Comments on the IDSA 2006 Lyme Disease Guidelines
Submitted by Lyme Disease Action

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Despite the facts that Lyme disease is caused by at least two further genospecies of *Borrelia burgdorferi* sensu lato in Europe than in the USA and that there are clear differences in the resulting disease presentation, the IDSA guidelines are recommended for use within Europe and specifically within the UK by the UK Health Protection Agency (HPA). Lyme Disease Action believes that the IDSA guidelines should be presented with a clear delimitation of usage to the USA and a warning that other national authorities must conduct clinical trials and develop and publish independent guidelines specific to the conditions in their own regions.

Other individuals and organisations have made general points about many aspects of the guidelines. In the interests of efficiency Lyme Disease Action has not repeated these but has restricted the following comments to specific points pertinent to Europe and the UK that are preventing UK Lyme disease patients from obtaining adequate treatment.

IDSA 2006 Guidelines	Lyme Disease Action comments
Early Lyme Disease Recommendations Doxycycline (100 mg twice per day), amoxicillin (500 mg 3 times per day), or cefuroxime axetil (500 mg twice per day) for 14 days (range for doxycycline, 10–21 days; range for amoxicillin or cefuroxime axetil, 14–21 days) is recommended for treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans in the absence of specific neurologic manifestations (see Early Neurologic Lyme Disease) or advanced atrioventricular heart block (tables 2 and 3) (A-I). **Background and Diagnosis of Early Neurologic Lyme Disease** In the absence of erythema migrans, neurologic manifestations are too nonspecific to warrant a purely clinical diagnosis; laboratory support for the diagnosis is required.	A European study has shown that 100mg doxycycline twice per day is insufficient and that 200mg twice per day is safer: "The time required to reach adequate doxycycline levels in CSF with the higher dose was short. Doxycycline concentrations had reached the 0.6-p.gIml level in CSF after the second dose of 200 mg. With lower doses of doxycycline, it has taken 3 to 5 days to reach the same level. Since the risk of irreversible neurologic symptoms is increased with duration of infection, it is desirable to reach a therapeutic level in CSF as rapidly as possible." (1) The European manifestation of disease caused by *Borrelia afzelii* has been shown to display non specific symptoms and to be difficult to diagnose using current guidelines. (2) This pattern of symptoms clearly requires further European study. A Health Protection Agency report on laboratory confirmed cases in 1997 notes that only one third had erythema migrans. (3) The Western Blot used in the UK uses antigens from *B. burgdorferi, B. garinii* and *B.afzelii.* The manufacturer of this test states that an evaluation of 115 well characterized clinically defined Lyme patients was performed in Europe. Excluding patients with erythema migrans, 1 in 17 of patients with later disease tested negative. (4) In addition it is becoming clear that other *Borrelia* species are also pathogenic in Europe (12,13) but not yet included in test kits. The consequence of adherence to the IDSA 2006 guidelines within the UK is therefore that considerable numbers of UK patients go undiagnosed and untreated. Those that are treated with 100mg doxycycline twice per day may well not forestall disease progression.

IDSA 2006 Guidelines	Lyme Disease Action comments contd.
Background and Diagnosis of Cardiac manifestations of Lyme disease In the absence of concomitant erythema migrans (present in up to 85% of cases), the clinical manifestations of Lyme carditis are too nonspecific to warrant a purely clinical diagnosis. Under these circumstances, support for the diagnosis requires the presence of *B. burgdorferi* antibody in acute- or convalescent-phase (2–4 weeks after the acute phase) serum specimens. The vast majority of patients with cardiac manifestations of Lyme disease are seropositive at the time of presentation.	As noted above, significant numbers of European patients have negative serology and non specific symptoms. Considerably more than 15% of patients fail to note an erythema migrans: in the UK this is closer to 65% (3). This recommendation effectively cuts them off from treatment. This recommendation also discourages thorough consideration of seronegative patients presenting with cardiac symptoms. Because of the non specific nature of some European presentations and the possibility of multi-strain infection, the distinction between Lyme carditis and neurologic Lyme is less clear than in the USA (11)
Lyme Arthritis If patients have no resolution of arthritis despite intravenous therapy, and if PCR results for a sample of synovial fluid (and synovial tissue, if available) are negative, symptomatic treatment is recommended.	This indicates a way forward for negative patients but no way forward for those with positive results. This is an omission that needs rectifying. It should be borne in mind that because of the differing *B. burgdorferi* species, European patients may not show what are considered to be typical USA symptoms and the distinction between Lyme arthritis and neurologic Lyme is therefore less clear. It has been demonstrated that in Europe inflammatory back pain, even without radiculitis, may be related to Lyme disease in endemic areas (5)
Background and Diagnosis of Rheumatologic Manifestations In the vast majority of patients, the clinical manifestations are too nonspecific to warrant a purely clinical diagnosis of Lyme arthritis. Confirmation of the diagnosis requires serologic testing.	As already stated, given the number of *Borrelia* genospecies that have been implicated in Lyme disease in Europe this is likely to exclude a significant number of patients from treatment (4, 12, 13).
Late neurologic disease Re-treatment is not recommended unless relapse is shown by reliable objective measures.	Many symptoms of the European disease are not objective (2); this should not preclude treatment.
Recommended therapy Table 3 Regardless of the clinical manifestation of Lyme disease, complete response to treatment may be delayed beyond the treatment duration. Relapse may occur with any of these regimens; patients with objective signs of relapse may need a second course of treatment.	Hassler et al demonstrated that four courses could effect a cure when the first and second courses had failed. (9) Therefore the recommendation for only one re-treatment may not be sound.
Statement on Post Lyme Disease Syndromes Chronic joint swelling in these circumstances, if not treated with other approaches (such as synovectomy), will eventually disappear, but it has lasted for up to 4–5 years in a few patients. *B. burgdorferi* has not been demonstrated to persist in such patients.	*B. burgdorferi* has been demonstrated to persist (6, 7).

