## EMBERS MONKEY TRIALS: IDSA GUIDELINES IMPLICATIONS

A new study by Drs. Monica Embers, Stephen Barthold, Mario Phillip and colleagues has found that the bacteria that cause Lyme disease, Borrelia burgdorferi (Bb) persist in monkeys after antibiotic treatment. It is the latest in a number of studies that have demonstrated persistent infection in animal models despite treatment. The study also found that the C6 antibody test gave false negative results in all of those treated with antibiotics and in more than ½ of those untreated. This study contradicts the IDSA guidelines as set forth in the table below:

| Topic | IDSA | Embers Monkey Trials |
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| **Mandatory Use of Antibody Laboratory Tests for Diagnosis** | Clinical findings are sufficient for the diagnosis of erythema migrans, but clinical findings alone are not sufficient for diagnosis of extracutaneous manifestations of Lyme disease. . . . Diagnostic testing performed in laboratories with excellent quality-control procedures is required for confirmation of extracutaneous Lyme disease. | The C6 antibody test failed to detect Lyme disease in 60% of untreated monkeys with persistent Lyme disease over time even though direct evidence of the bacteria confirmed persistence. The C6 failed to detect Lyme disease in 100% of treated monkeys with persistent Lyme disease.<br>This means the test is not sensitive enough to be required for diagnosis. |
| **Treatment of Early Disseminated Lyme Disease** | Doxycycline, amoxicillin, and cefuroxime axetil are effective for the treatment of early Lyme disease. Most patients respond promptly and completely. Some individuals have persistent subjective complaints, despite receiving therapy that otherwise appears curative. Less than 10% of individuals do not respond to antibiotic therapy, as evidenced by the presence of objective clinical manifestations, and rarely is re-treatment required. | All infected monkeys treated with this protocol failed to clear the infection. Early disseminated was defined as 4 months after inoculation.<br>This means short term protocols are expected to fail in monkeys with early disseminated Lyme disease. |
| **Persistence of Lyme disease bacteria (Borellia burdorferi)** | 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. | Embers found direct evidence of persistence in all monkeys treated with 28 days of antibiotics and in 8 out of 11 treated with 90 day Klempner protocol.<br>This means Bb persistence is the norm in monkeys. |
| **Antibiotic therapy is not useful for late Lyme disease that has failed a 28 day protocol.** | Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (6 months) subjective symptoms after recommended treatment regimens for Lyme disease (E-I). | Embers found that 3 of 11 infected monkeys cleared the infection using the 90 day Klempner protocol.<br>This means that 90 days of antibiotics worked in about 25% of the monkeys. |
| **Recommended modalities of treatment** | 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: . . . .combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not | "Finally, the use of variable and pulse-dosing regimens of antibiotics may improve efficacy [43] and this warrants testing in an appropriate model."<br>This means that non-standard approaches may improve efficacy. Also note that 90 days was better than |

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| | others), long-term antibiotic therapy. . . | 28 in the Embers study. |
| **Mechanisms of persistence** | 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]. | "The nature of the persistent organisms and the acquisition of tolerance to antibiotics are questions that need to be addressed. The B. burgdorferi spirochete is known to invade collagenous tissue as a possible mechanism of immune evasion."<br>. . . ."The fact that organisms can persist in the presence of antibiotics such as penicillin and cephalosporins (ceftriaxone) that interfere with cell wall synthesis appears to stem from their ability to enter a dormant, non-dividing state [43,44], thus avoiding the need for cell wall synthesis to continue growth."<br>. . . ."A ''persister'' phenotype may possibly be responsible for the recalcitrance of persisting spirochetes made evident by previous studies in mice and dogs [37,42,45], and by those presented in this report."<br><br>This means there are lots of plausible mechanisms for persistence. |
| **Antibody Level Decline** | 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 all of the infected animals, the C6 antibody index rose steeply within the first 5–8 weeks post-inoculation (PI). Thereafter, the responses fit into three patterns, depending on whether the animals were or were not treated with antibiotics. In the treated group, the response declined steadily during the treatment period and reached background levels at the endpoint in all animals. In contrast, the responses of the untreated group remained either largely unchanged (5 out of 12 animals, or returned to background levels (7 out of 12 animals) but not in parallel with the kinetics of the treated group's decline in specific antibody (Figure 2B). |

Embers ME, Barthold SW, Borda JT, Bowers L, Doyle L, Hodzic E, et al. Persistence of Borrelia burgdorferi in Rhesus Macaques following Antibiotic Treatment of Disseminated Infection. PLoS ONE. 2012;7(1):e29914. Available at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0029914.

Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006 Nov 1;43(9):1089-134.

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