

TICK-BORNE DISEASE TODAY

PHYSICIAN INFORMATION- REFERENCES- DATA

In Memory of Dr. Randall Ceaglske

Gypsy moths, emerald ash borer beetles, zebra mussels, sea lamprey, flying carp, Eurasian watermilfoil and purple loosestrife draw attention to our imperiled earth.

Along with these concerns, media attention focused on brain-eating amoebas found in warm freshwater lakes. Death has become the potential consequence of simply swimming.

Unfortunately, the grave human consequences of tick-borne diseases draw a back seat to a changing landscape that harbors other invaders.

If half the money spent posting invasive species signs was spent on preventing tick-borne diseases, we could be in the drivers seat, combatting tick predators found in our own backyards.

In your hands, *Tick-Borne Disease Today* is but one small step toward taking back the wheel, steering a path toward better health. Read, Note, Remember. Pass it on, please.

Marina

lymelady@lakeland.ws

Fast Facts

In 2011, 96% of Lyme disease cases were reported from 13 states:

- Connecticut
- Delaware
- Maine
- Maryland
- Massachusetts
- Minnesota
- New Hampshire
- New Jersey
- New York
- Pennsylvania
- Vermont
- Virginia
- Wisconsin

Lyme disease is the most commonly reported vector-borne illness in the United States. In 2011, it was the 6th most common [Nationally Notifiable disease](#). However, this disease does **not** occur nationwide and is concentrated heavily in the northeast and upper Midwest. <http://www.cdc.gov/lyme/stats/index.html>

Newsorthy in 2012

Missouri: Two severely ill farmers who had been bitten by ticks contracted the first phlebovirus (bunyaviridae) in the Western Hemisphere known to infect humans.

Virginia: Lone Star tick saliva that seeps into bite wounds has caused those bitten to have allergic reactions upon ingesting meat. Reactions range from hives to anaphylactic shock.

Canada: A cross-Canada study of birds and their tick stowaways concluded, "Because songbirds disperse *B. burgdorferi*-infected ticks outside their anticipated range, health-care providers are advised that people can contract Lyme disease locally without any history of travel."

Course Offerings on Tick-Borne Diseases

Partnership for Healing and Health (PHH) offers accredited, "live" continuing medical education courses on tick-borne diseases for healthcare professionals. Physician CME courses range from 1-hour offerings on a specific topics to multi-hour presentations covering details from the basic science and clinical evidence.

Sessions of the course "Case Studies in Lyme disease: Diagnostic and Therapeutic Considerations" can be scheduled for local presentation through June 1, 2013. This course is accredited for 4.0 prescribed credits by the AAFP. Similar courses are available for nurses and mental health professionals. PHH will also work with professional healthcare organizations to create programs of specific interest for their members.

Contact *Partnership for Healing and Health* by email: md@phhmd.com.

Of Note: The Wisconsin Department of Health, citing overburdened workers and budgetary constraints, decided the state would no longer count or confirm cases of Lyme disease that were not accompanied by an *Erythema migrans* rash, the most well-known of which is the bull's-eye rash. This decision means the state's 2012 statistics can no longer be contrasted or compared with those of other US states.

Also Note: TBD statistics and maps on the Minnesota Department of Health website are predominantly four to five years old, in need of updating.

On the Horizon

A New Technique Examines Neuroborreliosis

Researchers plan to use non-invasive Magnetic Resonance Spectroscopy (MRS) to examine brains for damage caused by neurological Lyme disease. To learn more about the technique, watch a short video from the Neurology Research Foundation, Inc. at: <http://www.youtube.com/watch?v=DS-bIp--W9k&feature=share>.

Soda pop—Squirt and TBD Prevention?

Nootkatones, a substance in grapefruit, Alaskan yellow cedar trees, and, yes, *Squirt*, hold promise for preventing tick-borne diseases. Non-toxic to humans but deadly to ticks, nootkatones will be used in repellants and, perhaps, the first insecticidal soap. At the behest of CDC, private companies are hard at work developing nootkatone-based prevention products.

On The Horizon, Continued

Medical College of Wisconsin in the News

The National Institute of Allergy and Infectious Diseases, a division of the National Institutes of Health, awarded a \$1.9 Million five-year grant to Dr. Jennifer Coburn, Professor of Medicine at the Medical College of Wisconsin. She will use the grant to study a protein of the Lyme bacterium, *Borrelia burgdorferi*. The specific protein, called P66, is necessary for tick transmission of the bacteria to humans. Dr. Coburn's research may one day be used to aid Lyme disease prevention.

Babesiosis

Wisconsin recorded its first case of babesiosis in 1983. A slow but steady increase in the state's cases has been followed by a sharp escalation: From 2010 to 2011 reported cases of babesiosis rose roughly 225%. Over the same time periods Minnesota saw similar increases and reported one death from complications of babesiosis in 2010.

Babesiosis infections can be asymptomatic or produce mild to fulminant disease. The parasitemia may have both intraerythrocytic and extraerythrocytic presence (PMID 14560566) characterized by hepatosplenomegaly, hemolysis, disseminated intravascular coagulation, splenic rupture, and death, which is most likely in asplenic or immunocompromised patients (30%).

Babesiosis patients may report:

- frontal headaches/migraines
- left upper quadrant pain
PMID 2125131
- labored breathing or "air hunger"
- excessive fatigue
- sweats, chills
- erratic heart beat
- blood pressure changes.

Fast Facts

87% of reported cases of transfusion-transmitted babesiosis occurred in seven states. Minnesota and Wisconsin are two of those states.
PMID 21893613

Transfusion-transmitted Babesiosis

The first case of transfusion-transmitted babesiosis in the US was reported in 1979. Several years ago, the state of Wisconsin, considered endemic for babesiosis, was included in a study of blood donors in endemic areas. At that time the Health and Human Services analysis found 1.4 - 4.3% of blood donors in endemic areas were infected with babesiosis.

Two of Wisconsin's babesiosis cases reported in 2010 were transfusion-transmitted. After transfusion of blood or blood products, anemia, thrombocytopenia, fever, hepatic dysfunction, hypotension, and renal failure may signify babesiosis infection in patients.

The results of an analysis of 2,000 Minnesota and Wisconsin blood donations given in 2011 have not been released by the Red Cross. These blood donations were to be analyzed for "exposure to Babesia." <http://www.redcrossblood.org/news/northcentral/american-red-cross-studying-prevalence-rare-growing-tick-borne-parasite-donated-bl>

Blood donors are asked if they have ever had babesiosis, which would disqualify them, but asymptomatic or recently infected donors may have no knowledge of their infection. Regional screening of the blood supply in babesiosis-endemic areas has been proposed, but, so far, an accurate affordable test has not been settled on, although several types of tests have been considered.

