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"Encouraging awareness, prevention & treatment of Lyme Disease (Borreliosis) in Ireland."

Letter of Concern regarding issues faced by Lyme Disease Patients UK & Ireland

A Statement from Tick Talk Ireland

Table of Contents:

References:

To David Cameron Prime Minister, London (UK), Dr James Reilly Minister Health, Dublin (Ireland) & Dr Paul McKeown, Health Protection & Surveillance Centre, Dublin (Ireland) March 2012

Lyme Disease is a serious bacterial infection triggered most often by the bite of *the ixodes ricinus* tick otherwise known as sheep or castor bean tick. The main problem resulting from this disease is there exists a divide in the medical & political community as to the best methods for testing & treatment of these patients – the ones most harmed by this are the patients themselves. We would like to summarise below our main concerns to try & enhance & encourage dialogue between physicians, patients, scientists, politicians & epidemiologists on how best to control cases of Lyme disease & how testing & treatment methods could be improved to ensure a swifter diagnosis & a better prognosis for recovery.

Concern One: Recognition – many patients have reported that the practising physician, whether it's the local GP or attending physician at A & E, have little knowledge of Lyme disease & its myriad of symptoms. This is not made easy by the fact that Lyme can imitate so many other conditions from arthritis to ME or MS & is often even confused with symptoms of depression. The patient may re-call a known tick bite, may show pictures of rashes & may declare that symptoms arose from this event & yet the attending physician is unable to make a diagnosis as they are often looking for too narrowed a definition. The first symptom known to develop can be a bulls-eye rash, which can be in concentric rings & expands outwards from the site of the bite. The downside is that the rash may not always appear at the site of the bite, may develop slowly (sometimes several weeks after the infection occurred) & may be uniform in nature. In some cases the rash does not appear at all. This provides a challenge for both physician & patient recognising a symptom which at the outset may appear minor, but can indicate a serious progression to disseminated disease if this early symptom is not promptly diagnosed & treated. Some patients have been known to skip stage one of the disease & begin to exhibit signs of late Lyme such as bell's palsy, meningitis, encephalitis, migrating joint pains & profound, overwhelming fatigue. The practicing physician may be at a lost as to the cause of joint pain, muscle aches & fatigue & begin to suggest a causation of depression, hindering diagnosis even further.

Another area in the subject of recognition is the misconception that Lyme can only be acquired in small geographic areas. Lyme infected ticks can be carried by a variety of hosts such as mice, squirrels, hedgehogs & deer. Even migrating birds can carry the disease. Members of the public travel within the boundaries of UK & Ireland as well as overseas. Infections therefore don't necessarily need to be restricted to areas of the New Forest or the Scottish highlands. In a recent pet study in the UK the spread of *borrelia* carrying ticks were more prominent countrywide & indeed the map published by Faith Smith, researcher at the University of Bristol shows ticks to be a problem right across the country. Where ticks reside so can infections arise. (Refer to bibliography for links).

Concern Two: Testing – testing is a contentious issue in the States made even worse in Europe due to the many strains being evident in the region. The current method of testing is to use a 2 tier system. ELISA is the 1st tier **indirect** antibody test which is not specific to a *borellia* & can be affected by the stage of the disease, the strain of *borrelia* infection & the level of immune response on the body. Trinity Biotech states that early Lyme & some manifestations of late Lyme can result in a negative result & should not be used to exclude diagnosis. The use of antibiotics early in treatment can abrogate immune response also creating false negative serology. Sadly the patient is often told with gusto that a negative test completely rules out Lyme but even the test kit manufacturer does not claim this fact to be true, they are clear in their instructions the pitfalls of testing, however this is rarely passed onto the GP or the patient. If the patient is fortunate enough to prove positive in the test they are then offered a 2nd tier test which is also an **indirect** antibody test called the Western

Blot. This test designed to rule out false positives as it is considered more 'specific' to Lyme bacteria. The principal of this test is that a specified number of bands have to be reactive. Unfortunately European studies between test kit manufacturers have shown differing results. More curiously is that in some studies a patient maybe completely negative in the 1st tier test but subsequently are positive in the 2nd tier, & yet WB is rarely offered after a negative ELISA, potentially missing some patients. The type of bands can also be an issue as each type of *borrelia* strain can produce a different set of reactive bands. The labs in Scotland headed by Ho Yen did a retrospective study & found that a subset of patients who were initially negative were actually positive once local strains were used & different bands were identified as relevant to the local population. To try & provide a level of standardization MiQ 12 2000 was developed whereby 3 bands are required for a positive result. Curiously in Germany only 2 bands are needed (details in references below). This leads to a strange situation where if you were being diagnosed in Germany or Scotland you may well be positive, but in the UK you will most probably not be treated at all.

Another problem which is potentially very serious is that in UK & Ireland there exists a strain called ***VS116 (B. valaisiana)***. In a study in Ireland 50% of ticks were discovered to carry this strain & some ticks carried mixed infections of *VS116*, *b.garinii & b.afzellii*. Little research has been done on the strain *VS116* & this is certainly not being picked up in current testing, as most tests are designed for the 3 predominant strains***, b.azfelii, b.garinii, & b.burgdorferi***. In studies however *VS116* was identified in an EM rash & in spinal fluid of a Lyme patient suggesting pathological causation. In Europe other strains such as ***B. bissettii***, ***B. valaisiana, B. lusitaniae, B. spielmanii***, and ***B. bavariensis*** may also cause disease, as shown in the bibiolography below.

A further area of concern is that antibodies may be bound immune complexes & may not be present in sufficient numbers to create a strong enough antibody response. Patients may be seronegative & yet still be seriously ill with Lyme disease. An example of studies regarding this can be found in the references section below.

Sadly if you have a false negative test but a known tick bite, possible rash, definitive symptoms & you are categorically told you DO NOT have Lyme disease based on serology, then often the diagnosis you are offered is one of chronic fatigue syndrome. Suggestions of CBT & GET are made by the physician who feels it is in your best interest to do more to 'get yourself better'. Meanwhile the bacterium is raging havoc in the body, disseminating to organs including the brain & making the patient more miserable as time progress. They are unable to function, cannot hold down a regular job & become dependent on their family for help. Relationships can break down & money can be a very serious problem for these patients who are being left undiagnosed & undertreated by the system. Studies have shown that Lyme bacteria can cross the blood brain barrier & affect the central & autonomic nervous system; the brain is an area where antibiotics may find it harder to reach. This is why IV rocephin may be a better choice for Lyme patients & why it is important to treat the infection promptly to prevent further damage to the brain function of Lyme patients.

