

# **Australasian College of Dermatologists Submission to Senate Inquiry on Lyme Disease**

## **What is Lyme Disease?**

Lyme disease is a zoonotic tick-borne disease caused by a certain members of a group of related spirochaetes – *Borrelia burgdorferi* sensu lato (s.l.) – that are transmitted by specific *Ixodes* spp. ticks. The *B. burgdorferi* s.l. complex is a diverse group of more than 18 spirochaete species. Four species comprising *B. americana*, *B. andersonii*, *B. californiensis*, and *B. kurtenbachii* are found only in North America; eleven species occur in and are restricted to Eurasia comprising *B. afzelii*, *B. bavariensis*, *B. garinii*, *B. japonica*, *B. lusitaniae*, *B. sinica*, *B. spielmanii*, *B. tanukii*, *B. turdi*, *B. valaisiana*, and *B. yangtse*; and three species occur in both North America and Europe, *B. burgdorferi* sensu stricto (s.s.), *B. bissettii*, and *B. carolinensis* (Rudenko et al 2011).

A new *Borrelia* species (*B. mayonii*) has recently been isolated in the USA, and has caused 6 reported cases of Lyme disease there so far.

There are *Ixodes* genus ticks present in Australia, but none of the overseas *Ixodes* species known to carry *Borrelia* spp. occur in Australia. The examination of Australian ticks to date has not detected *Borrelia* spp. in them, and although further investigations are warranted, to date Australian ticks have not been confirmed to carry the *Borrelia* spp. that can cause Lyme Disease.

As of the time of this report, there have been no confirmed cases of human infection in Australia by *Borrelia burgdorferi* s.l in non-travellers (i.e. locally acquired infections).

## **How is Lyme Disease Transmitted to humans?**

Transmission of Lyme borreliosis is through injection of tick saliva during feeding. In Europe, Asia and the United States, the disease is transmitted largely by four species of hard ticks in the *Ixodes ricinus* complex: *I. ricinus*, *I. persulcatus*, *I. scapularis*, and *I. pacificus* (Stanek et al 2012; Radolf et al 2012). Other hard ticks do not appear to play any significant role in Lyme borreliosis; they are either inefficient in the acquisition of *Borrelia* spirochaetes from blood meals, or they are unable to maintain the spirochaete. The risk of infection in humans increases with length of time of exposure to the tick, approaching 100% on the third day (Biesiada et al 2012). It usually requires a feeding period of more than 36 hr for transmission of *B. burgdorferi* by *I. scapularis* or *I. pacificus* ticks in North America, but can be significantly shorter, often less than 24hr, for transmission of *B. afzelii* by *I. ricinus* ticks in Europe (Hubalek 2009).

The identification of a tick in Australia that can maintain the spirochaete, and is able to bite humans effectively enough to transmit the infection has not yet definitely been proven e.g. most bird ticks do not bite humans, and if they did, would rapidly drop off before the opportunity to transmit the spirochaete.

### **What are the diagnostic clinical features of Lyme Disease?**

The initial clinical manifestations of Lyme disease are the typical annular lesion at the site of the bite (erythema migrans, or EM ) and an influenza-like illness, with fatigue, headache, myalgia, arthralgia, and malaise, although some early infections may be completely asymptomatic.

The incubation period between tick bite and appearance of EM is typically 7 to 14 days, but may be as short as a day and as long as 30 days (Marques 2010).

Erythematous lesions occurring within a few hours of a tick bite represent hypersensitivity reactions rather than EM, and are more typical of insect bite reactions, or urticarial lesions.

Other manifestations in the early stages may include multiple erythema migrans lesions, (~20%), nervous system involvement (~15%) with headache, lymphocytic meningitis, mild neck stiffness, or facial palsy, cardiac involvement (~5%)- with acute onset of high grade atrioventricular conduction defects, or myopericarditis and arthritis .

Other specific manifestations of Lyme borreliosis may include arthritis, neurological symptoms, and lymphocytoma, although these symptoms are less common, and then, still more uncommonly, acrodermatitis chronica atrophicans and carditis.

Late Lyme disease may occur in some patients after months to several years of untreated infection. ~60% present with rheumatologic involvement, intermittent attacks of joint swelling and pain in large joints.

~5% present with neuroborreliosis, peripheral neuropathy, spinal radicular pain, distal paraesthesias, or encephalopathy leading to subtle cognitive disturbances.

Acrodermatitis chronica atrophicans is a rare skin condition, which presents with lower limb atrophic lesions, peripheral neuropathy, and joint deformities.