In-cites

Six case reports of splenic rupture due to babesiosis were published between 2008 and 2011. PMID 22108020; 21514529; 1500704; 21251311; 18988934; 18419430

New York Medical College, Wormser GP, et al, 2011.

"Our cases demonstrate the need to be vigilant for babesiosis in patients undergoing splenectomy." [This study describes three patients as febrile after splenectomy.]

University of Minnesota, Wudhikam K, et al, 2011.

"Patients with advanced age, asplenia, or other immune compromise are at risk for severe babesiosis and may require prolonged treatment to eradicate parasitemia"

Fast Fact

Cases of congenital babesiosis have been reported.
PMID 16462298

Transfusion-associated babesiosis in the United States: a description of cases.

Herwaldt BL, et al. *Annals of Internal Medicine* 2011 October;155(8):509-19.

In a comprehensive study of 162 cases of transfusion-transmitted *Babesia microti* (159) and *Babesia duncani* (3), two strains of Babesia that are tested for in the US, researchers made these observations:

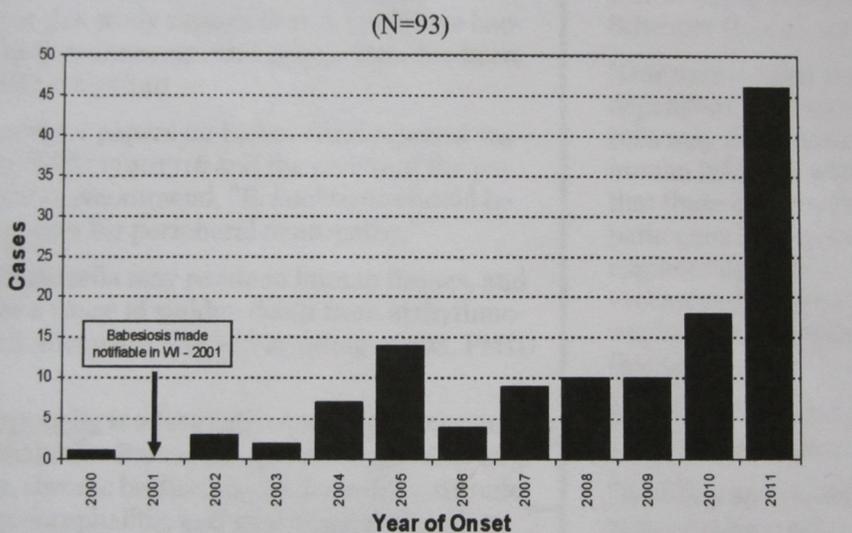
"Babesiosis should be included in the differential diagnosis of unexplained post-transfusion hemolytic anemia, with or without fever, regardless of the season or US region . . .

"The 162 transfusion-associated cases we enumerated undoubtedly represent a fraction of those that occurred. The extent to which cases were not detected, investigated, or reported (to the CDC, to other public health authorities, or in publications) is unknown, both in general and with respect to periods, regions, and various case characteristics and outcomes . . .

"As underscored by the incidental diagnosis of Babesia infection, even severe cases in babesiosis-endemic regions can be missed or misdiagnosed, not just cases that are asymptomatic or mild or that occur in other US regions. Even if a case is diagnosed, a transfusion investigation might not be considered, conducted, completed, or conclusive . . .

"Our findings underscore the year-round vulnerability of the US blood supply—especially, but not only, in and near babesiosis-endemic areas. They also highlight the importance of multiagency collaborative efforts to detect, investigate, and document transfusion cases; to assess the risks for transfusion transmission; and, thereby, to inform the scope of prevention measures." PMID 21893613

Reported Confirmed Babesiosis, Wisconsin 2000–2011*



Totals include 3 transfusion-associated cases and 1 acquired via organ transplant

*2011 data provisional

From the CDC

"Babesiosis is caused by microscopic parasites that infect red blood cells and are spread by certain ticks. In the United States, tick-borne transmission is most common in particular regions and seasons: it mainly occurs in parts of the Northeast and upper Midwest and usually peaks during the warm months." <http://www.cdc.gov/parasites/babesiosis>

From the FDA

"Anti-Babesia antibody positivity in the US ranged between 0.3% to 17.8% suggesting either low assay specificities or very high rates of asymptomatic infections." [Power Point presentation from Sanjai Kumar, PhD, July 26, 2010.]

Bartonellosis

2000 B.C. Bartonella present in a human tooth. PMID 15655785

1905 Alberto Barton isolates the bacterium causing severe anemia and fever in 14 patients. The bacterium is later named Bartonella.

1915-1918 During WWI Bartonella species, *B. quintana*, is transmitted by lice to servicemen who fought the battle from trenches, hence the name Trench Fever.

2001 Researchers caution *Bartonella henselae* and *Borrelia burgdorferi* could be a novel tick-borne disease complex. They suggest ". . . patients with a history of neuroborreliosis who have incomplete resolution of symptoms should be evaluated for *B. henselae* infection." PMID 11559306

2010 Drs. Telford and Wormser maintain that the presence of *Bartonella henselae* in *Ixodes scapularis* ticks in the US does not establish transmission of the bacterium to humans. <http://www.cdc.gov/EID/content/16/3/379.htm>

"*Bartonella* is carried by more vectors than any infection on earth."

Dr. Ed Breitschwerdt

Bartonellosis (timeline, cont'd)

2011 French researchers establish tick transmission of the *Bartonella* species, *birtlesii*, by *Ixodes ricinus*, also known as the sheep tick, in the (following) paper:

Vector Competence of the Tick *Ixodes ricinus* for Transmission of *Bartonella birtlesii*.

Reis C, et al. *PLoS Neglected Tropical Diseases* 2011;5(5):e1186.

"This work represents the first in vivo demonstration of a *Bartonella* sp. transmission by ticks. It does not claim that ticks are principal vectors of *Bartonella* spp, but it does corroborate a prospect that ticks play a role in the natural cycles of some of the bartonellae including those pathogenic for humans. Consequently, bartonelloses should be included in the differential diagnosis for patients exposed to tick bites . . .

