/medical/LDPersist.pdf

www.lymeinfo.net/medical/LDSymptoms.pdf

www.lymeinfo.net/medical/LDSupplement.pdf

www.lymeinfo.net/medical/LDSeronegativity.pdf

www.lymeinfo.net/medical/LDCysts.pdf

www.lymeinfo.net/medical/LDAdverseConditions.pdf

www.lymeinfo.net/medical/LDBibliography.pdf

Immune system evasion methods of *Borrelia burgdorferi* references

Two excellent review articles:

Embers, M. et al., Survival strategies of *Borrelia burgdorferi*, the etiologic agent of Lyme disease. *Microbes and Infection* 2004; 6:312-318

Singh and Girschick. Molecular survival strategies of the Lyme disease spirochete. *Lancet Infect Dis* 2004; 4:575-83

also:

Norris, Steven J. The dynamic proteome of Lyme disease *Borrelia*. *Genome Biology* 2006; 7(3): 209

Norris, Steven J. Antigenic variation with a twist - the *Borrelia* story. *Molecular Microbiology* 2006; 60(6):1319-1322

Hanincova, et al., Epidemic Spread of Lyme Borreliosis, Northeastern United States. *Emerging Infectious Diseases* 2006 ; 12(4):604-611

Seinost, et al., Infection With Multiple Strains of *Borrelia burgdorferi* Sensu Stricto in Patients With Lyme Disease *Arch Dermatol* 1999; 135:1329-1333

Casjens et al. A bacterial genome in flux: the twelve linear and nine circular extrachromosomal DNAs in an infectious isolate of the Lyme disease spirochete *Borrelia burgdorferi*. *Mol Microbiol* 2000; 35:490-516

Porcella, S.F. and Schwan, T.G. *Borrelia burgdorferi* and *Treponema pallidum*: a comparison of functional genomics, environmental adaptations, and pathogenic mechanisms. *J. Clin. Invest.* 2001 107: 651-656

Ehlich et al., Bacterial plurality as a general mechanism driving persistence in chronic infections. *Clin Orthop Relat Res.* 2005 Aug; 437:20-4

IDSA quotes, just for giggles

Note that the bolded names are authors of the Infectious Diseases Society of America's 2006 guidelines. These quotes show these authors scientific findings and opinions 10-15 years ago in direct opposition to their currently held positions.

“...a 1 month course of oral antibiotics may not always eradicate viable spirochetes.”
Steere, AC *American Journal of Medicine* **1995**;88:4A-44S-51S

“*B burgdorferi* spirochetes can survive antibiotic treatment through intracellular sequestration within fibroblasts...fibroblasts and keratinocytes were able to protect *B burgdorferi* from the action of this B-Lactam antibiotic (ceftriaxone) even at antibiotic concentrations greater or equal to 10 times the MBC of the antibiotic.”
Klempner, MS *Journal Infectious Diseases* **1993**;167:1074-1081

“These chronic neurologic abnormalities began months to years after the onset of infection, sometimes after long periods of latency, as in neurosyphilis...The likely reason for relapse is failure to eradicate the spirochete...with antibiotic therapy. This last article is one of many studies that show continuing symptoms are most likely due to persistence of the spirochete.”
Steere, AC *New England Journal Medicine* Nov 22, 1990; 323(21): 1438-44

“We studied 17 patients who had presented with acute Lyme disease and received prompt treatment with oral antibiotics, but in whom chronic Lyme disease subsequently developed.”
Dattwyler, RJ *New England Journal Medicine* **1988**; 319(22): 1441-6

“Five of seven patients remained symptomatic at a median of four months after treatment.”
Wormser, GP *American Journal of Medicine* **1990**; 66:21-26

more laughs:

The October 2006 **IDSA guidelines authors** (identified in bold) say now, in 2007, that testing is reliable, Bb infection is hard to catch, easy to kill, simple to treat and they deny or ignore nervous system infection completely. This is what three of them said nearly twenty years ago:

“...the development of optimal therapeutic modalities has been hampered by the lack of reliable microbiologic or immunologic criteria for the diagnosis or cure of this infection”
testing reliable??

“...rapid bacterial dissemination...”
hard to catch??

“...takes 72-96 hours to kill 99% of organisms... remarkably similar to those for *Treponema pallidum* in that prolonged exposure to antibiotic at sustained bactericidal levels are necessary for effective killing.”
easy to kill??

“ Regardless of the chronicity of infection, if CNS involvement is discovered or there is significant compromise of an organ system as a result of infection, the patient should receive parenteral therapy so that adequate CNS drug levels are attained”
simple to treat??

Luft, BJ, Halpern, JJ, Datwyler, RJ et al., A perspective on the Treatment of Lyme Borreliosis *Reviews of Infectious Diseases* **1989** 2(6): S1518-S1525