### **Chronic Lyme Disease**

Chronic Lyme disease is a widely used but poorly defined term. It is frequently used as a diagnosis for patients with persistent pain, fatigue, or neurocognitive complaints without clinical evidence of previous acute Lyme borreliosis and in some instances even without serological identification of borrelial infection. This term is sometimes used, without definitive corroborative evidence, for patients with chronic, vague and non-specific symptoms. Some of these patients may be classified as having other, poorly defined chronic conditions such as “fibromyalgia” or “chronic fatigue syndrome”, and some of these patients’ symptoms may be explained by psychiatric conditions such as depression.

The term “chronic Lyme disease” should therefore not be used unless there is firm evidence of previous acute Lyme disease which has been proven by laboratory testing in a NATA-accredited Australian laboratory, or overseas laboratory to similar or higher standard.

### **Evidence of Lyme Disease in Australia**

Lyme borreliosis has been reported in Australia (eg Mayne 2011; Hudson et al 1998; B Hudson, personal communication), but the vast majority of cases were patients who had travelled to Lyme endemic areas overseas. It is important to state that in the few cases of patients with no travel history, and where additional confirmatory testing of putative positive specimens has been done in NATA-accredited Australian laboratories, the results could not be confirmed to international standards for Lyme diagnoses.

For the purposes of this report, an internet survey was carried out to all Australian dermatologists, whereby they were asked if they had ever seen, or were aware of, a case of confirmed Lyme disease in their practicing lifetime.

This included dermatologists who have worked for many years in coastal regions, and who have seen many cases of tick-bites and other insect bites. The responses were all negative.

### **Laboratory Testing for Lyme Disease: Culture**

Culture of spirochaetes in the laboratory from a patient sample remains the gold standard for specificity, but it is a slow process with long incubation times, and because of the low numbers of viable spirochaetes in most biopsies and the fastidious nature of the organism, the results can be very variable. Culture is thus only attempted in Reference laboratories.

### **Laboratory Testing for Lyme Disease: Molecular detection of DNA from *Borrelia sp* in patient specimens:**

The same samples as used for culture may also be tested by molecular techniques. If DNA from *Borrelia sp* is detected in the patient sample (e.g. by real-time PCR), then a conventional PCR, with gel-electrophoresis of the amplified DNA, should be undertaken and any DNA of the correct/expected molecular weight should be excised from the gel and sequenced.

A variety of targets and platforms exist, but still require standardisation. Any Australian *Borrelia spp* that cause Lyme Disease-like presentations (assuming that such bacteria exist) are likely to be very different (genetically and antigenically) from *Borrelia spp* in other parts of the world. It is not known if tick species indigenous to Australia can transmit *Borrelia spp*.

Thus, when looking for "Australian" *Borrelia spp*, primers detecting conserved *Borrelia* genes are essential. Undertaking the search with only known *Borrelia*-specific primers runs the risk of missing slightly different Australian *Borrelia spp*. Molecular investigations are valuable for clinical research investigations but are of limited clinical utility at present.

### **Laboratory Testing for Lyme Disease: Serology.**

Indirect tests through serological assays for antibodies to *B. burgdorferi* s.l. are the most common diagnostic methodologies employed; not only are the prerequisite laboratory facilities widely available, but specimens are easy to obtain.

As with *all* infectious diseases, infection with *B. burgdorferi* s.l. leads initially to an IgM antibody response, followed 2-4 weeks later by an IgG antibody response. IgM positivity alone may be a false positive result unless IgG sero-conversion is demonstrated subsequently. The IgM response tends to be relatively short-lived in most patients, but the IgG response remains for decades following infection (Glatz et al 2008; Kalish et al 2001)

However the sensitivity and specificity of serological tests are questionable. The recognized limitations of serological tests include that the antibody response may be weak or absent, especially in EM and early in infection ; seroconversion may be ablated by early antibiotic treatment , and they do not distinguish between active and inactive infections .

In Australia and overseas the recommended serological diagnostic protocols are a “two tier system”, with the first stage most commonly “enzyme-immuno-assay” (EIA) followed, if positive, by a Western immunoblot assay ; this is the current standard protocol in Australian Reference Laboratories.

The number of positive bands seen in the western blot, and their specificity and clinical significance varies (e.g. there are differences in USA and European criteria), and must be interpreted with caution, especially in the absence of an Australian *Borrelia* sp. It is important that the 2-tier protocol is undertaken; if the first tier ELISA is omitted or interpretation of the Western blot is carried out using criteria that are not evidence-based, this will potentially decrease the specificity of the testing and lead to misdiagnosis. Interpreting the IgM Western blot can lead to false positive results if insufficient care is taken as non-specific weak bands can often occur.

At this point, it is worth noting that a new generation EIA test for the antibody to the Lyme C6 peptide is available, and FDA approved in the USA. The C6 test has resulted in improved sensitivity of diagnosis in earlier disease as well as increased specificity, and may soon overtake the use of the two tiered method.