"The lack of *B. birtlesii* in the midgut of feeding ticks and its presence in the salivary glands confirms that its transmission to the host occurs with saliva . . . It remains to be studied whether initiation of the next feeding is necessary for bacterial invasion of salivary glands and the subsequent transmission into a susceptible host."

<http://www.plosntds.org/article/info:doi/10.1371/journal.pntd.0001186>

A Groundhog, a Novel *Bartonella* Sequence, and My Father's Death

Breitschwerdt EB, et al. *Emerging Infectious Disease* 2009; Dec 15(12):2080-6.

In this case report, Dr. Edward Breitschwerdt, Professor of Veterinary Medicine at North Carolina State University, and his colleagues present a lengthy examination of *Bartonella* infection in Breitschwerdt's father.

The father's illness began with migratory joint pains and progressed within a few months to subtle memory loss. Incoordination led to a fractured femur and subsequent hospitalization. While hospitalized the patient "showed cogwheel rigidity and a resting pill-roll tremor, suggestive of Parkinson [sic] disease."

Preoperatively the patient was seriously confused, and post-operatively "poor mentation" and "dementia persisted for more than a week." The patient improved and was due to be sent home the next week when he fell and became non-verbal. Stroke was suspected and confirmed by MRI. The patient was treated with three antibiotics, an antiviral, an antifungal, and dexamethasone.

Suspecting physicians attending his father had missed something in the tests that had been performed, Dr. Breitschwerdt obtained serum and CSF samples. Using his own laboratory at North Carolina State, Breitschwerdt found an amplicon of his father's blood was most similar to a species of *Bartonella* found in southern flying squirrels, and his CSF amplicon was most similar to *B. henselae*. Piperacillin and tazobactam were administered to his father in the hospital; a seizure followed shortly afterward; and he remained semi-comatose for 3 weeks.

The father eventually improved on antibiotics in the hospital and was sent home with prescriptions of doxycycline and rifampin for thirteen days. After continued improvement on these antibiotics, the father declined rapidly when the antibiotics were discontinued. Again, hospitalization was required, antibiotics administered, and again a seizure occurred. Following four weeks of antibiotics and a rocky course of multiple mental and physical infirmities while in the hospital the father recovered enough to be sent home, again on antibiotics. Having "lost his will to live," he began to refuse all medications. He died on May 2, 2008.

Breitschwerdt and colleagues wrote: "We propose that the initial arthritic signs, short-term memory loss, and incoordination were premonitory signs of *Bartonella* spp. infection, and that persistent infection contributed to localized edema, nonregenerative anemia, thrombocytosis, hyperglobulinemia, and a protracted debilitating illness accompanied by hallucinations, agitation, seizures, and death . . .

"Retrospectively, the relapse in encephalopathic signs might have been avoided if antimicrobial drugs were continued for a longer interval after discharge from hospital 2, and blood cultures were optimally obtained and sequentially tested to confirm therapeutic elimination . . .

"Elimination of *Bartonella* spp. by antimicrobial drugs in immunocompetent patients may be more difficult to achieve than is currently appreciated. [PMID 18632903] Although co-infection with *B. henselae* and *B. vinsonii* subsp. *berkhoffii* has been previously reported, DNA of 3 *Bartonella* spp. was detected in our father."

Supportive clinical findings & pathology, full article at: http://wwwnc.cdc.gov/eid/article/15/12/ad-1512_article.htm

PCR Amplification of *Bartonella koehlerae* from human blood and blood enrichment cultures. Breitschwerdt EB, et al. *Parasites and Vectors*. 2010 August; 3(76).

In this study of 8 patients infected with *B. koehlerae*, fatigue topped the list of symptoms. Three patients had atrial or ventricular tachyarrhythmias; 4 had neurologic involvement or neurocognitive deficits; 5 had tendon and joint pain, with 2 specifically noting hip-joint pain. One patient had TMJ and carpal tunnel syndrome; one had multifocal retinitis; and one had severe sinusitis. Following the administration of antibiotics, two of the patients suffered Jarisch-Herxheimer reactions.

The authors wrote: "Although biased by a study population consisting of individuals with extensive arthropod and animal exposure, [veterinarians] the results of this study suggest that *B. koehlerae* bacteremia is more common in immunocompetent people than has been previously suspected." PMID 20735840

With an eye cast toward previous papers on Bartonellosis-caused vasculitis, polyneuropathy PMID 17401716 and review of patients in this study, the authors recommend, "*B. koehlerae* should be among the differential diagnoses for peripheral neuropathy."

More than one Bartonella species may reside in human tissues, and *B. henselae* may be a cause of sudden death from arrhythmogenic right ventricular cardiomyopathy in young adults. PMID 186661874

What is Bartonella?

Bartonella is a facultative intracellular organism with a tropism for endothelial cells. Bartonella can cause bacillary angiomatosis, peliosis hepatitis, chronic bacteremia, endocarditis, chronic lymphadenopathy, meningoencephalitis, and neurological disorders. Some diseases due to Bartonella species resolve spontaneously without treatment; in other cases the disease is fatal without antibiotics or surgery. PMID 15155180

Outside the United States *Dermacentor* ticks, commonly called wood or dog ticks, are believed to transmit Bartonella. *Dermacentor occidentalis* and *Dermacentor variabilis* ticks from California counties have tested PCR-positive for Bartonella. PMID 12135237, 16584332

Bartonella henselae was found more often than *Borrelia burgdorferi* in ticks studied in the high-risk Lyme disease state of New Jersey. PMID 15184475

More than 26 species of Bartonella have been named worldwide. Some species that infect humans: *B. henselae*, *B. elizabethae*, *B. vinsonii subsp. arupensis*, *B. vinsonii subsp. berkhoffi*, *B. washoensis*, *B. koehlerae*, *B. bacilliformis* (*B. rochalimae*, *B. grahamii*), *B. quintana*. Bartonella causes trench fever, Carrion's disease, Orroyo fever, verruga peruana, and cat scratch disease, (CSD) also called cat scratch fever.

Some Bartonella species have known tropisms. *B. henselae*, *B. elizabethae*, *B. quintana*, and *B. washoensis* have been found in the heart. *B. grahamii* is associated with neuroretinitis and carditis, and *B. vinsonii subsp. arupensis* causes fever and neurologic symptoms.

Peculiar rashes may be a sign of Bartonellosis. These rashes may look like stretch marks; others appear as streaks, like the arc of a comet.

