

CACLD Discussion Paper on Lyme Disease

The Australian Government Chief Medical Officer, Professor Chris Baggeley, has established a Clinical Advisory Committee on Lyme disease (CACLD) to provide him with advice on the evidence for Lyme disease in Australia, diagnostic testing, treatment and research requirements. The Committee will also provide advice on the most appropriate ways to disseminate information to health professionals and the general public.

The first meeting of the CACLD was held on 19 March 2013 and this paper was developed in response to the following meeting outcome.

Outcome 3: More information regarding borreliosis in Australia is required in order to understand the requirements to resolve issues detailed in the committee's terms of reference. Each member of the committee will be contacted out of session to discuss issues arising about borreliosis in Australia, which will assist the development of a discussion paper on Lyme borreliosis.

What was discussed?

Members of the CACLD were contacted and each conversation included the member's perspective on:

- The existence of Lyme disease in Australia
- The diagnostic pathway for Lyme disease in Australia
- The treatment options for Lyme disease in Australia

Summary

The existence of Lyme disease in Australia

It was acknowledged at the first meeting by the chair that professionally there were two sides to the debate regarding Lyme disease. Based on the member interviews it is clear there is a spectrum with members positioned around two main points. A cluster who believe that an indigenous form of Lyme disease exists in Australia and the other cluster around the middle of the spectrum who are not prepared to exclude the existence of an indigenous form but who require proof of its existence. When asked about the form of proof, the common response was the identification and characterisation of a causative microorganism. Identifying a causative microorganism would also require identifying the indigenous hæmatophagous¹ vector(s)².

The identification and characterisation of a causative microorganism and vector would shift the centre clustered members into the definite existence of an indigenous causative agent cluster.

Diagnostic pathways for Lyme disease in Australia

The spectrum for this aspect of discussion spanned from an adherence to the current CDC two tiered approach using a screening enzyme immunoassay (EIA) or immunofluorescent assay (IFA) followed by the specific western blot (WB)/immunoblot (IB) to a variety of alternative approaches some depending on a single test platform whether it be serological

¹ Blood feeding

² Assuming it to be an arthropod

or direct detection through nucleic acid amplification assays. Within this spectrum emerged some interesting alternative proposals such as a closer consideration of the European definitions for IB assays or consideration of a two tiered EIA approach similar to what is currently accepted for the diagnosis of Hepatitis C Virus (HCV) infection.

There was a strong push amongst some members for a reference capability focussing on culture and nucleic acid amplification techniques.

For patients diagnosed with Lyme disease after acquiring the infection from overseas endemic areas, it was pointed out that the two tiered approach has been successful.

Serological diagnosis is fraught because of the problem of cross reactions that serum antibodies have to a variety of antigens. Understanding the affinity maturation and avidityⁱ is critical to interpretation of serological assays.

Some members felt that relying on assays for *Borrelia* species found overseas is a problem and more needs to be done to identify antigens that will consistently provide sensitive and specific results. Identifying the best antigens to use in Australia can occur either by examining the results of current patients and comparing those results with known patterns from overseas and/or identifying and characterising an indigenous causative agent from which antigens can be derived for diagnostic assays.

Some members felt it was not possible to comment on this and the treatment options component until the existence issue was resolved.

Until a causative agent can be identified and characterised we need to explore further the value of various testing platforms and approaches.

An interim approach may rely heavily on the results of the antigenic profiling from the serum of Australian patients who have been diagnosed with Lyme disease that is currently being conducted at the University of Sydney. The results of this work once published may provide pathologists and medical laboratory scientists with the information necessary to develop appropriate in vitro diagnostic devices with suitable specificity, sensitive, and positive and negative predictive values for the Australian context.

Until then an examination of available immunoassays may be required to find the best compromise solution for diagnosis in Australia. Until sufficient validation can be provided a screening and confirmatory approach or two test best match approach may be required.