Concern Three: Persistence – there has been a worrying trend in America by members of the Infectious Disease Society of America who suggest that Lyme disease once found can be easily treated with a 3 weeks course of antibiotics. This may be true for acute cases of Lyme but what about disseminated disease? We know that antibiotics have trouble penetrating areas where the bacteria may hide. *Borrelia* spirochetes are spiral shaped with a flagella or tail which propels them to various sites in the body, into the joint fluid, in tissue, in brain matter & even the heart. In some cases the eyes are affected causing uveitis & on occasion even blindness. Brain & spinal cord inflammation can cause paralysis, & heart block can lead to death in extreme cases. The bacteria divides very slowly so even if the antibiotics are managing to target the effected site a much longer

dose is needed to knock down the number of bacteria. ***Streptococcus*** bacteria have a dividing time of 20 minutes thus allowing 10 days of treatment to do the job, bacteria such as ***borrelia*** divides every 24 hours however, requiring a much lengthier form of treatment to eradicate the disease.

It was identified in syphilis, another spirochetal infection that cyst formations can occur. This is a defense mechanism that allows the spiros to 'ball up' & become cell wall deficient creating another challenge for the treating physician. He must be sure that the antibiotics chosen can tackle these cell wall deficient forms as well. These cyst forms can also lead to persistence of infection. Imagine a bacteria so intelligent that it can ball up to evade antibiotics & then get moving again once the coast is clear. This may also explain the waxing & waning symptoms of the disease. Often the presence of spiros in joints & organs can cause an inflammatory response which can also lead to a surge of cytokines. During treatment this surge of cytokines can cause healing crisis known as a 'herxheimer reaction'. The patient may worsen greatly as the bacteria are being killed - the treating physician may mistake this to be an allergic reaction & stop all treatment. They may also feel that a patient must be hugely improved after a short course of treatment & if not 'it couldn't have been Lyme'. This can also be a false notion which is a challenge for both doctor & patient.

Concern Four: Co-infections – physicians familiar with Lyme are also familiar that ticks can harbour concomitant diseases. Known as nature's dirty little needle ticks can also carry rickettsia, babesia, ehrlichia, & bartonella. Animals can be infected with red water, tick pyaemia, louping ill virus & tick-borne fever. In mainland Europe tick born encephalitis can paralyse & may even kill & in Africa tick-borne relapsing fever is of grave concern. Sadly the symptoms of tick-borne infections can sometimes overlap & the tests may not always pick up the various infections; the number of strains can also be a challenge in testing. It has been known however that treatment for various co-infections may be different to treatment for solely Lyme & also recovery may be a lot slower for these patients. We feel that more research must be done on this area. A separate article on co-infections pertinent to UK & Ireland is attached for your reference.

Concern Five: Transmission – Syphilis, Lyme's closest cousin is known to be a sexually transmitted disease. Lyme meanwhile is transmitted through the bite of an infected tick. However studies have shown that Lyme can be passed on congenitally & can even cause fetal damage. One study showed spirochetes were found in breast milk & semen suggesting the possibility of transmission through other means. More studies need to be done urgently as the possibility of Lyme being transmitted between couples is of major concern. Another worrying area of transmission is within the blood bank. A study in Ireland found that 15% of blood was infected with Lyme. Studies in American show that babesia can be transmitted by blood transfusion methods. Spiros have also been known to survive freezing (refer to references below).

Some patients say that they don't recall a tick bite before illness. This is not surprising as ticks are very small; they inject an anesthetic into the bite wound so the patient may not feel a thing. The rash if present is not normally itchy so may go unnoticed, particularly if tucked in behind the knee or in the hairline. Rashes are not always present either making diagnosis difficult. But what if some of these patients actually didn't have a tick bite at all but received their illness via congenital, or sexually transmitted means or by way of blood transfusion? This opens up a number of questions for our society, particularly a society that is trying hard to minimise the number of sick patients in our midst. Perhaps more needs to be done to help them recover, to help them being treated effectively & quickly & help ensure the blood banks are safe.

Concern Six: Guidelines – In the year 2000, the IDSA (Infectious Disease Society of America) decided to issue some guidelines on how to manage Lyme disease cases. The recommendation of 2-4 weeks

treatment is based on acute cases of Lyme disease. Little thought is given to persistence of infection which has been shown in studies as listed below. All too often patients who seek help with further treatment are turned away from disbelieving practitioners. Physicians in the U.S. who do treat further are being bullied by IDSA members or insurance companies for daring to treat beyond the recommended guidelines. Sadly infectious disease consultants in UK & Ireland have cited they are also afraid to treat long term for fear of repercussion. The patient is left wondering what happened to the rules of good medical practice which states that patients should be treated with dignity & that each patient should be treated as an individual as well as to 'encourage patients who have knowledge about their condition to use this when they are making decisions about their care.'

Despite lengthy workshops & seminars on the disease & the lack of effectiveness of current testing & treatment little has changed. Lyme expert Sue O'Connell of the Lyme Borreliosis Unit UK attended a seminar in 2010 called **'A Workshop on the Critical Needs and Gaps in Understanding Prevention, Amelioration, and Resolution of Lyme and Other Tick-borne Diseases: the Short-Term and Long-Term Outcomes'.** She mentioned the following. *'Greater efforts are needed to provide education for prevention and early diagnosis to avoid late complications. Further improvements in diagnostic tests would be welcomed. More research is required to assess the causes and management of post-Lyme symptoms'* (Sue O'Connell 2010 - IOM)(further comments are posted in the bibliography below).

This sounds like a change in the right direction; sadly since this meeting we have seen very little evidence of any change at all. Patients are still being under diagnosed & under treated & testing is still an issue for many. Lyme specialists in the UK are dwindling with one refusing more patients, one retiring, one with a suspended license & another recently told of a GMC case against them which was thankfully dropped, for the time being anyway. Quite why Lyme patients & their physicians have to be bullied in this way we do not know. We feel that more needs to be done to improve the lives of patients & that specialists should be protected, as their knowledge is invaluable. The NHS & HSE are under so much pressure as it is & often do not have the knowledge to deal with this insidious disease. In fact we need more help not less, the more that bullying goes on the more that patients end up back where they started & putting more pressure on the system. They will end up being hospitalised more as their disease progresses & will become more & more dependent on benefits for a long period of time. It is therefore important to see a change in direction with regards to this disease. Anyone can be next, a close friend, a neighbour, the local priest, the farmer down the road, a hard working business man who likes to spend time in the country at the weekend. We owe it to them to make sure things improve & we owe it to all the current patients who have been ridiculed, told it is in their heads, that they can't possibly have Lyme disease otherwise they'd be 'better by now'. Let's start afresh & make a change!