In-Cites at Home and Abroad

Loyola University

Vander Heyden HK, et al, 2012:

"Thirteen months after initial presentation, hepatic bartonellosis was diagnosed by PCR studies from surgically excised liver tissue. Interestingly, hepatic granulomas persisted and *Bartonella henselae* was isolated from the patient's enriched blood culture after several courses of antibiotic therapy."

University of Basel, Switzerland

Schroder G, et al, 2011:

"Our data suggest that T4SS-dependent DNA transfer into host cells may occur naturally during human infection with Bartonella and that these chronically infecting pathogens have potential for the engineering of in vivo gene-delivery vectors with applications in DNA vaccination and therapeutic gene therapy."

Hospices Civils de Lyon, France

Moulin C, et al, 2012:

"Bacillary angiomatosis (BA) is a rare vasculoproliferative disorder due to *Bartonella henselae* (BH) or *Bartonella quintana*. It can involve many organs, including the skin, and has been mainly reported in patients with acquired immunodeficiency syndrome. In organ transplant recipients (OTR), this disorder remains misdiagnosed and therapeutic guidelines are nonexistent. We report 3 cases of BA with skin involvement in OTR."

University of Palermo, Italy

Mansueto P, et al, 2012:

"Among healthy blood donors 11.4% had IgG class antibodies to *B. henselae*; 9.8% showed a titer 1:64 and 1.6% 1:128. All the human serum samples did not show positive results for *B. henselae* IgM class antibodies."

USC INRA Maisons-Alfort, France

Deng HK, et al, 2012:

"The spleen seems to retain and filter infected erythrocytes rather than to be a sanctuary for chronic Bartonella infection."

Bartonella spp. bacteremia and rheumatologic symptoms in patients from a Lyme disease-endemic region. Maggi RG, et al. *Emerging Infectious Disease* 2012 May;18(5):783-91.

[Abstract] *Bartonella* spp. infection has been reported in association with an expanding spectrum of symptoms and lesions. Among 296 patients examined by a rheumatologist, prevalence of antibodies against *Bartonella henselae*, *B. koehlerae*, or *B. vinsonii* subsp. *berkhoffii* (185 [62%]) and *Bartonella* spp. bacteremia (122 [41.1%]) was high. Conditions diagnosed before referral included Lyme disease (46.6%), arthralgia/arthritis (20.6%), chronic fatigue (19.6%), and fibromyalgia (6.1%). *B. henselae* bacteremia was significantly associated with prior referral to a neurologist, most often for blurred vision, subcortical neurologic deficits, or numbness in the extremities, whereas *B. koehlerae* bacteremia was associated with examination by an infectious disease physician. This cross-sectional study cannot establish a causal link between *Bartonella* spp. infection and the high frequency of neurologic symptoms, myalgia, joint pain, or progressive arthropathy in this population; however, the contribution of *Bartonella* spp. infection, if any, to these symptoms should be systematically investigated.

Long-term survival of *Bartonella bacilliformis* in blood stored at 4° C.

A risk for blood transfusions. Ruiz J, et al. *Blood Transfusion* 2012 March 29:1-2. doi: 10.2450/2012.0152-11

"... the present results clearly show the risk of long term survival of *B. bacilliformis* in infected human blood stored at 4° C, and therefore the potential risk of a transfusion transmission of this microorganism. This potential risk is enhanced firstly because this microorganism requires a prolonged incubation period (usually more than 21 days), which exceeds the usual period of blood cultivation for detection of bacterial infections², and secondly because of the high rates of asymptomatic infections that have been reported in some studies¹. Thus, it is necessary to reinforce the screening to detect *B. bacilliformis* in blood banks in endemic areas, as well as in those of nearby areas due to the interchange of population with endemic ones."

1 Pachas PE. *Enfermedad de Carrion (Bartonellosis) en el Perú*. Módulo técnico 13. Ministerio de Salud del Perú, Lima, Perú. 2001.

2 Magalhães RF, Urso Pitassi LH, Lania BG, et al. Bartonellosis as cause of death after red blood cell unit transfusion.

Ultrastruct Pathol 2009;33:151-4.

Recommendations for Treatment of Human Infections Caused by Bartonella Species.

Rolain JM, et al. *Antimicrobial Agents and Chemotherapy* 2004 June;48(6):1921-33.

Eight years old, this paper offers an extensive list of antibiotics for the treatment of Bartonella infection.

"Bartonella infections present a unique treatment challenge because they are persistent and often relapse and they involve an intraerythrocytic phase that apparently provides a protective niche for the bartonellae. The extreme diversity of disease manifestations is dependent on the infecting species of Bartonella and on the immune status of the patient. Because there are only two reports of randomized clinical trials for the treatment of Bartonella infections, an unequivocal treatment for all Bartonella infections does not exist, and thus, antibiotic treatment recommendations differ for each clinical situation. Treatment of Bartonella infections should be adapted to each clinical situation, to the infecting Bartonella species, and to whether the disease is in the acute or the chronic form. It is important that when the more severe Bartonella infections are recognized, diagnosed, and treated in a timely manner, the outcome is usually favorable."

Patients Associate Bartonellosis with these Symptoms.

Fatigue

Low-grade fevers, especially morning and or late afternoon

Fevers may accompany flu-like symptoms

Sweats in morning, late afternoon, sometimes at night; sweat described as thick or sticky.

Frontal headaches, often confused with sinus, or top-of-the-head headaches

Eye symptoms include episodes of blurred vision, red eyes, dry eyes

Tinnitus, hearing difficulties, decreased or increased sound sensitivity: hyperacusis

Sore throats, recurrent

Swollen glands, especially in the neck and underarms

Anxiety and worry attacks, perceived by others as being "extremely anxious"

Transient confusion and disorientation, described as "seizure-like"

Poor sleep, difficulty falling asleep, poor quality of sleep

Bilateral joint pain and stiffness

Muscle pains, specifically in the calves where there may also be twitching and cramping

Pain in the heels and soles of the foot, especially in the morning (misdiagnosed as *plantar fasciitis*)

Neuropathies: burning, vibrating, numbness, shooting pains

Tremors, muscle twitching

Heart palpitations, crushing chest pains

Episodic shortness of breath

Odd recurring rashes, red stretch marks, tender lumps and nodules on the sides of legs or arms, spider veins

Gastrointestinal symptoms, abdominal pain and acid reflux

Shin bone pain and tenderness

Curiosities

Since 2008, physicians need not report cases of bartonellosis in Wisconsin.

