Erythema migrans: Lyme disease does not need prolonged therapy

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Antibiotic therapy duration is a major public health issue worldwide. Shortening antibiotic treatment is a way to limit the use of antibiotics and to limit adverse effects, costs, and the risks related to the emergence of antibiotic resistance. The consensus is to treat patients with the shortest possible duration of the antibiotic treatment without compromising the effectiveness of said treatment. However, observation shows that there is still progress to be made for the correct prescription of antibiotics in Europe.[1] In *The Lancet Infectious Diseases*, Stupica and colleagues[2] report the non-inferiority of a 7-day-course regimen of doxycycline versus 14 days in the treatment of erythema migrans in a randomised, open-label non-inferiority trial enrolling 300 patients in Slovenia. This study is of major interest by advocating for a reduced duration of antibiotic treatment in early Lyme disease. This study is published 10 years after a previous study from the same team showed the non-inferiority of reducing the duration of erythema migrans treatment from 14 days to 10 days, which contributed to the current international guidelines.[3,4]

This study is of particular importance in the context of the treatment of Lyme disease, in which clinicians are hesitant to prescribe a shorter course of doxycycline for the fear that such a course will be insufficiently effective. Prolonged treatments are used to prevent persistence of bacterial infection that could serve as the origin of a disseminated and chronic infection. Clinicians ask the question: "why take a risk by treating insufficiently?". This anxiety of the prescriber hinders a rational analysis and can even lead to strategies that are opposed to reduced treatment duration, such as the one advocated by the International Lyme and Associated Diseases Society that still recommends a 21-day doxycycline regimen for erythema migrans.[5] This debate is not recent;[4] for several decades, discussions have arisen with each attempt to reduce the duration of antibiotic treatment for Lyme borreliosis.[6-8]

In addition to a robust statistical method to conclude the non-inferiority of 7 days of doxycycline, one of the major results of the study by Stupica and colleagues[2] is the group of patients with treatment failure at 2 months. Only eight patients (five patients from the 7-day group and three patients from the 14-day group) had persistent erythema migrans at 2 months, with four patients (all from the 7-day group) being retreated with further antibiotics. In all patients, residual erythema migrans disappeared at 6 months, and patients were asymptomatic at 12 months, thereby suggesting no evolution toward disseminated infection. In one patient, the culture of the skin biopsy of persistent erythema migrans was negative for *Borreliae* at 2 months. Even if the sample is small, this result illustrates the difficulty for clinicians to correlate clinical symptoms and bacterial persistence in Lyme borreliosis; in other words, does the disappearance of erythema migrans guarantee successful cure of the infection? And should its persistence be considered as a clinical inefficiency? On the one hand, the skin is a site of bacterial persistence, especially in animal models.[9] On the other hand, residual erythema migrans could represent post-inflammatory consequences and might not require retreatment.

Another strength of the study is that it analysed unspecific signs present during erythema migrans diagnosis and during follow-up. The authors considered eight unspecified signs: fatigue, arthralgias, headache, myalgias, paresthesias, memory difficulties, concentration difficulties, and irritability. The analysis of their results regarding this endpoint leads to two conclusions. First, during erythema migrans, the presence of one of these symptoms should not lead to the diagnosis of disseminated borreliosis because they frequently accompany solitary erythema migrans, as in the case of 85% of patients in the study at enrolment. Second, the authors found no significant difference regarding unspecific symptoms between their patients and a control group at 12 months. This result suggests that due to the poor clinical relevance of these symptoms, under no circumstances should they be misinterpreted as disseminated *Borrelia* infection when a patient has a history of past erythema migrans.

In conclusion, based on objective and well-defined criteria, we have assured the effectiveness of doxycycline's short 7-day treatment for erythema migrans. After this trial, there is no reason to maintain the fear of failing to eradicate the bacterium causing

borreliosis in the early phase of the disease. These results also stress the tremendous importance of well-defined clinical syndromes and criteria for diagnosis and follow-up of patients with Lyme borreliosis. Stupica and colleagues[2] state that unspecific signs are present at the time of diagnosis of Lyme disease but that they should not justify an extension of antibiotic therapy. Any extension of antibiotic duration could itself induce doubt in patients about the effectiveness of the treatment, and this doubt could result in anxiety for the clinicians.[10,11]

We declare no competing interests.

Carole Eldin, Yves Hansmann
carole.eldin@gmail.com

Unité des Virus Émergents, Aix-Marseille University, Marseille, France (CE); Comité de Lutte Contre les Infections Nosocomiales (CLIN) Équipe Opérationnelle d'Hygiène (EOH), Hôpital Nord, Assistance-Publique Hôpitaux de Marseille, Marseille 13015, France (CE); Service des Maladies Infectieuses et Tropicales, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasborg, France (YH)

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