Lyme Disease Action

Comment on the British Infection Association's Position Statement on Lyme Borreliosis*

(* British Infection Association. 2011. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. The Journal of infection 62, no. 5 (May): 329-38. http://www.ncbi.nlm.nih.gov/pubmed/21421007.)

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Introduction and Summary

This document is written to highlight only the perceived shortcomings of the BIA paper: there are a number of sound points in this position statement but comments on these are not included.

Overall the BIA statement appears to be a presentation of evidence to support an already confirmed view, and not a statement, or even discussion of, the present state of knowledge concerning Lyme borreliosis (LB).

The overall view of LDA is that the paper displays

- an unrealistic confidence in the sensitivity of laboratory tests;
- a neglect of the range and importance of clinical diagnostic factors;
- a misleading account of likely Lyme disease presentations;
- a selective bias in the use of references and a failure to mention papers and evidence which conflict with the overall view;
- a tendency to quote from other reviews without examining the evidence;
- an uncritical acceptance of fellow members' informally published reports;
- a complete failure to point out the thin evidence base on which the quoted treatment recommendations have been drawn up.

The danger of the biased view portrayed is that if BIA members are led to believe that this statement really does reflect the present state of knowledge concerning LB then they will be faced with difficulties when communicating with patients who may well have read otherwise and who have had a lived experience at odds with the BIA statement. This will result in an unfortunate deepening of the distrust felt by many patients towards clinicians who fail to acknowledge what patients experience and know to have been reported in research literature. LDA urges the BIA to consider that this can only exacerbate an already difficult situation.

The BIA paper states that account was taken of the report[1] of an independent panel commissioned by the Health Protection Agency (HPA), which reviewed the 2004 guidelines of the International Lyme and Associated Diseases Society (ILADS). The panel concluded that:

> "The ILADS guidelines are poorly constructed and do not provide a scientifically sound evidence-based approach to the diagnosis and care of patients with Lyme borreliosis. The ILADS working group does not provide evidence that it used a Cochrane- based or similar approach in developing the guidelines. Some references do not provide evidence to support statements for which they were cited in the guidelines. Some good-quality peer-reviewed articles are selectively quoted, using sub-group analyses without regard for the broader findings of the full studies. Some references were published in an advocacy group-sponsored journal that was not Medline-listed, others are available only as conference / symposium abstracts or are unpublished. Some reference citations are inaccurate, demonstrating poor attention to detail."

The panel recommended that the HPA should not include the ILADS guidelines amongst references that it recommends.

It is unfortunate that most of these criticisms, and others, can be levelled at the BIA position statement.

Clinical manifestations and the natural course of untreated LB

The impression given is of an early stage of readily identifiable early signs and symptoms including a rash said to occur "in about 90%" followed by a late stage "only in a minority" that is "almost always strongly seropositive". The risk is that this can only lull clinicians into a false sense of certainty.

UK studies have noted EM in 59%[2] and 65%[3] and common sense says that rashes will not always occur on areas of skin easily visible to the person. In contrast to adults, children are more likely to be bitten above the waist, with one UK study[4] finding 20% of tick bites above the neck on children: noticing an EM on the scalp is unlikely. LDA knows of several patients who have been told "You haven't had the rash, so you can't have Lyme disease". An authoritative association suggesting that 90% have a rash is not going to help this situation.

The brief discussion of neurological presentations focuses mainly on meningoradiculitis and facial palsies and fails to do justice to the other more diffuse symptoms. Strle et al[5] examining patients with *Borrelia garinii* or *B afzelii* isolated from their CSF found that "Patients with *B. garinii* isolated from their CSF have a distinct clinical presentation, compared with patients with B. *afzelii. B. garinii* causes what, in Europe, is appreciated as typical early Lyme neuroborreliosis (Bannwarth syndrome), whereas the clinical features associated with *B. afzelii* are much less specific and more difficult to diagnose." Nowhere is this difficult presentation made clear as a genuine feature of Lyme disease.