Ehrlichiosis/Anaplasmosis

Cases of anaplasmosis and ehrlichiosis continue to rise in Wisconsin and the Upper Midwest. Until 2009, only two species of Ehrlichia found in the US, *E. chaffeensis* and *E. ewingii*, were known to infect humans. *E. chaffeensis*, thought to occur only in the southern states, has caused confirmed cases of ehrlichiosis in Wisconsin. In one case the patient had no history of travel to other states where the pathogen and the disease are more common.

In an early paper on anaplasmosis, Dr. Johan Bakken and colleagues observed "HGE appears to be a common sub-clinical or mild infection among residents in northwestern Wisconsin." Usually ehrlichiosis signals an invasion of monocytes, but *E. ewingii* affects granulocytes as does *Anaplasma phagocytophilum*. Ehrlichiosis has been considered more serious and more severe than anaplasmosis, though both infections may require hospitalization.

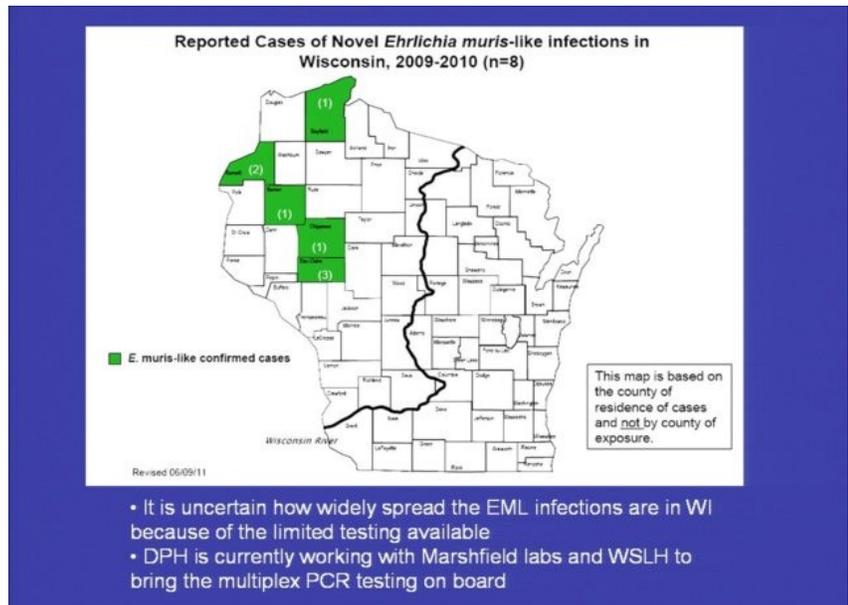
An as yet unnamed Ehrlichia, 98% similar to a species found in Eastern Europe and some parts of Asia, is called "species Wisconsin" in excerpts from the Pritt, et al paper [below]. That moniker has changed. The bacterium is now referred to as *E. muris-like*, or EML. Minnesota and Wisconsin pathologists, state and county health departments, Mayo Clinic and Health System, the U of M, UW and the CDC collaborated in the collection of tick specimens and testing to ascertain prevalence of EML.

Emergence of a New Pathogenic Ehrlichia Species, Wisconsin and Minnesota, 2009.

Pritt BS, et al. *New England Journal of Medicine* 2011 August;365(5):422-9.

"The identification of ehrlichia species Wisconsin in humans has important clinical and epidemiologic implications. Ehrlichiosis was not previously thought to be endemic in Minnesota and Wisconsin and would not be routinely tested for among patients from these areas. Also, commercial tests for ehrlichiosis may fail to provide an accurate identification of this organism. The considerable serologic cross-reactivity of the Wisconsin isolate with *E. chaffeensis* could confound diagnostic and epidemiologic studies and may explain the recent increase in the numbers of cases attributed to *E. chaffeensis* infection in Wisconsin and Minnesota on the basis of serologic testing only . . .

"Finally, detection of morulae in peripheral-blood samples from infected persons is an unreliable means of diagnosing infection with ehrlichia species Wisconsin. Morulae are detected infrequently in blood from patients infected with ehrlichia species 1 and were not found in blood from our four patients." PMID 21812671



Ehrlichiosis/Anaplasmosis Symptoms

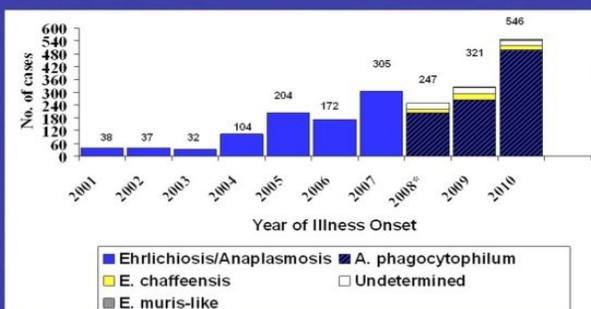
Fever (102°)	Chills and shaking
Severe headache	Muscle aches
Joint pain	Confusion
Change in mental status	Nausea
Vomiting	Diarrhea
Loss of appetite	Weight loss
Abdominal pain	Cough

Lab Evidence of Ehrlichiosis/Anaplasmosis may include:

- neutropenia
- lymphopenia
- thrombocytopenia
- elevated liver enzymes, C-reactive protein and sedimentation rate

Neurologic involvement due to these infections may occur in acute and convalescent stages. Severe neutropenia may allow opportunistic infections to take hold in affected patients.

Total Cases of Ehrlichiosis/Anaplasmosis Infections Wisconsin, 2001-2010



*In 2008, cases were classified using the new CDC case definition

Rhabdomyolysis-induced Acute Kidney Injury Secondary to *Anaplasma phagocytophilum* and Concomitant Statin Use

Talsness SR, et al. *WJM*. 2011 April;110(2):82-4.

The authors present a detailed examination of this case that began when the 84 year-old male patient was admitted to hospital suffering from confusion, weakness, diarrhea, and fever. He was treated initially with ceftriaxone, as meningitis was suspected; nonetheless, the patient's symptoms persisted. The patient's wife remembered her husband had had an attached tick in his groin area 5 days before admission to the hospital.

Observations made by the authors, who often cited others:

- * Infections other than anaplasmosis have caused rhabdomyolysis in patients who use statins.
- * In endemic areas, patients with fever, subjective symptoms of headache and myalgias, and laboratory evidence of leukopenia and thrombocytopenia should be given a presumptive diagnosis of anaplasmosis.
- * Granulocytic morulae, observed by trained pathologists, add weight to the diagnosis, however . . .
- * "Laboratory diagnosis should not delay treatment, given the rapid progression of this potentially fatal infection . . .