Summary: *Tick Talk Ireland would like to see patient testing improved greatly & in the interim a greater awareness among physicians that a negative test result does NOT rule out a Lyme diagnosis. We would like to see physicians being reassured that the patient/doctor relationship is key, & the use of restrictive guidelines does little to improve the health of patients. Expert physicians should not be made to feel threatened if they feel that a patient requires a lengthier course of treatment to help them get better. Lyme is a serious illness which is very complex & requires more than 'treatment in a box' mentality. We would like to see more awareness being raised on the various strains in Europe beyond the common ones such a b. garinii & b. afzellii but also b. bissettii & b. valaisiana (VS116) which are currently not being picked up in testing, despite VS116 being widely identified in UK & Irish ticks. We would like to encourage co-infections to be tested for & treated in tick infected patients. Ticks are known to carry a multitude of diseases which can hinder a patient's recovery greatly.*

"The good physician treats the disease; the great physician treats the patient who has the disease" - Sir William Osler

Sources & References:

Concern One: Recognition –

Role of Migrating Birds:

Differential Role of Passerine Birds in Distribution of *Borrelia* Spirochetes, Based on Data from Ticks Collected from Birds during the Postbreeding Migration Period in Central Europe ▽

Lenka Dubska,[1*] Ivan Literak,[1] Elena Kocianova,[2] Veronika Taragelova,[3] and Oldrich Sychra[1]
Appl Environ Microbiol. 2009 February; 75(3): 596–602.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2632145/

Borrelia spirochetes in bird-feeding ticks were studied in the Czech Republic. During the postbreeding period (July to September 2005), 1,080 passerine birds infested by 2,240 *Ixodes ricinus* subadult ticks were examined. *Borrelia garinii* was detected in 22.2% of the ticks, *Borrelia valaisiana* was detected in 12.8% of the ticks, *Borrelia afzelii* was detected in 1.6% of the ticks, and *Borrelia burgdorferi* sensu stricto was detected in 0.3% of the ticks. After analysis of infections in which the blood meal volume and the stage of the ticks were considered, we concluded that Eurasian **blackbirds** (*Turdus merula*), **song thrushes** (*Turdus philomelos*), **and great tits** (*Parus major*) are capable of transmitting *B. garinii*; that juvenile blackbirds and song thrushes are prominent reservoirs for *B. garinii* spirochetes; that some other passerine birds investigated play minor roles in transmitting *B. garinii*; and that the presence *B. afzelii* in ticks results from infection in a former stage. Thus, while *B. garinii* transmission is associated with only a few passerine bird species, these birds have the potential to distribute millions of Lyme disease spirochetes between urban areas.

Pets spreading Lyme:

Ticks are on the march in Britain

Press release issued 23 March 2011 http://bristol.ac.uk/news/2011/7541.html

The prevalence of ticks attaching to dogs in Great Britain has been mapped by scientists as part of a national tick survey. The findings reveal that the number of dogs infested with the blood-sucking parasites was much higher than expected. The study also confirms that a European tick species now exists in Great Britain.

The research, carried out by academics from the University of Bristol's Veterinary Parasitology Group and published in the journal *Medical and Veterinary Entomology*, found that at any one time 14.9 per cent of dogs were infested with ticks.

Professor Richard Wall, head of the Veterinary Parasitology Group at the University, said: "This is an important study because the results suggest that the risk of tick infestation is far higher in dogs than was previously thought. This has serious implications for the incidence of tick-borne disease. The study also confirms that a non-native species of tick, which is also a major disease vector in Europe, is now established in southern England. It will be of considerable interest to monitor its spread."

Dogs can be infected with a number of tick-borne diseases, including Lyme disease. A non-native species of tick could help spread new diseases from Europe in the UK.

Concern Two: Testing –

Affects of Antibiotics:

Laboratory Testing for Lyme Disease : Possibilities and Practicalities.

Reed, K.D., 2002. *Journal of clinical microbiology*, (Feb), pp.319-324.

http://jcm.asm.org/content/40/2/319.full

Both IgG and IgM responses can be greatly diminished or absent in patients receiving antimicrobial therapy early in the course of disease (Reed 2002)

Seronegativity:

From Trinity Biotech test kit:

http://www.trinitybiotech.com/Product%20Documents/40-8696P-29EN%20.%20burg.%20EI\A%28%20IgG,%20IgM%29%20Test%20System.pdf

The diagnosis of Lyme disease should be made based on history and symptoms (such as erythema migrans), and other laboratory data, in addition to the presence of antibodies to *B. burgdorferi*.

B. burgdorferi strains exhibit considerable antigenic variation. Patients often develop early antibodies to the flagellar antigen which can be cross reactive.

*Negative results (either first or second-tier) should not be used to exclude Lyme disease. High Complexity Test.

*Patients in the early stage of disease and a portion of patients with late manifestations may not have detectable antibodies.

*Early antimicrobial treatment, after appearance of EM may lead to diminished antibody concentrations.

*Serologic tests have been shown to have low sensitivity and specificity and, therefore, cannot be relied upon for establishing a diagnosis of Lyme disease.

Limitation of serologic testing for Lyme borreliosis: evaluation of ELISA and western blot in comparison

Tylewska-Wierzbanowska S, Chmielewski T. Wien Klin Wochenschr. 2002 Jul 31;114(13-14):601-5.

http://www.ncbi.nlm.nih.gov/pubmed/12422608

The aim of the study was to evaluate a one-step procedure using an ELISA test of high specificity and a two-step procedure using immunoblot as a confirmation test, and to compare the results of serological testing with detection of bacterial DNA and living spirochetes. Sera, synovial (SF) and cerebro-spinal fluids (CSF) were obtained from 90 patients with clinical symptoms of Lyme borreliosis. Serum samples were tested with recombinant ELISA and Western blot assay. Citrated blood, cerebrospinal and synovial fluids samples were cultured in cell line and tested by PCR to detect spirochetes. No correlation was found between levels of specific B. burgdorferi antibodies detected with a recombinant antigen ELISA and the number of protein fractions developed with

these antibodies by immunoblot. Moreover, Lyme borreliosis patients who have live spirochetes in body fluids have low or negative levels of borrelial antibodies in their sera. This indicates that an efficient diagnosis of Lyme borreliosis has to be based on a combination of various techniques such as serology, PCR and culture, not solely on serology.