There is no mention of psychiatric symptoms and no help for clinicians dealing with children or elderly people, both vulnerable groups who may present with behavioural and attention difficulties which, together with non-specific symptoms, may so easily be put down to "their age". There have been suicides in recent years and this is a real possibility that should not be ignored.

Lyme arthritis is quoted in the paper as usually affecting the knee with synovitis, effusion and pain. Yet Dillon et al[6] reporting on cases diagnosed over 5 years in London noted that out of 33 patients with musculoskeletal symptoms "Fourteen patients (42%) had arthralgia without swelling or tenderness of the affected joints and 18 (55%) experienced myalgias." This is an example of a prevailing trend in papers on Lyme disease to simply pass on what previous reviews have said without looking for the evidence.

Discussing the natural course of untreated borreliosis, the paper quotes only one reference and gives the impression that antimicrobials simply shorten the duration of arthritis. Szer at al[7] studying the course of untreated Lyme arthritis in children, found that although recurrent attacks of arthritis decreased over the years "The course of initially untreated Lyme disease in children may include acute infection followed by attacks of arthritis and then by keratitis, subtle joint pain, or chronic encephalopathy." In addition "the use of antibiotic therapy later in the illness in one third of the patients may have reduced the frequency of late manifestations." This progression is important, and clinicians should know this when trying to balance the risks and benefits of antimicrobials.

A misleading impression is given of the incidence of encephalomyelitis: "European neurologists, who saw a lot of untreated disease in the years before the spirochaetal cause was determined, estimated that the MS-like syndrome occurred in fewer than 1 in 1000 cases of untreated Lyme Borreliosis". This is opinion only and it should be noted that a Swedish study found 11/91 cases of neuroborreliosis presenting to one hospital in Southern Sweden had encephalomyelitis[8] and this is in relatively early disease.

Laboratory tests

The paper states that laboratory support "should be sought" for later manifestations. This needs clarification as there is a difference between seeking laboratory support and relying on laboratory support. Later statements on seronegative Lyme disease imply that laboratory confirmation is essential in late-stage disease.

Although the BIA paper states that account has been taken of the report of a Lyme Disease Review Panel of the Infectious Diseases Society of America (IDSA) the paper seems to have ignored the statement on the insistence on a positive laboratory test for diagnosis of extracutaneous Lyme disease. This was "felt to be problematic by some members of the Review Panel. Ultimately the Panel was evenly split on whether this statement would benefit from modification or clarification." It was considered that certain classic complications "in a patient with epidemiologic risk of Lyme disease and in whom alternative diagnoses have been excluded or are unlikely, may be sufficiently convincing as to constitute an exception to the statement in the Executive Summary."

In stating that the two-stage approach uses a "sensitive" screening step, no figures are given for sensitivity. This may be because local laboratories use different tests, but it should be noted that Ang et al[9] found sensitivity of 34-59%. Ang et al also stated that "some immunoblots gave positive results in samples that had been tested negative by all eight ELISAs."

There have been UK examples of serum testing negative in a screening test and positive in a Western Blot, though LDA does not know how often this occurs. Dillon et al[6] in their retrospective analysis, reported that of 11 patients with negative screening ELISAs, thought clinically to have Lyme, 6 had positive immunoblots when serum was forwarded to Southampton.

There is no acknowledgement in the paper that antibodies may be species and strain specific. Although the tests have improved a great deal in the past years, and proteins from *B afzelii* have been shown to be the most antigenic, there is still a lot that is unknown about this aspect of the tests. The paper says that *B valaisiana* has been found in about 50% of infected ticks in the UK (no references given) and is regarded on p334 as non-pathogenic and on p330 as only rarely causing erythema migrans. This geno-species has been implicated in neuroborreliosis[10, 11].

There is a risk that the BIA will mislead its members by saying that there have been no reliable reports of seronegative late-stage Lyme disease and this is to some extent a self-fulfilling statement since a pre-requisite of diagnosis is seropositivity. Proven seronegative cases are likely to be rare because of the difficulty of proving infection, given the low sensitivity of PCR or culture. As Bacon et al[12] point out "For late disease, the case definition requires at least 1 late manifestation and laboratory confirmation of infection, and therefore the possibility of selection bias toward reactive samples cannot be discounted."