"In our case, the serologic testing was negative for HGA. The false negative result may be attributable to testing during the first week of the illness when sensitivity for this test is at its lowest . . . Laboratory diagnosis based upon blood smear interpretation has a sensitivity of 25% to 75%." PMID 21560563

The Name Game

At one time ticks that carry Lyme disease were called *Ixodes dammini*. Later, taxonomists realized *I. dammini* was not a new species at all, but the common deer tick, *Ixodes scapularis*. Significant taxonomical name changes may languish, unaccepted and unused. For example, in recently published papers researchers used HGA and HME to describe anaplasmosis and ehrlichiosis, even though usage of the latter terms was recommended by the Council of State and Territorial Epidemiologists (CSTE) in April, 2008.

For confused physicians ordering tests the Mayo Clinic lists the following as "aliases" for Ehrlichia or Anaplasma infection:

Anaplasma phagocytophilum HA (Human Anaplasmosis)

HGA (Human Granulocytic Anaplasmosis)

Ehrlichia chaffeensis (*E. chaffeensis*) *Ehrlichia ewingii*

Ehrlichia muris-like (EML) HE (Human Ehrlichiosis)

HME (Human Monocytic Ehrlichiosis)

EML (*Ehrlichia muris-like*) HGE (Human Granulocytic Ehrlichiosis)

http://www.mayomedicallaboratories.com/test-catalog/print.php?unit_code=84319

In-cites

Rush University Medical Center
Kallick CA. 2011

"EA infections [Ehrlichiosis/Anaplasmosis] may be an underlying, undiagnosed cause for these [leukemia, systemic lupus erythematosus, myelodysplastic disease, multiple sclerosis, amyotrophic lateral sclerosis, and rheumatoid arthritis] and other immune system diseases. This hypothesis, long overlooked, has never been subjected to adequate, rigorous study sufficient to prove or disprove its truth."

Division of Vector-Borne Diseases, Bacterial Disease Branch, Centers for Disease Control and Prevention, Fort Collins, Colorado
Dolan MC, et al. 2011

"Results from this study indicate that doxycycline-impregnated bait is an effective means of reducing infection rates for *B. burgdorferi* and *A. phagocytophilum* in both rodent reservoirs and questing *I. scapularis* ticks."

Gunderson Lutheran Medical Center
Lovrich SD, et al. 2011

"The findings therefore confirmed that the upper Midwestern focus for HGA endemicity now includes the regions immediately surrounding La Crosse, WI."

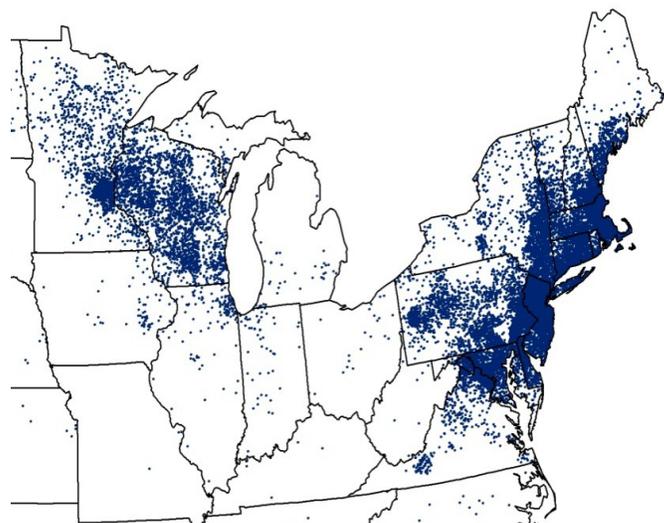
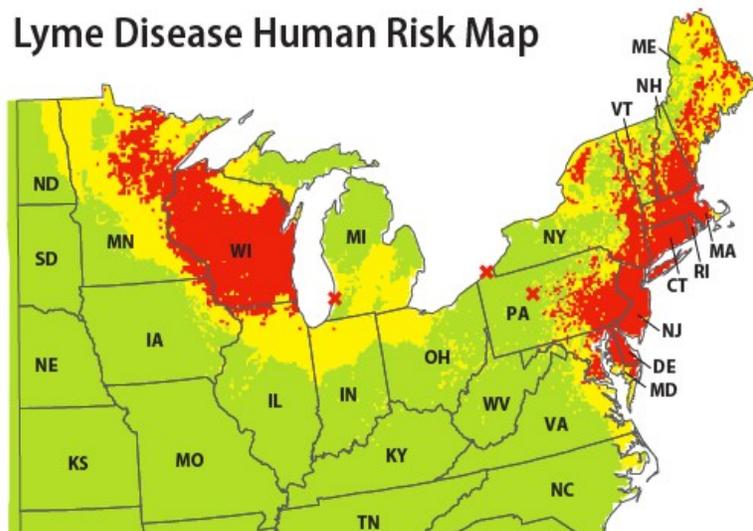
Marshfield Clinic Ghera P, et al. 2011

"In our patient, the lab work was consistent with anaplasmosis, the hearing loss improved [on doxycycline] with no other specific treatment, and there was no other possible explanation for the former. Therefore, we concluded that the patient's acute transient bilateral sensorineural hearing loss was associated with anaplasmosis."

More Name Games

Now, there's another rickettsial illness with another name change: Rocky Mountain spotted fever is supposed to be called Spotted Fever Rickettsiosis.

Lyme Disease Human Risk Map



Yale, Lyme Disease Risk Map—US, 2012

An acarological map completed by Yale researchers Diuk-Wasser, et al, illustrates high risk areas for contracting Lyme disease. Ticks examined by study participants were collected between 2004 and 2007 at random sites in state parks and other public-access forested lands. Each site was visited five times.

Yale researchers explained the need for the study:

"Accurate information on spatial patterns of human risk of exposure to infected ticks is essential for the public to make personal protection decisions and for efficient allocation of public health resources. Delineation of Lyme disease-endemic areas also assists local medical communities in considering a diagnosis of tick-borne disease. Accurate and timely diagnosis is critical as delay may lead to severe disease requiring more aggressive treatment. . .

"Significant Lyme disease underreporting and misdiagnosis and geographic expansion in vector distribution limit the reliability of using past human cases to predict risk. In addition, the variable interval between time of exposure to infected ticks and manifestation of symptoms confounds the precise determination of exposure location, and can result in the incorrect association of cases with specific counties . . .