Serodiagnosis of Borreliosis: Indirect Immunofluorescence Assay, Enzyme-Linked Immunosorbent Assay and Immunoblotting

Wojciechowska-Koszko et al, 2011. Arch Immunol Ther Exp (Warsz). Feb;59(1):69-77.

http://www.ncbi.nlm.nih.gov/pubmed/21258869

"The IIFA screening test used for diagnosing Lyme borreliosis produced the highest percentage of positive results, which were then confirmed by immunoblot, but *not by ELISA*. Therefore using only ELISA as a screening test or for diagnosing Lyme borreliosis seems debatable."

Our experience with examination of antibodies against antigens of *Borrelia burgdorferi* in patients with suspected Lyme disease.

Durovska et al 2010;111(3):153-5. Bratisl Lek Listy

http://www.ncbi.nlm.nih.gov/pubmed/20437826

RESULTS:

All patients had specific antiborrelial antibodies confirmed by using the westernblot in spite of negative ELISA. Immunological investigations revealed a deficiency of cellular immunity in all patients and in a part of them (15.6%) a deficiency of humoral immunity was also found. The presence of different types of autoantibodies was detected in 17 (53.1%) patients.

CONCLUSION:

In patients with persisting difficulties that could be associated with Lyme disease, it is necessary to use the westernblot test which could prove the presence of specific antibodies. It is probably due to the very low production of specific antibodies caused also by the status of immune deficiency detected in all our patients

CLINICAL STUDY Significance of specific antibody determination in Lyme borreliosis diagnosis

Bazovska S et al, Institute of Epidemiology, Faculty of Medicine, Comenius University, Bratislava (2001)

http://www.bratislmedj.sk/2001/10210-02.pdf

To diagnose LB in neurological patients is a difficult process, considering the wide scale of clinical symptoms. Proof of anti-borrelia antibodies in itself does not establish the base of a causal relationship between the infection and its clinical manifestation. Results of serological tests should be evaluated very carefully, as these tests are not standardised and correlation of results among the various commercial sets and laboratories is weak, requiring consideration of possible false-positive or false-negative data. Some of the problems can be resolved by immunoblot examination that may confirm the presence of specific antibodies and exclude certain nonspecific ones, however when taking the variability of borreliae circulating through Europe and variability of the immune response of patients in account even a negative immunoblot test cannot exclude the disease. Presently it is

recommended to use immunoblot, as this test has higher specificity in the framework of a two-step serological examination. Results of serological tests have only supportive value in the diagnosis, their correct evaluation requires knowledge of their strong and weak points, thereby emphasizing the need for close co-operation of clinical and laboratory workers.

Seronegative Lyme disease. Dissociation of specific T- and B-lymphocyte responses to *Borrelia burgdorferi*.

Dattwyler et al, 1988 N Engl J Med. Dec 1;319(22):1441-6.

http://www.ncbi.nlm.nih.gov/pubmed/3054554

The diagnosis of Lyme disease often depends on the measurement of serum antibodies to *Borrelia burgdorferi*, the spirochete that causes this disorder. Although prompt treatment with antibiotics may abrogate the antibody response to the infection, symptoms persist in some patients. 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. Although these patients had clinically active disease, none had diagnostic levels of antibodies to B. burgdorferi on either a standard enzyme-linked immunosorbent assay or immunofluorescence assay. On Western blot analysis, the level of immunoglobulin reactivity against B. burgdorferi in serum from these patients was no greater than that in serum from normal controls. The patients had a vigorous T-cell proliferative response to whole B. burgdorferi, with a mean (+/- SEM) stimulation index of 17.8 +/- 3.3, similar to that (15.8 +/- 3.2) in 18 patients with chronic Lyme disease who had detectable antibodies. The T-cell response of both groups was greater than that of a control group of healthy subjects (3.1 +/- 0.5; P less than 0.001). We conclude that the presence of chronic Lyme disease cannot be excluded by the absence of antibodies against B. burgdorferi and that a specific T-cell blastogenic response to B. burgdorferi is evidence of infection in seronegative patients with clinical indications of chronic Lyme disease.

Evaluating Frequency, Diagnostic Quality, and Cost of Lyme Borreliosis Testing in Germany: A Retrospective Model Analysis

Müller, I. Freitag, M. H. Poggensee, G. Scharnetzky, E. Straube, E. Schoerner, Ch. Hlobil, H. Hagedorn, H.-J. Stanek, G. Schubert-Unkmeir, A. Norris, D. E. Gensichen, J. Hunfeld, K.-P., Clinical and Developmental Immunology 2012

http://www.hindawi.com/journals/cdi/2012/595427/

The disease is usually diagnosed clinically based on a characteristic clinical picture, a history of tick bite, and the diagnosis then can be supported further by serological testing. However, both false negative and false positive serologic test results do occur, and together with a lack of standardization of current diagnostic methods can clearly impede a clear and concise diagnosis. Moreover, current law in most European countries does not require profound clinical evaluation of such commercially available diagnostic test kits for LB prior to market registration. Most significant, however, is the high seroprevalence of anti-B. burgdorferi antibodies that correlates with manifest disease in only a minority of patients. Therefore, serology should only be used to confirm but not to primarily establish the diagnosis of LB.

Differences between UK, Scotland & Germany:

Per Trinity Biotech test kit for western blot, Lyme Borreliosis:

http://www.trinitybiotech.com/Product%20Documents/44-2020GV-29EN%20EU%20Lyme%20+VLsE%20IgG%20WB.pdf

Modified MiQ 12 2000 interpretive Criteria for Europe excluding FDR Germany IgG positive = = Any 3

of the following bands : p14, p17, 22kD OspC, p30, p39, p43, p58, p100, B. garinii OspC,B. burgdorferi VlsE. IgG

Modified MiQ 12 2000 interpretive Criteria for Europe for FDR Germany IgG positive = = Any 2 of the following bands : p14, p17, 22kD OspC, p30, p39, p43, p58, p100, B. garinii OspC,B. burgdorferi VlsE.