The use of domestic and international pathology services was raised by many of the members. To satisfy the current Australian requirements for reimbursement, a laboratory requires accreditation to AS ISO 15189 (Medical laboratories – Particular requirements for quality and competence). This standard is based on ISO 15189:2007 and is the foundation for National Pathology Accreditation Advisory Council's (NPAAC's) requirements for National Association of Testing Authorities, Australia/Royal College of Pathologists of Australasia (NATA/RCPA) accreditation.

Some members felt the requirement for medical testing accreditation was not appropriate while other members felt having an accredited and recognised quality management system in place was a benchmark for performance.

Some members raised concerns about the diagnosis of coinfections associated with Lyme disease and hæmatophagous arthropod exposure. In several conversations with the chair of the CACLD it has been stated that we need to remain focussed on Lyme disease for now.

Treatment options for Lyme disease in Australia

Again a spectrum of opinion was revealed in discussion with members. Many members acknowledging they did not possess clinical qualifications refrained from comment. Some felt that until the matter of existence of Lyme disease in Australia was resolved the treatment options for indigenous Lyme disease remain moot.

The spectrum of opinion was more of a dichotomy roughly aligning with the positions of the Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society (ILADS). IDSA treatment guidelines recommend short course (2–3 weeks) therapy with a single antimicrobial. ILADS treatment guidelines recommend long course (months to years) therapy with multiple cycling antimicrobials plus other pharmaceutical agents.

The discussion of treatment options also revealed the integration of understanding pathogenesis and pathogenicity with treatment. This is further complicated if coinfections are considered. Some members have a position of pleomorphism³ that is not universally accepted. An acceptance of pleomorphism may require a less specific form of treatment regimen encompassing the specific targeting of each form with a single or multiple antimicrobials. Including coinfections into a management regimen broadens the variety of antimicrobial and duration of therapy. As a consequence the adverse effects of prolonged multiple antimicrobial use must also be considered.

The development of an Australian treatment protocol rests on an accepted diagnostic pathway plus a clinical evaluation of the patients with long term manifestations after an initial diagnosis of Lyme disease in Australia. It is not currently possible with the available diagnostic assays, including nucleic acid amplification assays, to determine if long term infection and disease exists. The proponents of long term infection and the existence of dormancy rely on the acceptance of specific bacterial pleomorphism for *Borrelia* species.

What else was raised?

One member suggested some emphasis should be placed on the avoidance of exposure to hæmatophagous vectors, especially ticks. While most members agreed with the logic of this strategy, some were concerned it would detract from the focus on recognising that Lyme disease patients exist in Australia and are suffering from a lack of affordable diagnostic and treatment options plus a lack of recognition that the disease exists in Australia.

Conclusions

A common theme from almost all of the telephone meetings was the need for further research into identifying and characterising a causative agent in Australia. Should an agent and its vector be identified, the development of diagnostic assays and an Australian diagnostic pathway becomes easier. Likewise, a definitive diagnostic pathway makes the decision to treat easier. The matter of how to treat and for how long can also be studied more thoroughly with a causative agent and good models for pathogenicity.

ⁱ AFFINITY AND AVIDITY

³ The ability of some bacteria to alter their shape or size in response to environmental conditions

Affinity

Antibody affinity is the strength of the reaction between a single antigenic determinant and a single combining site on the antibody. It is the sum of the attractive and repulsive forces operating between the antigenic determinant and the combining site of the antibody.

Affinity is the equilibrium constant that describes the antigen-antibody reaction. Most antibodies have a high affinity for their antigens.

Avidity

Avidity is a measure of the overall strength of binding of an antigen with many antigenic determinants and multivalent antibodies. Avidity is influenced by both the valence of the antibody and the valence of the antigen. Avidity is more than the sum of the individual affinities.

Affinity refers to the strength of binding between a single antigenic determinant and an individual antibody combining site whereas avidity refers to the overall strength of binding between multivalent antigens and antibodies.