A patient presenting with non-specific symptoms and genuine late stage seronegative Lyme disease to a clinician in the UK who has read this BIA paper would be very unlikely to be considered for any further testing or treatment. Where are these reports of seronegative late stage Lyme disease going to come from? The lack of reports does not mean these patients do not exist.

There are in fact many indications that genuine cases do exist [6, 13, 14, 15, 16].

It would have been helpful if the paper had listed and emphasised the common circumstances in which a negative test can occur. It is surprising that infectious diseases

clinicians amongst the membership did not raise the difficulties of diagnosis where patients have been previously treated with antibiotics or immunosuppressive drugs in early infection. We know of many cases of patients being denied treatment because of negative serology following antibiotics: when facial nerve pain has been misdiagnosed as a possible tooth infection, or erythema migrans been mistaken for cellulitis. The same thing may happen when patients are treated with steroids for facial palsy.

In the case of suspected erythema migrans to suggest that waiting 4 weeks for a measurable immune response to develop is an acceptable recommendation, in a disease that can have serious and long lasting effects the longer it is left untreated, is not acting in patients' best interests.

Although seropositivity can continue for years in patients, there is some evidence that it declines markedly in successfully treated patients[17]. It is also acknowledged that increasing positive antibody responses following treatment can be evidence of continuing active disease that warrants repeat treatment[6] and yet clinicians are not told of this and are not encouraged to request follow up tests because "Seropositivity persists indefinitely in some patients".

In addition insufficient is known about the decline of the antibody response in untreated patients who may have had the disease for years. Patients tested 20 years ago, before the development of modern tests, may well have continuing disease but with very low levels of antibodies.

On IgM immunoblots there is also insufficient data, particularly in European patients. Szer et al[7] found that at long term follow up the symptomatic patients "had IgM responses to the spirochete more often than did the asymptomatic patients". Long term IgG antibody responses in symptomatic patients declined faster in those with encephalopathy than those with arthritis. This was an American study: what is known of the European disease?

These uncertainties should be made clear to treating clinicians in order that they may make informed clinical judgements.

The paper states that there is no role for microscopic examination of blood. Presumably there would be a role in very early disease if expertise was available at a reasonable cost. This was the routine diagnostic method for syphilis, though after early infection it is hard to find *Borrelia* in blood. In the case of an uncertain EM, microscopic evaluation of blood or tissue might be a more acceptable route than waiting weeks for an antibody response to develop whilst withholding treatment. There is also no mention of new techniques such as Focus Floating Microscopy[18] which might prove similarly useful.

Antimicrobial prophylaxis

The BIA paper has a long discussion on recommendations on prophylaxis. It is important to point out to clinicians the possible dangers of short courses of prophylactic antibiotics:

- The bacteria may not be eradicated but the immune system response is likely to be diminished. This can lead to cases of seronegative chronic Lyme[19] which in the current climate are unlikely to be diagnosed.
- The main antibiotics used for LB treatment have been shown to precipitate atypical forms of *Borrelia*[20] against which they are not effective. This could lead to chronic Lyme.

It is possible that the immune response itself will eliminate any possible infection more effectively, and until more is known of the biology of the disease, short prophylactic courses are possibly unwise.

Treatment of Lyme Borreliosis

Nowhere in this section does the BIA paper make clear the thin evidence base of treatment recommendations.

The paper states that there is "broad overall agreement" between the American and European guidelines that are referenced. This is only so because the paper omits guidelines which differ eg the German DGA guidelines[21] and the USA ILADS guidelines[22]. The HPA independent review of the ILADS guidelines has been taken into account, and this may be why these guidelines themselves have not been included. It is worth stating that although that review included some valid points, it was clearly written with the intention of finding fault: it was not the "appraisal" that it claimed to be.

Many of the European guidelines are not available in English, which makes the content difficult to check, and it is clear (from the same errors in the references) that these guidelines have been lifted unchanged from a conference poster and used in the BIA paper without verification.