"In terms of public health applications, the lack of spatial structure in nymphal infection prevalence, combined with the difficulty in accurately estimating prevalence with small sample sizes, brings into question the validity of using an exact prevalence threshold to guide clinical decisions on treatment, such as the current [Infectious Diseases Society of America] recommendation of tick-bite prophylaxis when infection prevalence is > 0.2 . Our results indicate that the presence of any number of infected nymphs may be considered sufficient to recommend post-exposure prophylaxis. Infected nymphs were found in 92.3% of the sites where a threshold of 14 nymphs per 1,000 m² were collected."

<http://www.ajtmh.org/content/86/2/320.full>

Lyme Disease in Wisconsin

<i>Cases by year</i>	<i>National Ranking for Cases Reported by year</i>	<i>National Ranking for Incidence by year</i>	<i>(per 100,000 population)</i>
2007 1,814	7	8	32.4
2008 1,493	7	9	26.5
2009 1,952	6	9	34.5
2010 2,505/3,488*	3	4	44.0
2011 2,408/3,649	4	6	42.2

**Beginning in 2010, both confirmed and probable cases were counted and recorded by public health departments and CDC.*

CDC, Reported Cases of Lyme Disease—US, 2010

One dot is placed randomly within the county of residence for each confirmed case. Though Lyme disease cases have been reported in nearly every state, cases are reported based on the county of residence, which is not necessarily the county of infection.

Lyme Disease Testing: Under Fire for Decades

1990 The Minnesota State Health Department tests seventeen foresters for Lyme disease and sends serum samples from all seventeen to four outside laboratories. For the same samples, no positives are found at one laboratory; six positives are recorded at another.

1991 Forty-five laboratories are tested by the Wisconsin State Laboratory of Hygiene for proficiency in identifying *Borrelia burgdorferi* in serum samples. The proficiency testing reveals 4% to 21% of the labs cannot identify titers of 512 or more. With lower levels of anti-Bb antibody in the samples 55% of the laboratories cannot correctly identify case-defined serum samples. PMID 1640618

1992-1994 Known-positive serum samples are again tested by the labs that had participated in the previous study. Testing accuracy shows no improvement. PMID 9041384

1994 With discrepancies in lab testing for Lyme disease apparent to regulatory agencies, the Council of State and Territorial Epidemiologists (CSTE) decides to standardize testing. Henceforth, physicians are required to follow a two-step testing algorithm, ELISA or IFA followed by Western blotting. New criteria for the interpretation of Western blot tests are instituted; borrelia-specific bands 31 and 34 are no longer considered indicative of Lyme disease infection. Nearly all labs comply with this change.

1995 1996 Between 8% [Hilton, et al] and 69% [Fawcett, et al] of patients previously considered positive by Western blot no longer meet CSTE criteria [used by the CDC] for [positive] Western blot results.

2005 A two-year study from Johns Hopkins reveals commercial tests may miss up to 75% of Lyme disease infections. To reach this conclusion the researchers employed culture, two-tier serology [ELISA or VIDAS assays followed by Western blotting], and PCR analysis. To achieve 100% diagnostic accuracy for Lyme disease all three test methods had to be combined. Two-tier serologic testing was accurate in just 18% of samples tested. PMID 16207966

From the CDC:

"Lyme disease is diagnosed based on: Signs and Symptoms. A history of possible exposure to infected black legged ticks. Laboratory blood tests are helpful if used correctly and performed with validated methods." <http://www.cdc.gov/lyme/diagnosistreatment/index.html>

"Like blood tests for many other infectious diseases, the test for Lyme disease measures antibodies made by white blood cells in response to infection. It can take several weeks after infection for the body to produce sufficient antibodies to be detected. Therefore, patients tested during the first few weeks of illness will often test negative." <http://www.cdc.gov/lyme/diagnosistreatment/LabTest/>

From the FDA:

"Tests should be used only to support a clinical diagnosis of Lyme disease and should never be the primary basis for making diagnostic or treatment decisions. Diagnosis should be based on a patient history, which includes symptoms and exposure to the tick vector and physical findings . . .

"A negative result indicates only that there was no serologic evidence of infection with *B. burgdorferi*. It should not be used as the basis for excluding *B. burgdorferi* as the cause of illness, especially if the blood was collected within 2 weeks of when symptoms began. A positive or equivocal result is presumptive evidence of the presence of anti-Bb. It should always be followed by second-step testing and should not be reported until the second step testing is completed." <http://www.canlyme.com/fdatests.html>

In-Cites

University of Connecticut Health Center

Harman MW, et al, 2011: "*B. burgdorferi* is able to penetrate matrices with pore sizes much smaller than the diameter of the bacterium."

University of California, Davis

Tunev SS, et al, 2011: "Together, these findings suggest a novel evasion strategy for *B. burgdorferi*: subversion of the quality of a strongly induced, potentially protective borrelia-specific antibody response via *B. burgdorferi*'s accumulation in lymph nodes."

University of New Haven

Sapi E, et al, 2011: "Antibiotics have varying effects on the different morphological forms of *B. burgdorferi*. Persistence of variable organisms in round-body forms and biofilm-like colonies may explain treatment failure and persistent symptoms following antibiotic therapy for Lyme disease."

Curiosity The western fence lizard, on which ticks feed, can purge *B. burgdorferi* from its intestines.

Lyme meningitis, the major cause of childhood meningitis in an endemic area: A population based study.

Tveitnes D, et al. *Archives of Disease in Childhood*. 2012 March;97(3):215-20.

A retrospective study in a Lyme disease-endemic area of Norway identified 211 children with CSF pleocytosis. Two-thirds of these pediatric patients (142 or 67%) had Lyme disease meningitis. Children in the study ranged from 3 months to 14 years of age. The researchers stated, "The positive predictive value for having LM [Lyme Meningitis] if the child had facial nerve palsy or head and/or neck stiffness (meningism) as the only symptom was 97% for both variables." PMID 22247243

Lyme arthritis presenting in children with joint effusions.

Milewski MD, et al. *J Bone Joint Surgery Am*. 2011 February 2;93(3):252-60.

