DBG Objections to the IDSA Lyme Guidelines (24 Apr. 2009)

The Deutsche Borreliose-Gesellschaft (German Society of Lyme-Borreliosis) raises objections to the IDSA Lyme Guidelines published in 2006. The fundamental basis for our objections is that the implementation of the IDSA guidelines extends beyond the United States and into Europe. Accordingly, our ability to diagnose and treat patients with Lyme disease is being severely restricted by these guidelines, and we believe that the guidelines must be revised to provide greater flexibility in the diagnosis and treatment of Lyme disease given the poor laboratory test sensitivity, the persistence of the organism despite adherence to IDSA protocols, and the seriousness of this illness.

We are raising objections to the following guideline recommendations:

Challenge to Lab Diagnostic Test Requirement--Page 1090 :"*Diagnostic testing performed in laboratories with excellent quality-control procedures is required for confirmation of extracutaneous Lyme disease*…."

Challenge to Restrictions on the Use of Clinical Judgment—Pages 1089-90 : "*Clinical findings are sufficient for the diagnosis of erythema migrants, but clinical findings alone are not sufficient for diagnosis of extracutaneous manifestations of Lyme disease or for diagnosis of HGA or babesiosis.*"

Challenge to Persistence--Page 1118

The Basis for Treatment Limitations for Early and Late Lyme Disease and Post-Lyme Syndrome: "The notion that symptomatic, chronic *B. burgdorferi* infection can exist despite recommended treatment courses of antibiotics (tables 2 and 3) in the absence of objective clinical signs of disease, is highly implausible as evidenced by (1) the lack of antibiotic resistance in this genus [39, 40, 310], (2) the lack of correlation of persistent symptoms with laboratory evidence of inflammation or with the eventual development of objective physical signs [223, 257, 288, 289], and (3) the lack of precedent for such a phenomenon in other spirochetal infections [315–317]. Additional compelling evidence against the hypothesis that persistent symptoms are the result of persistent infection is the fact that the concentrations of antibodies against *B. burgdorferi* in many of these patients diminish to undetectable levels [257, 286, 288, 318]. The panel is unaware of any chronic infection in which antibody titers diminish despite persistence of the causative organism. In syphilis, patients who are regarded as having treatment failure typically have persistent or rising titers of antibodies [319]. Finally, Lyme disease lacks characteristics of other infections that justify longer treatment courses, such as infections in immunodeficient hosts, infections in which a pathogen is inhibited but not killed by antimicrobial therapy or in which available antimicrobials are minimally active in vitro, infections caused by an intracellular pathogen, infections involving a biofilm, infections on a heart valve, or infections involving a clinical site in which there is ischemia, a foreign body, a sequestrum, or frank pus [170]. The 'cystic' forms of *B. burgdorferi* that have been seen under certain growth conditions in vitro have not been shown to have any clinical significance [320]."

Challenge to Restriction on Specific Therapeutic Options--Recommendation 5, Page 1105 : *"Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are not recommended for treatment of patients with any manifestation of Lyme disease: first generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine*

penicillin G, combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), long-term antibiotic therapy, anti-Bartonella therapies, hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, specific nutritional supplements, and others (see table 4) (EIII)."

Late Neurologic Lyme Disease--Recommendation 3, Page 1113: "Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone (2 g once per day intravenously for 2–4 weeks) (tables 2 and 3) (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-II). *Response to treatment is usually slow and may be incomplete. Re-treatment is not recommended unless relapse is shown by reliable objective measures.* Ceftriaxone is also recommended for children with late neurologic Lyme disease (tables 2 and 3) (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-III)."

Post Lyme Disease Syndrome Definition—Recommendation 1, Page 1120: *There is no well-accepted definition of post–Lyme disease syndrome. This has contributed to confusion and controversy and to a lack of firm data on its incidence, prevalence, and pathogenesis. In an attempt to provide a framework for future research on this subject and to reduce diagnostic ambiguity in study populations, a definition for post–Lyme disease syndrome is proposed in table 5. Whatever definition is eventually adopted, having once had objective evidence of B. burgdorferi infection must be a condition sine qua non*. Furthermore, when laboratory testing is done to support the original diagnosis of Lyme disease, it is essential that it be performed by well-qualified and reputable laboratories that use recommended and appropriately validated testing methods and interpretive criteria [117, 118]. Unvalidated test methods (such as urine antigen tests or blood microscopy for detection of *Borrelia* species) should not be used [337].