The use of local isolates in Western blots improves serological diagnosis of Lyme disease in Scotland

S. Mavin, R. M. Milner, R. Evans, J. M. W. Chatterton, A. W. L. Joss and D. O. Ho-Yen
Microbiology Department, Raigmore Hospital, Old Perth Road, Inverness IV2 3UJ, UK, Journal of Medical Microbiology (2007), 56, 47–51

http://jmm.sgmjournals.org/content/56/1/47.full.pdf+html

Recommended practice for the laboratory diagnosis of Lyme disease is a two-step procedure, involving a sensitive screening enzyme immunoassay (EIA), followed by a Western blot to confirm EIA-positive or equivocal results (Wilske 2003). Some patients with clinical evidence of Lyme disease have been found to be EIA negative and Western blot positive. The presence of only one pathogenic species, B. burgdorferi sensu stricto, in the USA has allowed the Western blot test to be well standardized (Centers for Disease Control, 1995; Hauser et al., 1997). In Europe it has been more problematic. Strain and protocol variation has meant that a consensus has not been reached (Hauser et al., 1998; Robertson et al., 2000; Heikkila et al., 2002). Historically, the Western blot test utilized by the National Lyme Disease Testing Service Laboratory at Raigmore Hospital, Inverness, UK, has been based on antigen prepared from a reference strain of B. burgdorferi sensu stricto. However, there is concern that false-negative Western blot results may be reported, particularly from patients with acute symptoms of Lyme disease. Although false negatives may be a result of treatment, or of testing a patient too soon after infection, the strain of B. burgdorferi used in diagnostic assays has been shown to influence test sensitivity (Hauser et al., 1997; Kaiser 2000; Robertson et al., 2000). In this study, antigen from Scottish B. burgdorferi isolates was incorporated into an IgG Western blot, and the results were compared with those of the reference strain of B. burgdorferi sensu strict currently used in the Western blot test.

Two isolates, E5 (B. afzelii) and G4 (B. burgdorferi sensu stricto), were selected for further investigation based on their ability to produce the appropriate IgG Western blot-positive and -negative results. The inclusion of antigen from both B. afzelii and B. burgdorferi sensu stricto Scottish isolates in the same Western blot could increase the detection of Lyme disease. Kaiser (2000), from a study of false-negative serology in patients with neuroborreliosis, concluded that a negative serological result with one strain should prompt the repetition of the test with other strains from the B. burgdorferi sensu lato complex.

Of the 15 samples that tested IgG Western blot equivocal with the B. burgdorferi sensu stricto reference strain, 11 (73 %) became weak or strong positive when tested with the B. afzelii/B. burgdorferi sensu stricto antigen mix ($x^2=14.35$, Yates' correction, $P<0.001$). In seven of these, a clinical picture of Lyme disease was consistent with the new results. The use of Scottish strains of B. afzelii and B. burgdorferi sensu stricto to provide antigen for the IgG Western blot improves the diagnosis of Lyme disease for patients in Scotland. An increase in sensitivity, without compromising specificity, means that more patients with Lyme disease will be detected, and this should aid patient management.

Effect of Strains in Europe:

Detection of *Borrelia afzelii, Borrelia burgdorferi sensu stricto, Borrelia garinii* and group VS116 by PCR in skin biopsies of patients with erythema migrans and acrodermatitis chronica atrophicans

Rijpkema SG, Tazelaar DJ, Molkenboer MJ, Noordhoek GT, Plantinga G, Schouls LM, Schellekens JF.

Clinical Microbiology and Infection The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases 1997 Feb;3(1):109-116.

http://onlinelibrary.wiley.com/doi/10.1111/j.1469-0691.1997.tb00259.x/full

Objective: To evaluate the diagnostic performance of two poLymerase chain reaction (PCR) procedures using skin biopsies of 20 erythema migrans (EM) and 24 acrodermatitis chronica atrophicans (ACA) patients.

Results: Among EM patients, both assays detected *Borrelia* DNA in 15 samples. Among ACA patients, the *ospA* PCR detected 15 positives and 10 samples were positive by 5S–23S PCR. In 19 samples one species was detected, 15 skin biopsies contained *Borrelia afzelii*, and *Borrelia garinii* was found in two patients. Group VS116 was detected in two EM patients, and therefore this group has pathogenic potential. Mixed infections of *B. afzelii* and *B. garinii*, group VS116 or *B. burgdorferi sensu stricto* were found in three EM and three ACA patients.

Conclusions: Diagnosis of EM and ACA by PCR is useful and knowledge of the presence of species may be used to predict the course of disease or the need for further antibiotics.

Molecular Typing of Borrelia burgdorferi Sensu Lato : Taxonomic , Epidemiological , and Clinical Implications.

Wang, G., Alje, P. & Dankert, J., Clin Microbiol Rev. 1999 October; 12(4): 633–653

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC88929/

B. bissettii sp. nov. isolates may represent the fourth *Borrelia* species that could cause human LB. ***B. valaisiana*** is widely distributed in European countries as well as in Asia. *B. valaisiana* has been cultured or detected in ticks or avian reservoirs from at least eight European countries, including the United Kingdom, Ireland, The Netherlands, Switzerland, Germany, Italy, Croatia, and the Czech Republic. This species seems abundantly present in ticks in Ireland, Germany, and Croatia. Only a few ***B. lusitaniae*** strains have been isolated in Portugal, the Czech Republic, Moldova, and Ukraine. Nine isolates with genotypic and phenotypic similarity to *B. bissettii* sp. nov. have been cultured in Slovenia. Mixed infections of multiple *B. burgdorferi* sensu lato species have been found in ticks, reservoir hosts and in patients with LB. The prevalence of mixed infections in ticks varies from 5 to 40% in different geographic regions. In the United States, a two-step protocol for the evaluation of the *B. burgdorferi* antibodies in sera was recommended by the Centers for Disease Control and Prevention. The performance of this protocol, as well as its simplified approach, may improve the specificity of serodiagnosis for LB, but the high percentage of seronegativity in 20 to 50% of patients, probably dependent on the stage of LB, remains a problem and limits the value of serological tests. In addition, the antigenic heterogeneity of *B. burgdorferi* sensu lato may influence the sensitivity and specificity of serological tests for LB, especially on the European continent, where three pathogenic species of *B. burgdorferi* sensu lato and at least eight OspA serotypes are well documented. *Differences in the regional distributions of borrelial species may also affect preferential reactivities of sera from patients with LB.* Several studies have shown differences in the reactivity patterns in Western blot analysis, depending on the species, strain, or serotype used as the source of antigen. This issue should be readdressed, since molecular typing results based on hundreds of isolates have indicated that the genetic diversity of *B. burgdorferi* sensu lato is much greater than was previously thought.