In this study, joint aspirations from 391 pediatric patients in an endemic area were reviewed. Thirty-one per cent (123 patients) tested positive for Lyme disease. Thirteen per cent (51 patients) were diagnosed with septic arthritis. Researchers found that patients with higher nucleated cell counts [123,000 cells/mm] had septic arthritis, while patients with Lyme arthritis showed lower cell counts [60,200 cells/mm]. Fever was found in both groups, but septic arthritis patients produced more low grade fevers and more high fevers than those with Lyme disease arthritis. Additionally, nearly all septic arthritis patients refused to put weight on the affected leg, while 39% of those with Lyme arthritis refused to bear weight on the affected leg. PMID 21266639

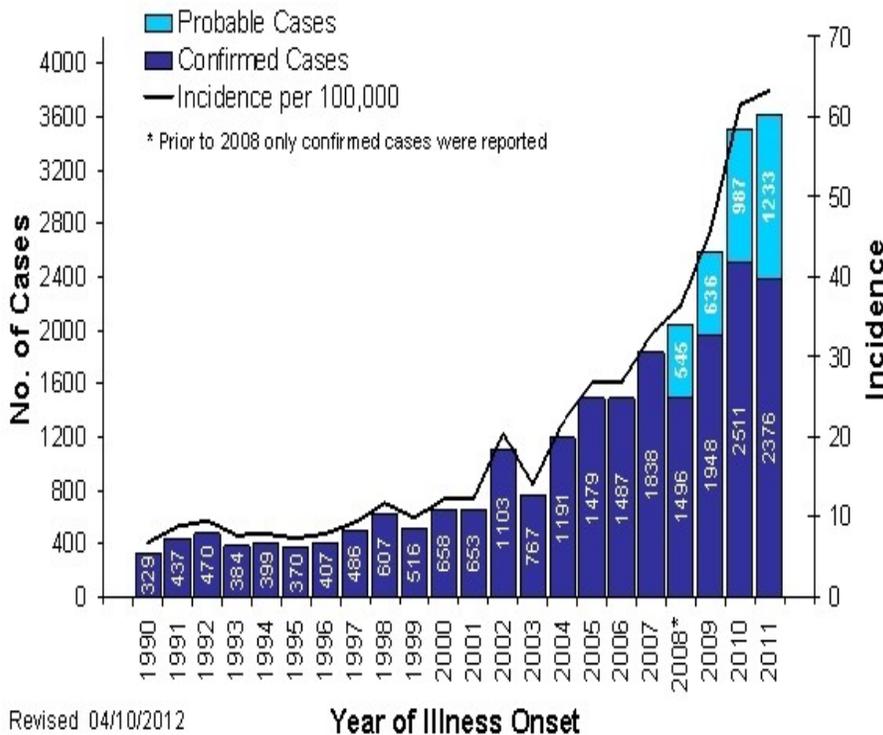
Stroke Due to Lyme Neuroborreliosis: Changes in Vessel Wall Contrast Enhancement.

Lebas A, et al. *J of Neuroimaging*. 2010 December doi: 10.1111/j.1552-6569.2010.00550.x.

From the abstract: "Neuroborreliosis is a rare cause of stroke in children . . . Gadolinium-enhanced MRI provided additional information facilitating the diagnosis of vasculitis in a child with Lyme neuroborreliosis and stroke. The location of vessel wall enhancement was correlated with the topography of the acute infarct, and the lack of vessel lumen obstruction supported the diagnosis of vasculitis rather than any other cause." PMID 21122000

Reported Lyme Disease, WI, 1990-2011

(n=25,313)



Revised 04/10/2012

Tips and Bits

Busy with Bugs

Wisconsin's Department of Health processed more than 4,000 reports of tick-borne diseases in 2011. View a lecture and Power Point on TBDs from WI DOH at <http://dhsmedia.wi.gov/main/Catalog/catalogs/default.aspx> In the search box, type in "Hoang Johnson" (state epidemiologist).

Acne and Antibiotics? No worries. . .

For physicians, warnings on over-prescribing antibiotics abound. Nonetheless, dermatologists pose a challenge to current cautions: "In our study, the prolonged use of antibiotics from the tetracycline class that are commonly used to treat acne lowered the prevalence of colonization by *S. aureus* and did not increase resistance to the tetracycline antibiotics." PMID 21482860

CTS (No, not the hot new Cadillac)

The National Center for Health Statistics sought information on employed people with carpal tunnel syndrome in the prior 12 months. Women were more likely than men to have CTS. Those 14-29 years old had the fewest cases of CTS, while those aged 45-64 had the highest. Three point one per cent of responding workers were affected. [Carpal tunnel syndrome has been associated with Lyme disease. PMID 2725567]

Persistence of Non-Cultivable *Borrelia burgdorferi* Following Antibiotic Treatment: Critical Need for Further Research. Stephen W. Barthold, DVM, PhD, Distinguished Professor and Director Center for Comparative Medicine Schools of Medicine and Veterinary Medicine University of California, Davis. Selections from his testimony before the House Subcommittee on Africa, Global Health and Human Rights, **July 17, 2012**, Washington, D.C.

- Studies in mice, dogs and non-human primates have demonstrated persistence of non-cultivable spirochetes following treatment with several different bacteriostatic and bactericidal antibiotics.
- Non-cultivable spirochetes can be visualized as morphologically intact, antigen-positive spirochetes in ticks feeding upon antibiotic-treated mice and macaques, and in tissues of antibiotic-treated mice for 12 or more months after completion of antibiotic treatment.
- Non-cultivable spirochetes in antibiotic-treated mice can be acquired by ticks, transmitted by ticks, and survive molting of ticks from larvae to nymphs and to adults, confirming their viability.
- Non-cultivable spirochetes can be transmitted from antibiotic-treated mice to recipient SCID mice through tick-borne infection or transplantation of tissue allografts, and disseminate in recipient mice.
- Persisting non-cultivable spirochetes transcribe RNA, confirming their metabolic viability.
- Low copy numbers of target DNA of non-cultivable spirochetes are present in tissues of mice following antibiotic treatment, with evidence of very low but increasing levels of replication when acquired by ticks, transmitted by ticks, in different stages of ticks, and following transmission to recipient hosts.
- Non-cultivable spirochetes resurge at 12 months after antibiotic treatment, with increased *Bb*DNA copy numbers and widespread dissemination in host tissues.
- Preliminary results [from a not-yet-published Barthold study] suggest that resurgent non-cultivable spirochetes have lost small linear and circular plasmids, which may explain their attenuated, low-replicative behavior.

Conclusion: Persisting viable but non-cultivable *B. burgdorferi* is now a convincing phenomenon based upon a number of animal-based (mouse, dog and primate) studies using a number of different antibiotics, and the significance of continued infection indeed needs to be better understood. **It is time to recognize that Lyme disease is not a simple bacterial infection.**