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Letter to the editor

Commentary re: "Efficacy of a 14-day course of amoxicillin for patients with erythema migrans" by Wormser et al. DMID Jan 2019☆,☆☆

I read with great interest the above noted article by Wormser et al. but am concerned about the assumptions and factual accuracy of the article (Wormser et al., 2019).

In their quest to show the efficacy of a 14-day course of amoxicillin in Lyme disease (LD) the authors' choice of using resolution of erythema migrans (EM) as a primary endpoint and claiming that "erythema migrans (EM) resolved in all patients" is a bit misleading. It is widely known that in the majority of cases of LD the EM rash resolves spontaneously regardless of intervention. Also in this study 2 of 24 developed another episode of EM which could have reflected ongoing illness and should not necessarily be attributed to reinfection as might be assumed (Leigner et al., 1993).

Concluding that a 14-day course of amoxicillin was "highly effective" despite finding that 4 of 24 or 16.7% had post-treatment Lyme disease symptoms (PTLDS) translates into 71,380 cases annually (i.e. 16.7% of 427,430 reported LD cases annually) (Lymedisease.org, n.d.). This is not an insignificant number of affected individuals. In addition, the subjective symptoms of PTLDS including headache, fatigue, brain fog and peripheral neuropathies can be very disabling, and objective biologic evidence supporting their existence is beginning to be demonstrated. A recent study of Coughlin et al. using PET scans found evidence of elevation of a chemical marker indicative of widespread brain inflammation in 12 individuals with documented PTLDS which was absent in 19 healthy controls (Coughlin et al., 2018). Therefore there appears to be evidence of a physiological basis for the "brain fog" that many patients describe. Another study by Novak et al. found that small fiber neuropathy may be responsible for certain sensory symptoms and dysautonomia seen in PTLDS. In addition, the abnormal cerebral blood flow velocity found in the PTLDS individuals studied, may also contribute to the cognitive symptoms observed (Novak et al., 2019).

There are intrinsic limitations in the data presented that do not support the final conclusions. Making firm statements from the small sample size of 24 with a follow-up at 1 year of only 22/24 or 91.7% is easily fraught with errors. Looking only for "objective evidence "of cardiac and, neurologic difficulties developing in the first 3 months while doing a 12-month assessment for the development of arthritis to determine primary clinical success is not explained. The medical literature documents that the onset of cardiac or neurologic symptoms can occur months to years after the initial infection.

Closer review of the findings indicate the actual rate of treatment failure in this study is greater than the 16.7% with PTLDS. Only 22/24 were 100% compliant, 4 developed "PTLDS" with 2 more having had recurrent EM. Reanalysis reveals that 6/22 or 27% of the cohort failed treatment. How does a 27% failure rate equate with "highly effective treatment"?

The authors state that the data presented in this study was taken from 3 ongoing prospective studies. Prospective longer term studies are strongly needed in the area of LD. In the interim, perhaps more caution is required as premature extrapolation of data can risk coming to potentially incorrect conclusions.

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A 14-day course of amoxicillin is a highly effective treatment for adult patients in the United States with erythema migrans☆

We thank Dr. Greenberg for her interest in our study demonstrating that a 14-day course of amoxicillin is highly effective for treating adult patients in the United States with early Lyme disease manifested by the skin lesion erythema migrans (Greenberg, n.d.; Wormser et al., n.d.). Contrary to the assertions of Dr. Greenberg (Greenberg, n.d.), the primary endpoint was *both* the resolution of the erythema migrans skin lesion and the absence of an objective neurologic, cardiac, or rheumatologic manifestation of Lyme disease (Wormser et al., n.d.). The natural history of untreated patients with erythema migrans is remarkably different from that which we observed. In untreated patients, over 50% will develop joint swelling from Lyme arthritis within 12 months, approximately 11% will develop an objective neurologic manifestation within 3 months, and approximately 4% will develop objective evidence of Lyme carditis within 3 months (Steere et al., 1980, 1987). None of our patients developed any of these complications over the entire

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