For example, in the USA, a new *Borrelia* species (*B. mayonii*) has recently been reported to cause Lyme disease in 6 cases. The C6 antibody test was superior to the two tiered traditional testing in these cases.

The introduction of C6 (or VlsE) EIA has called into question the need for confirmatory western blot. However, the significance of these developments for the diagnosis of Australian syndromes resembling Lyme Disease is not clear in the absence of Australian *Borrelia* spp, knowledge of their antigens and how the antigens vary from mainstream *Borrelia* spp.

False-positive results of serological tests for Lyme disease can sometimes occur in the ELISA from cross-reactive antibodies from patients exposed to other spirochaetal infections, e.g., syphilis, leptospirosis or relapsing fever (Shapiro and Gerber 2000). It is also possible that antibodies directed at spirochaetes that are part of the normal oral flora may cross-react with *B. burgdorferi* (Shapiro and Gerber 2000). There have also been false positive reports in cases of recent primary infection with varicella-zoster virus (Feder et al 1991), Epstein-Barr virus (Beradi et al 1988; Goossens et al , 1999), cytomegalovirus (Goossens et al 1999), Herpes simplex type 2 virus (Strasfeld et al 2005), and *Rickettsia rickettsia* (Beradi

et al 1988). In addition to these examples associated with other infectious diseases, false positive *Borrelia* serology has been reported in de Quervain's thyroiditis and anaplastic lymphoma .

False-positive results will occur in low prevalence populations, such as Australia. Even with an assay having 98% sensitivity and specificity, in a low prevalence (e.g. 1%) population the positive predictive value only approaches 33%.

There is no confirmed agent of Lyme borreliosis in Australia at this time, and given that a putative causative bacterium has not yet been detected for Lyme disease in Australia, (making the assumption that it even exists) its antigenic make-up is unknown. Without knowing its antigenic makeup, it is impossible to design a proper serological test with measurable sensitivity and specificity. Cross-reactivity between patient antibodies and *Borrelia* antigens from overseas *Borrelia* used in vitro in Australian diagnostic assays are hard to predict.

### **What is "Lyme-like illness"?**

This term has no accepted definition and is best avoided because it implies a connection to Lyme disease for patients with otherwise undiagnosed illness.

Many diseases may cause symptoms similar to those seen in Lyme disease, such as fever, arthralgias, lethargy and so on, and when linked to a history of possible tick or insect bite, could be called "Lyme like illness", but the use of this term is unwise.

For example, other infective organisms may be transmitted by tick bites in Australia. Various viruses have been isolated from ticks in Australia and Australian territories, especially from seabird ticks, and from neighbouring countries of south-east Asia (flaviviruses).

Several rickettsial diseases occur in humans in Australia (Graves et al 2006), but not all are tick-borne. The tick-borne human pathogens are Queensland tick typhus (*Rickettsia australis*) transmitted by *I. holocyclus* and *I. tasmani* . There is also *R. honei*, the cause of Flinders Island Spotted Fever [FISF], transmitted by the Southern reptile tick, *Bothriocroton hydrosauri*, which occurs in Tasmania and southern parts of the mainland [ WA, SA & Vic ]. There is also a related bacterium, *R. honei*, subsp. *marmionii*, causing Australian Spotted Fever, for which the epidemiology is still very unclear but also appears to be tick-transmitted and more geographically widespread than FISF (Stephen Graves, personal communication).

A *Francisella* organism has now been obtained from hard ticks in the Northern Territory, but the *Francisella* species seen so far in Australia are not the species that are known human pathogens. This area of microbiology still needs further investigation.

### **Conclusion**

As of the time of this report, there has been no confirmed case of Lyme disease in Australians with no history of overseas travel.

The diagnosis of Lyme disease in Australia must be made by fulfilling criteria for diagnosis based on the appropriate clinical symptoms, in addition to confirmatory laboratory testing by a NATA accredited Australian laboratory.

The public should be educated to beware of being diagnosed with Lyme disease (especially “chronic Lyme disease”) by health practitioners who are not using approved confirmatory testing done in NATA-accredited laboratories. This has led to patients being charged large sums of money for questionable “alternative therapies” by various health practitioners, likely based on incorrect diagnoses.

Finally, even patients treated by “mainstream” doctors are often inappropriately given long term courses of antibiotics based on these incorrect diagnoses. It is inevitable that many of these patients will suffer the adverse effects of these treatments.

### **References and Sources.**

1. Mackenzie, John S. Scoping Study To Develop A Research Project to Investigate the Presence or Absence of Lyme Disease in Australia. Final Report. 2013.  
( Note : for details of the references in parentheses in my report, see the above reference)
2. The Royal College of Pathologists Australasia Position Statement. February 2014.
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