Borrelia valaisiana **in cerebrospinal fluid**

Eudoxia Diza, Anna Papa, Eleni Vezyri, Stefanos Tsounis, Ioannis Milonas, and Antonis Antoniadis

Aristotle University of Thessaloniki, Thessaloniki, Greece, (2004)

http://www.thefreelibrary.com/Borrelia+valaisiana+in+cerebrospinal+fluid.-a0122552757

Indirect evidence suggests that **B. valaisiana** is involved in some chronic clinical manifestations . We report the genetic detection of B. valaisianain the CSF of a 61-year- old man with a history of spastic paraparesis, which is strong clinical evidence of advanced neuroborreliosis. **Borreliosis is difficult to diagnose by serologic evaluation and Western blot interpretation. In our patient, no intrathecal antibodies were produced to support clinical suspicion of disease. The low antibody titers could be attributed to antigenic variation between B. valaisiana and B. burgdorferi sensu stricto, which was used as antigen because no commercial kit is specific for B. valaisiana. Differences between the strain causing infection and the antigen may play a role in the false-negative results.**

Local variations in the distribution and prevalence of *Borrelia burgdorferi* sensu lato genomospecies in *Ixodes ricinus* ticks.

Kirstein, F. et al., 1997. Applied and environmental microbiology, 63(3), pp.1102-6.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC168399/

Unfed nymphal and adult Ixodes ricinus ticks were collected from five locations within the 10,000-ha Killarney National Park, Ireland. Four genomospecies were identified as B. burgdorferi sensu stricto, Borrelia afzelii, Borrelia garinii, and VS116 [**B. Valaisiana**]. Additionally, untypeable B. burgdorferi sensu lato genomospecies were identified in two nymphs. VS116 was the most prevalent of the genomospecies and was identified in 50% of the infected ticks. Prevalences of *B. garinii* and *B. burgdorferi sensu stricto* were similar (17 and 18%, respectively); however, significant differences were observed in the prevalence of these genomospecies in mixed infections (58.8 and 23.5%, respectively).

Molecular detection of *Borrelia bissettii* DNA in serum samples from patients in the Czech Republic with suspected borreliosis.

Rudenko, N. et al., 2009. FEMS microbiology letters, 292(2), pp.274-81.

http://www.ncbi.nlm.nih.gov/pubmed/19187198

Molecular analysis of 12 selected serum samples collected in the regional hospital confirmed the presence of ***B. bissettii*** DNA in cases of single and multiple infection in patients with symptomatic borreliosis or chronic borrelial infection. The presence of *B. bissettii* as a single strain in patients provides strong support of the fact that *B. bissettii* might be a causative agent of the disease. After the first isolation of *B. bissettii* from the samples of human origin in Slovenia, following the detection of this species in cardiac valve tissue of the patient with endocarditis and aortic valve stenosis in the Czech Republic, here we present additional molecular data supporting the involvement of *B. bissettii* in LB in Europe.

Relationships of a novel Lyme disease spirochete, *Borrelia spielmani* sp. nov., with its hosts in Central Europe.

Richter, D. et al., 2004. Applied and environmental microbiology, 70(11), pp.6414-9.

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=525186

At least four Lyme disease genospecies, *Borrelia burgdorferi* sensu stricto, *Borrelia afzelii*, *Borrelia garinii*, and *Borrelia bissettii*, cause human disease in Central Europe. A fifth pathogenic variant, designated A14S **[*spielmani*],** has been isolated from a Dutch patient by culturing spirochetes from an erythema migrans lesion, and similar spirochetes have recently been identified in a German patient with chronic skin disease. The reactivity with monoclonal antibodies and the protein profile of this spirochetal variant are unique.

Inadequate binding of immune regulator factor H is associated with sensitivity of *Borrelia lusitaniae* to human complement.

Dieterich, R. et al., 2010. Infection and immunity, 78(11), pp.4467-76.

http://iai.asm.org/cgi/content/abstract/78/11/4467

In central Europe, *B. burgdorferi* sensu stricto, *B. afzelii*, *B. garinii*, *B. spielmanii*, and *B. bavariensis* are the causative agents of Lyme disease, while the pathogenic potential for *B. bissettii*, *B. valaisiana*, and *B. lusitaniae* remains unclear. The isolation of ***B. lusitaniae*** from two Portuguese patients with clinical manifestations similar to the pathogenesis of Lyme disease suggests that this spirochete is pathogenic to humans. Compared to that of other genospecies in central or eastern Europe, the geographic distribution of *B. lusitaniae* is restricted to areas where lizards are widespread throughout Portugal, Spain, Morocco, and Tunisia or where they are distributed focally in Germany, Poland, France, and Switzerland.

Immune Complex creating poor antibody response:

Diagnosis of Lyme Borreliosis

Aguero-rosenfeld, Maria E Wang, Guiqing Schwartz, Ira Wormser, Gary P, Clin Microbiol Rev. 2005 July; 18(3): 484–509.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1195970/

The enzyme-linked IgM capture IC biotinylated antigen assay was found to be more sensitive and specific than the aforementioned tests and furthermore detected antibodies more consistently in those patients with clinical evidence of active disease / Potential utilities of this type of assay include detection of antibodies in seronegative patients during early disease and ascertainment of whether persistent seropositivity is due to ongoing infection, since IC are speculated to be present only in active infection.

Immune complexes from serum of patients with Lyme disease contain Borrelia burgdorferi antigen and antigen-specific antibodies: potential use for improved testing.

Brunner, M Sigal, L H, J Infect Dis. (2000) 182 (2): 534-539.

http://jid.oxfordjournals.org/content/182/2/534.full

Serum from a patient with Bannwarth syndrome (lymphocytic meningitis, cranial neuropathy, and radiculoneuritis) was seronegative by standard isotype-specific IgG ELISA and immunoblot and was positive by IgM ELISA. When the ICs [immune complexes]-and FAs [free antibodies] were used at equal concentrations of IgM, more Bb antigens were bound by IC derived IgM than by FA IgM, including the 23-, 30/31-, and 66-kDa bands of the Centers for Disease Control and Prevention interpretation criteria. Thus, specific IgM was sequestered within ICs.

Binding to the 23-kDa protein was more intense in ICs than in the FA fraction;** FA immunoblot reactivity would have been classified as negative, according to the manufacturer's instructions. **

We found OspA within ICs of some patients with later features of LD, which is analogous with the persisting infection in the mouse. These findings suggest that OspA may be expressed in long-term infection; the appearance of anti-OspA antibodies in later disease suggests that this antigen is present to elicit that humoral response.

One potential explanation for the absence of serological reactivity with OspA in standard serological assays in many patients with later manifestations of LD may be that anti-OspA antibodies are sequestered within ICs.

Brain Involvement with Lyme Disease:

OspA-CD40 dyad: ligand-receptor interaction in the translocation of neuroinvasive Borrelia across the blood-brain barrier.