Treatment recommendations from several guidelines are quoted, and members are left to assume that these treatment recommendations are based on evidence. This is so only for early disease without complications. It is of note that the independent, evidence based advice provided to UK clinicians (Map of Medicine[23] under NHS Choices and CKS guidelines[24]) only gives recommendations for early disease. Under all other situations, the advice is to refer to an expert.

Where recommendations from the EFNS guidelines[25] are quoted, there is no mention that of the 5 recommendations on treatment, 3 are based on opinion, not evidence. This is not because the evidence has been ignored, but simply because it does not exist.

EFNS guidelines state

- On early LNB duration of treatment: "There are no class I comparisons of different treatment durations. In most European treatment studies, the duration ranged from 10 to 14 days, and few studies for as long as 28 days."
- On effective agents: "There are no randomized treatment studies of European late LNB."
- On duration of treatment: "There are no comparative controlled studies of treatment length in European late LNB."

It would be more helpful if members were made aware of this and not led to believe that the treatment recommendations are based on evidence.

Despite the lack of trials, the BIA paper says that the treatment strategies of antimicrobial combinations, pulsed-dosing and long term antimicrobials can be harmful. All treatment strategies have the potential for harm, and until these have been included in properly designed trials, the balance of benefit versus harm will be unknown.

Combination treatment is now routine for stomach ulcers and long term antimicrobials an established treatment for Q fever.

It is notable that further treatment is recognised as useful in the case of persisting Lyme arthritis but not in the case of other persisting symptoms. This appears to reflect a view that subjective symptoms (pain, photophobia, hyperacusis, myalgia, dermatomal itching etc) are less valid than objective signs such as a swollen joint; that what a patient feels is not as valid as what a clinician sees; that, in fact, what a patient feels can be discounted. This is unsettling.

Persistent symptoms following treated LB

What is "treated LB"? Treated with what and for how long and to what endpoint?

If a patient with LNB has been treated for 14 days at 200 mg doxycycline/day - a dose that has been shown to provide insufficient concentration in the CSF[26] - does that count as "treated"?

The paper advises that patients with continuing symptoms should be evaluated for "clinical and laboratory evidence of *Borrelia burgdorferi* infection". However, there is no advice on what might constitute clinical evidence of infection, as opposed to tissue damage or an auto-immune response or a post-infection syndrome. Laboratory evidence is hard to come by as "Seropositivity persists indefinitely in some patients and does not per se indicate continuing disease or a need for re-treatment" and PCR is not sensitive enough.

The absence of a routine diagnostic test for persisting Lyme disease is not in itself sufficient reason for saying that Lyme disease does not persist. There are, in fact, studies showing that it does[27, 28, 29, 30].

There is no advice on what re-treatment is advised in the situation of new clinical signs; whether because one drug has failed, another should be tried, or a different dose.

What is needed here is an effort to address the situation in the UK, not a simple repetition of reviews all quoting the same few trials of prolonged treatment, some of which have been heavily criticised and some of which have been misreported.

A recent editorial in the Netherlands Journal of Medicine[31] states "Thus, there is a need for well-designed studies on this subject, rather than misusing outcomes of underpowered trials of disputed quality to either defend or deny the possible effect of antimicrobial therapy".

The BIA paper states that the Association is "particularly concerned" about patients with other serious conditions who have received diagnoses of chronic Lyme disease. LDA was similarly concerned on reading this, but is the BIA aware that none of the four references quoted to support this statement relate to UK patients? How many clinicians reading this will check? Inclusion of this statement is seriously disquieting.

Conclusion

LDA is concerned that in the UK patients with Lyme disease have been misdiagnosed with a variety of other conditions (polymyalgia rheumatica, rheumatoid arthritis, depression, idiopathic facial palsy etc). This is partly due to lack of awareness of LB symptoms but also due to an unrealistic reliance on laboratory testing and to biased statements from the HPA and DH.

The BIA paper does nothing to improve this situation and certainly heightens the anxiety that LDA feels on these issues.

It is supremely disappointing that the BIA has added to the pool of biased publications and LDA views this as a missed opportunity to draw professional attention to some of the diagnostic and treatment uncertainties.

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