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The Reply

We appreciate Dr. Maloney responding to our Lyme disease guideline review.[1]

Clinicians should have confidence that the Infectious Diseases Society of America (IDSA)/American Academy of Neurology (AAN)/American College of Rheumatology (ACR) 2020 Lyme disease guideline[2] used an established and rigorous evidence-based methodology in arriving at the recommendation to use a 10-day course of doxycycline for treating patients with erythema migrans. There has clearly been no compelling evidence that longer courses of doxycycline provide any better outcome. Shorter antibiotic treatment, when feasible, is a desired objective for all infections.

A key concept for the 2020 Lyme disease guideline that Dr. Maloney may have overlooked is that evidence for antibiotic treatment was explicitly stated to be based on both US and European studies.[2] In both locations, the *Borrelia* species causing Lyme disease are similarly susceptible to antimicrobials in in vitro studies.

Two clinical trials served as the basis for the 10-day recommendation for doxycycline treatment of patients with erythema migrans. Using the gold-standard design for assessing drug effectiveness, a randomized, double-blind, placebo-controlled trial, Wormser et al[3] in Westchester, NY compared 3 treatment regimens: 10 days treatment with doxycycline alone, 10 days treatment with doxycycline plus one intravenous dose of ceftriaxone on day 1, and 20 days treatment with doxycycline alone, with outcomes assessed at multiple time points over 30 months (20 days, 3 months, 12 months, 30 months, and at the last study visit). Notably, at study entry, nearly three-quarters of enrollees had systemic symptoms or multiple erythema migrans skin lesions. The primary analysis was based on evaluable patients, meaning they adhered to the treatment regimen prescribed. A second analysis, however, was an intent-to-treat analysis of all patients for whom information was available.

Irrespective of the type of analysis, at no time point was there a significantly better outcome for the 20-day treatment group compared with either of the 10-day treatment groups. Among the evaluable subjects, more than 90% in the 10-day doxycycline arm had a complete response at 30 months after initiation of treatment, vs 83.9% in the 20-day group and 86.5% in the 10-day doxycycline group, who also received a single dose of ceftriaxone. Only 1 patient in the entire study was considered to have treatment failure at any time point. The 95% confidence intervals for the outcome comparisons at 1 year and 30 months were consistent with, at most, a 10.2% better outcome for the 20-day treatment group. Of note, at the 20-day, 3-month, or 1-year time points, 20 days of doxycycline would not have been significantly more effective than 10 days of doxycycline, even if all of the unassessable patients in the 10-day groups were hypothetically classified as incomplete responders and all of those in the 20-day group were classified as complete responders. Furthermore, the duration of follow-up and treatment outcomes were similar at last study contact for all groups.

Similarly, Stupica et al[4] found equivalence in outcome success of 10 days vs 15 days of doxycycline in their study based in Slovenia. Efficacy was assessed for the 225 study subjects at 14 days and 3, 6, and 12 months. At the 12-month mark, 91.9% of the 10-day doxycycline group who were evaluable had a complete response, compared with 93.4% in the 15-day group, a comparable result.

The IDSA/AAN/ACR 2020 Guidelines for Lyme disease used Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to determine antibiotic choice and duration recommendations, using the 2 trials described above for the noted reasons.[2-4] This methodology values clinical trial design and avoids trials with confounding effects. The small 3-arm trial with 57 per-protocol patients with either erythema migrans or a flu-like illness, conducted by Massarotti et al,[5] had an investigator-based option to extend treatment by an additional 10 days with no prespecified details, which affected 23% of the study participants. This trial was used to compare the relative effectiveness of azithromycin, amoxicillin/probenecid, and doxycycline in the Guideline. However, the Massarotti trial[5] was not meant to examine the duration of antibiotic treatment. It therefore was not used in this aspect of evidence grading due to biases inherent in the study design.

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References

1. Auwaerter PG, Kobayashi T, Wormser GP. Guidelines for Lyme disease are updated. *Am J Med* 2021;134(11):1314–6.
2. Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Clin Infect Dis* 2021;72(1):e1–e48.
3. Wormser GP, Ramanathan R, Nowakowski J, et al. Duration of antibiotic therapy for early Lyme disease. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003;138(9):697–704.
4. Stupica D, Lusa L, Ruzic-Sabljic E, Cerar T, Strle F. Treatment of erythema migrans with doxycycline for 10 days versus 15 days. *Clin Infect Dis* 2012;55(3):343–50.
5. Massarotti EM, Luger SW, Rahn DW, et al. Treatment of early Lyme disease. *Am J Med* 1992;92(4):396–403.