Pulzova et al, Sci Rep. 2011;1:86. Epub 2011 Sep 8.

http://www.ncbi.nlm.nih.gov/pubmed/22355605

Lyme borreliosis is the most widespread vector-borne disease in temperate zones of Europe and North America. Although the infection is treatable, the symptoms are often overlooked resulting in infection of the neuronal system. In this work we uncover the underlying molecular mechanism of borrelial translocation across the blood-brain barrier (BBB). We demonstrate that neuroinvasive strain of Borrelia readily crosses monolayer of brain-microvascular endothelial cells (BMECs) in vitro and BBB in vivo.

Concern Three: Persistence –

Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis

Preac-Mursic V, Weber K, Pfister HW, Wilske B, Gross B, Baumann A, Prokop J. Neurologische Klinik Grosshadern, Munchen, FR Germany. : Infection. 1989 Nov-Dec;17,6:355-9..

http://www.ncbi.nlm.nih.gov/pubmed/2613324

The persistence of *Borrelia burgdorferi* in patients treated with antibiotics is described. The diagnosis of Lyme disease is based on clinical symptoms, epidemiology and specific IgG and IgM antibody titers to *B. burgdorferi* in serum. Antibiotic therapy may abrogate the antibody response to the infection as shown in our patients. *B. burgdorferi* may persist as shown by positive culture in MKP-medium; patients may have subclinical or clinical disease without diagnostic antibody titers to *B. burgdorferi*. **We conclude that early stage of the disease as well as chronic Lyme disease with persistence of *B. burgdorferi* after antibiotic therapy cannot be excluded when the serum is negative** for antibodies against *B. burgdorferi*. [Persistence:] However, **some patients later developed symptoms of the disease despite antibiotic treatment,** 9-11. Because of these observations **it has become questionable if a definite eradication of B. burgdorferi with antibiotics is possible,** p.358.[Treatment:] In view of the hitherto failure of treatment, low CSF concentration of penicillin G, **survival of *B. burgdorferi* in patients treated with antibiotics, the moderate penicillin G susceptibility o f the organism and unpredictable progression of the disease, it seems appropriate to treat patients with substantially larger doses of antibiotics and/or longer than is provided in present treatment regimens.** p.358.[Seronegativity:] As shown, negative antibody-titers do not provide evidence for successful therapy; antibody-titers may become negative despite persistence.

Clinical implications of delayed growth of the Lyme borreliosis spirochete, *Borrelia burgdorferi*.

MacDonald AB, Berger BW, Schwan TG. Acta Trop. 1990 Dec;48, 2:89-94.

http://www.ncbi.nlm.nih.gov/pubmed/1980573

Lyme borreliosis, a spirochetal infection caused by *Borrelia burgdorferi*, may become clinically active after a period of latency in the host. **Active cases of Lyme disease may show clinical relapse following antibiotic therapy.** The latency and relapse phenomena suggest that the Lyme disease spirochete is capable of survival in the host for prolonged periods of time. We studied 63 patients with erythema migrans, the pathognomonic cutaneous lesion of Lyme borreliosis, and examined in vitro cultures of biopsies from the active edge of the erythematous patch. Sixteen biopsies yielded spirochetes after prolonged incubations of up to 10.5 months, suggesting that ***Borrelia burgdorferi* may be very slow to divide in certain situations. Some patients with Lyme borreliosis may require more than the currently recommended two to three week course of antibiotic therapy to eradicate strains of the spirochete which grow slowly.**

Molecular detection of persistent *Borrelia burgdorferi* in a man with dermatomyositis.

Fraser DD, Kong LI, Miller FW. Clin Exp Rheumatol. 1992 Jul-Aug;10,4:387-90.

http://www.ncbi.nlm.nih.gov/pubmed/1395222

A 40-year-old white man with a several year history of various immunologic disorders, including anti-Jo-1 autoantibody positive dermatomyositis, developed clinical Lyme disease after being bitten by a tick. **The patient was treated with oral tetracycline and his initial symptoms resolved;** however, he suffered an exacerbation of his muscle disease which was difficult to control despite cytotoxic therapy. **Antibiotic therapy was reinstituted after *Borrelia burgdorferi* was detected in the patient's peripheral blood leukocytes by the poLymerase chain reaction, PCR. All serologic, T-cell stimulation, and western blot analyses, however, were negative.** The patient's disease responded to oral ampicillin, probenecid therapy and concurrent cytotoxic therapy. Subsequent leukocyte PCR testing has been negative for the causative agent of Lyme disease. This case may provide an example of the in vivo immuno-modulatory effects of spirochetes in human autoimmune disease. **In addition, this case emphasizes the potential clinical utility of PCR technology in evaluating the persistent seronegative Lyme disease** which may occur in immunocompromised individuals.

Concern Four: Co-infections – please see separate paper for relevant studies on tick-borne co-infections pertinent to UK & Ireland

Concern Five: Transmission –

Pregnancy:

Gestational Lyme borreliosis. Implications for the fetus.

MacDonald AB. Rheum Dis Clin North Am, 15(4):657-77. 1989

http://www.ncbi.nlm.nih.gov/pubmed/2685924

Lyme disease can potentially adversely affect pregnancy. In 1985, researchers published the first proof of maternal-fetal transmission of *Borrelia burgdorferi* (Bb): A baby died shortly after birth and *Bb* spirochetes were found in the infant's spleen, kidney, and bone marrow. (Schlesinger P, Duray P, Burke B, Steere A, Stillman A. Maternal-fetal transmission of the Lyme disease spirochete *Borrelia burgdorferi*. Annals of Internal Med. 1985:(Vol 103) 67-68.)

“If false results are to be feared, it is the false negative result which holds the greatest peril for the patient.”

Transfusion:

Survival of Borrelia burgdorferi in human blood stored under blood banking conditions.

Nadelman RB, Sherer C, Mack L, Pavia CS, Wormser GP, Transfusion 1990 May;30(4):298-301.

http://www.ncbi.nlm.nih.gov/pubmed/2349627

Hematogenous dissemination of organisms occurs in many spirochetal diseases, including Lyme disease and syphilis. Although syphilis has been transmitted by transfusion, in the vast majority of cases, only fresh blood products were involved, in part because Treponema pallidum survives poorly when refrigerated in citrated blood. Because of the rising incidence of Lyme disease in certain areas, whether its causative agent, Borrelia burgdorferi, could survive under blood banking conditions was studied. Dilutions of stock cultures of two strains of B. burgdorferi were inoculated into samples of citrated red cells (RBCs). Viable spirochetes were recovered from RBCs inoculated with 10(6) organisms per mL, after refrigeration for as long as 6 weeks. It is concluded that B. burgdorferi may survive storage under blood banking conditions and that transfusion-related Lyme disease is theoretically possible.