Post Lyme Disease Syndrome Treatment Limitation—Recommendation 2, Pages 1120-1121: 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. *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 (E-I).*

Our objections relate to diagnosis and treatment of Lyme disease (LD), chronic Lyme borreliosis (LB) and the so-called "post-Lyme syndrome" (PLS).

1. Objections to the IDSA guidelines for diagnosis of LD and chronic LB:

- Seronegativity is frequent in LD and does not rule out a chronic persistent *Borrelia burgdorferi* (Bb) infection (1-18).
- The differential diagnosis between multiple sclerosis and neuroborreliosis based on CSF and serum analysis is not possible in at least 25% of cases (9-11, 21).
- Peripheral neuropathy is not rare but occurs in over 20% of LD cases (22-25).

- So-called two-tier testing is not suitable to diagnose LB, particularly in the late phase, for the following reasons:
    - The test methods available on the market are not standardized with respect to their diagnostic value.
    - The sensitivity of ELISA and IFA screening tests varies from 50% to 70%.
    - The sensitivity of the Lyme Western blot is around 10% higher than that of the screening test.
    - This difference in sensitivity means that there is a risk that the screening test will be negative whereas the Western blot shows positive, and the diagnosis of LD will be missed.
    - Neither the screening test nor the Western blot can rule out infection with Bb, i.e., there is a problem of seronegativity (based on the screening test and Western blot) even though the illness persists and has been confirmed by identification of the pathogenic agent (1-18).

2. Objections to the IDSA guidelines for treatment of LD and chronic LB:

- In Europe, LD is often associated with generalized dissemination throughout the entire body, including involvement of the central nervous system (CNS). Treatment should therefore be carried out with antibiotics that penetrate the CNS, irrespective of the various manifestations of the illness (arthritis, neuroborreliosis, neuropathy, acrodermatitis, carditis, encephalopathy).
- The oral antibiotics recommended by IDSA, namely low-dose doxycycline, amoxicillin and cefuroxime, do not penetrate the CNS; in contrast, minocycline, gemifloxacin and intravenous third-generation cephalosporins yield high concentrations in CSF above the minimal inhibitory concentration (MIC) for Bb (19).
- Contrary to the negative opinion of IDSA, the following antibiotics and methods of treatment have proven to be advantageous: carbapenems, ketolides and gemifloxacin (19); pulsed-dosing (20).

- The antibiotic treatment of EM displays a therapeutic failure rate of at least 10% (15, 41, 45, 47, 67-74).
- Bb could still be identified in the skin even after multiple antibiotic treatments with ceftriaxone, doxycycline and cefotaxime (47-49).
- The resistance of Bb to numerous antibiotics has been proven (61).

3. Objections to the proposed IDSA definition of “post-Lyme syndrome”:

- Antibiotic treatment according to the IDSA guidelines does not guarantee elimination of Bb.
- Subjective complaints may reflect ongoing infection with Bb rather than a different illness (PLS).
- The disease situation described by Steere et al (26) as “minor signs and symptoms” and by Bujak (27) as “post-Lyme syndrome” represents serious discomfort for affected patients that is comparable to decompensated cardiac insufficiency, degenerative joint diseases, pronounced diabetes mellitus or a condition after a myocardial infarction according to Klempner et al (2).
- The following facts suggest the existence of chronic LB due to persistent Bb infection:
    - Persistent symptoms of LB with Bb identification despite intensive antibiotic treatment (28-46).
    - Members of the Deutsche Borreliose Gesellschaft have documented 150 such cases (ISBN 978-3-640-19378-3, submitted for publication).
    - There is an extensive body of literature on the existence of chronic LB (45, 50-55).
    - Bb could be cultured in every stage of chronic LB (28-44), even after intensive antibiotic treatment (20, 41, 56-60).

- Numerous publications deal with chronic LB and the problems with its antibiotic treatment (20, 48-49, 62-66).
- There is a high therapeutic failure rate for the antibiotic treatment of LB in its late phase (52, 54-56, 65, 75-77).

- The so-called (according to the IDSA guidelines) adequate antibiotic therapy is subject to these restrictions:
  - Since Bb can possibly resist various antibiotics (including those recommended by the IDSA guidelines) switching antibiotics may be indicated (61).
  - While Bb may be resistant to erythromycin, related antibiotics appear to be suitable for treatment of LB (26, 83-85).
  - Duration of treatment depends on the organic manifestations, severity and course of disease, as outlined in numerous references (2, 20, 25-26, 41, 45-47, 49, 51, 53-54, 56, 60-66, 71-73, 75, 86-94).

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