IDSA 2006 Guidelines	Lyme Disease Action comments contd.
To date, there is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease.	See also a recent European review (8) which states "..failures of treatment, similar to those in patients with syphilis, have been reported for almost every suitable antimicrobial agent" and considers the potential mechanisms that spirochetes may have generated to overcome the presence of certain antimicrobial agents in vivo.
Recommendations Post Lyme Disease Syndromes Whatever definition is eventually adopted, having once had objective evidence of *B. burgdorferi* infection must be a condition sine qua non.	As already stated this effectively excludes a significant number of European patients.(2)
Recommendations Post Lyme Disease Syndromes Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (6 months) subjective symptoms after administration of recommended treatment regimens for Lyme disease.	This omits a recommendation for those with chronic objective symptoms who have been shown to improve over repeated courses of antibiotics. It also omits a recommendation for those with non specific, subjective presentations, as has been shown to occur in Europe (2). Hassler et al (9) demonstrated that four doses could effect a cure when the first dose had failed. There will be other submissions detailing the failings in the Klempner study but Lyme Disease Action would like to make the point that the patients in that study all acquired Lyme disease in the USA. However applicable the IDSA may consider this study to be in the USA it can not be applicable to European patients because of the documented differences in disease presentation and possible differences in dissemination and pathogenesis. (10)

References

1. Dotevall & Hagberg. Penetration of Doxycycline into Cerebrospinal Fluid in Patients Treated for Suspected Lyme Neuroborreliosis. Antimicrob Agents Chemother. 1989 July; 33(7): 1078-1080
2. F. Strle, E. Ruziic´ -Sabljic´ , J. Cimperman, S. Lotrici -Furlan, and V. Maraspin. Comparison of Findings for Patients with *Borrelia garinii* and *Borrelia afzelii* Isolated from Cerebrospinal Fluid. Clinical Infectious Diseases 2006; 43:704–10
3. Health Protection Agency. Epidemiology. Lyme borreliosis in England and Wales: 2007
4. Trinity BioTech Data sheet EU Lyme + VlsE IgG Western Blot. Western Blot Test System for the Detection of IgG Antibodies to *Borrelia afzelii* "PKO", *Borrelia garinii*, and *Borrelia burgdorferi* VlsE
5. Chanier S, Lauxerois M, Rieu V. Back pain without radiculitis as an initial manifestation of Lyme disease. Presse Med. 2007 Jan;36(1 Pt 1):61-3
6. V. Preasc Mursic et al. Formation and cultivation of *Borrelia burgdorferi* spheroblast-L-Form variants. Infection 24(1996); 218-226
7. Haupl T et al. Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis. Arthritis Rheum. 1993 Nov;36(11):1621-6.
8. Hunfeld & Brade. Antimicrobial susceptibility of *Borrelia burgdorferi* sensu lato: What we know, what we don't know, and what we need to know. Wien Klin Wochenschr (2006) 118/21–22: 659–668
9. Hassler et al. Disappearance of specific immune response after successful therapy of chronic Lyme Borreliosis. International Journal of Medical Microbiology; Apr 2004; 293
10. Rupprecht, Koedel, Fingerle, Pfister. The Pathogenesis of Lyme Neuroborreliosis – from Infection to Inflammation. MOLMED 14(3 - 4) 205 - 212, March-April 2008

11. Sparsa 2008 Recurrent ischemic strokes revealing Lyme meningovascularitis. Rev Neurol (Paris). 2009 Mar;165(3):273-7
12. Rudenko N, Golovchenko M, Ruzoek D, Piskunova N, Mallatova N, Grubhoffer L. Molecular detection of *Borrelia bissettii* DNA in serum samples from patients in the Czech Republic with suspected borreliosis. FEMS Microbiol Lett. 2009 Jan 28;
13. Diza E, Papa A, Vezyri E, Tsounis S, Milonas I, Antoniadis A. *Borrelia valaisiana* in cerebrospinal fluid. Emerg Infect Dis. 2004 Sep;10(9):1692-3.