Survival of *Borrelia burgdorferi* in blood products.

Baden et al Transfusion 1989 Sep;29(7):581-3. American Red Cross Blood Services, Connecticut.

http://www.ncbi.nlm.nih.gov/pubmed/2773025

To assess the potential of transmission of the disease through blood transfusion, we studied the survival of *Borrelia burgdorferi* in blood products under blood bank storage conditions… The organism was shown to survive in RBCs [red cells] (4 degrees C) and FFP [fresh-frozen plasma] (below -18 degrees C) for 45 days and in PCs [platelet concentrates] (20-24 degrees C) for 6 days. The results of this study do not exclude the possibility of transmission of Lyme disease through blood transfusion.

A Lyme borreliosis human serosurvey of asymptomatic adults in Ireland.

Smith et al Zentrabl Bakteriol 1991 Aug;275(3):382-9.,Department of Bacteriology, Stobhill Hospital, Glasgow, U.K.

http://www.ncbi.nlm.nih.gov/pubmed/1741921

Blood samples were obtained through the Blood Transfusion Service in Ireland in order to obtain information on the prevalence of asymptomatic *B. burgdorferi* infections and in an attempt to identify the type of habitat that presents the most risk of infection. Approximately 100 plasma samples from each of four areas were analysed for IgG anti-Borrelia antibodies by indirect immuno-fluorescence with a titre of 1 :80 indicating a positive reaction in asymptomatic individuals. Prevalence figures of 15, 11, 8 and 5% were obtained for high, high/medium, medium/low and low risk areas respectively. No positive samples were detected in blood from an Icelandic population which is not exposed to *I. ricinus* bites. The overall subclinical prevalence (9.75%) is surprisingly high in view of the apparent rarity of clinical cases in Ireland, though under-diagnosis probably occurs.

David A. Leiby* Clin Microbiol Rev. 2011 January; 24(1): 14–28.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3021205/

Summary: *Babesia* spp. are intraerythrocytic protozoan parasites of animals and humans that cause babesiosis, a zoonotic disease transmitted primarily by tick vectors. Although a variety of species or types of *Babesia* have been described in the literature as causing infection in humans, the rodent parasite *Babesia microti* has emerged as the focal point of human disease, especially in the United States. Not only has *B. microti* become established as a public health concern, this agent is increasingly being transmitted by blood transfusion: estimates suggest that between 70 and 100 cases of transfusion-transmitted *Babesia* (TTB) have occurred over the last 30 years. A recent upsurge in TTB cases attributable to *B. microti*, coupled with at least 12 fatalities in transfusion recipients diagnosed with babesiosis, has elevated TTB to a key policy issue in transfusion medicine. Despite clarity on a need to mitigate transmission risk, few options are currently available to prevent the transmission of *B. microti* by blood transfusion.

Breast milk & Semen:

Bach G (2001**). "Recovery of Lyme spirochetes by PCR in semen samples of previously diagnosed Lyme disease patients.".** *14th International Scientific Conference on Lyme Disease.*

Schmidt B, Aberer E, Stockenhuber C, *et al* (1995**). "Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in the urine and breast milk of patients with Lyme borreliosis.".** *Diagn Microbiol Infect Dis* **21** (3): 121-8. PMID 7648832.

Concern Six: Guidelines –

Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines

Dong Heun Lee, M.D.; Ole Vielemeyer, M.D. Arch Intern Med. 2011;171(1):18-22.

http://www.ncbi.nlm.nih.gov/pubmed/21220656

“More than half of the current recommendations of the IDSA are based on level III evidence (opinion) only. …Until more data from well-designed controlled clinical trials become available, physicians should remain cautious when using current guidelines as the sole source guiding patient care decisions.”

Dr. Kenneth Liegner, an MD treating a large number of Lyme patients in Armonk, New York, summarized the plight of Lyme physicians:

"Physicians who have cared for persons with chronic Lyme disease have faced harassment at a minimum and for some, their careers have been ruined. Researchers who have seriously dedicated themselves to the scientific study of chronic Lyme disease in humans and/or animals have often found themselves attacked or marginalized. To persist in their researches would have resulted in virtual career suicide and some have been forced, by exigencies of survival, to leave the field."

Despite physicians being ‘bullied’ for not adhering to IDSA/CDC guidelines, the IDSA have this to say:http://www.idsociety.org/Guidelines_Patient_Care/

Quote: "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. IDSA considers adherence to the guidelines listed below 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. "

A Workshop on the Critical Needs and Gaps in Understanding Prevention, Amelioration, and Resolution of Lyme and Other Tick-borne Diseases: the Short-Term and Long-Term Outcomes

Quote from Dr Sue O'Connell http://www.tvworldwide.com/events/iom/101011/default.cfm

I come up from both a clinical and laboratory background so I am going to talk about lab tests for the moment. And, I think, we all agree we need improved diagnostic tests for all the tick-borne diseases. We need, I do feel strongly, we need now to review the current state of play as far as 2 tier testing is concerned and time we have a workshop on this. And I would also flag out the point that some patients actually are misdiagnosed. They do not have Lyme. They have other conditions. Equally well, we are missing Lyme in patients. We need to begin considering both the over and under diagnosis of the condition. And I would like to say one idea. And that's that we need to resource a long-term study of patients. Who have got -- who have a Lyme label, persistent infection, chronic infection, call it what you will. I really do think we need again education for health care professionals as well as obviously people living in the community

Institute of Medicine Workshop 2010:

http://www.iom.edu/Reports/2011/Critical-Needs-and-Gaps-in-Understanding-Prevention-Amelioration-and-Resolution-of-Lyme-and-Other-Tick-Borne-Diseases.aspx

Importantly, the IOM Committee noted that the burden of disease is a growing concern. The Committee recognized that tick-borne diseases (TBDs) represent some of the world's most rapidly expanding arthropod-borne infectious diseases, yet significant gaps remain in our understanding and knowledge about them. Some of the themes discussed in the IOM report suggesting greater emphasis and more research are:

A national integrated research plan for advancing the science on tick-borne diseases;

* A long-term study of Lyme disease and other TBD patients; Educational programs for the public;

* The current status of diagnostic tests and biomarkers for tick-borne diseases;

* Biorepositories for tick-borne diseases; Biological understanding of persistent symptoms;

* The impact of coinfection in severity of human TBDs;

* The role of immune response to tick-borne infection and its effect on bacterial load and disease manifestations;

* Animal models that explore mechanisms of pathogen persistence following antibiotic treatment.

* A diverse group of scientists and physicians with expertise in tick-borne infections discussed a breadth of scientific topics.