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Efficacy of a 14-day course of amoxicillin for patients with erythema migrans

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ABSTRACT

Although a 14-day treatment course with amoxicillin is in wide clinical usage to treat early Lyme disease, only a few published studies exist to validate its efficacy and safety, with none in the United States. In this study, we reviewed the records of 24 prospectively followed adult patients with erythema migrans who were prescribed a 14-day course of amoxicillin, 500 mg 3 times daily. Treatment with amoxicillin was well tolerated and uniformly successful in resolving the erythema migrans skin lesion and in preventing the development of an objective neurologic, cardiac, or rheumatologic manifestation. Although the study was relatively small and only involved a single center, the findings provide additional evidence that a 14-day course of 500 mg amoxicillin given 3 times per day is highly effective therapy for patients with early Lyme disease.

Lyme disease, caused by *Borrelia burgdorferi*, is the most common tick-borne disease in North America, and the cutaneous lesion, erythema migrans, is the most common clinical manifestation (Nelson et al., 2015; Sanchez et al., 2016; Wormser et al., 2000, 2006). Convincing data indicate that a 10-day course of oral doxycycline is equally as effective as 15-day (Stupica et al., 2012) or 20-day (Wormser et al., 2003) treatment courses with this antibiotic. Based on a comparison of the pharmacokinetic parameters associated with oral doxycycline versus that of amoxicillin, it would be expected that a 14-day course of therapy of amoxicillin should be at least as effective as a 10-day course of doxycycline (Agwuh and MacGowan, 2006; Karlsson et al., 1996; Lee and Wormser, 2008). Although a 14-day treatment course with amoxicillin is in wide clinical usage (Sanchez et al., 2016; Wormser et al., 2000, 2006), only a few publications exist to validate its efficacy and safety (Arnez and Ruzic-Sabljic, 2015; Eliassen et al., 2017, 2018; Nizic et al., 2012), and none exists in the United States.

1. Methods

The records of adult subjects with erythema migrans who had been enrolled into prospective studies that systematically evaluated outcome at multiple time points extending up to 1 year or longer were reviewed. Each of the studies was approved by the institutional review board at New York Medical College and conducted at the Lyme Disease Diagnostic Center.

Charts of the enrolled subjects who were prescribed a 14-day course of amoxicillin, 500 mg three times daily, were selected for this analysis. Primary outcome measures were resolution of the erythema migrans skin lesion(s) without the need for retreatment and whether, over the first 3 months after initiation of treatment, an objective neurologic or cardiac complication developed consistent with early disseminated Lyme disease. Patients were assessed up to 12 months or longer for the development of Lyme arthritis. Clinical success was defined by resolution of the erythema migrans skin lesion and failure to develop an objective neurologic, cardiac, or rheumatologic manifestation of Lyme disease. A secondary endpoint was whether the subject had subjective symptoms attributed to Lyme disease that had persisted continuously or intermittently for at least 6 months following completion of antibiotic treatment with amoxicillin. In this analysis, such persistent symptoms are referred to as posttreatment Lyme disease symptoms (PTLDS) (Cerar et al., 2010; Nowakowski et al., 2003; Weitzner et al., 2015; Wormser et al., 2006). In each of the prospective studies, subjects were questioned about adherence with taking the amoxicillin. Also assessed were whether an adverse effect attributable to amoxicillin developed and whether, over the follow-up period, the subjects had received a greater than 1-day treatment course with antibiotics that have been used clinically to treat Lyme disease. The primary evaluation was an intent-to-treat analysis.

The C6 Lyme enzyme immunoassay (Immunetics, Inc., Boston, Massachusetts) was performed in accordance with the manufacturer's

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recommendations. Cultures of skin or blood samples for *B. burgdorferi* were performed as described elsewhere (Nadelman et al., 1996; Schwartz et al., 1992; Wormser et al., 1998).

2. Results

Twenty-four adult patients with erythema migrans who were enrolled in 1 of 3 prospective studies were prescribed a 14-day course of amoxicillin. The mean ± SD age was 48.4 ± 12.8 years (median 49.5 years, range 26–69 years). The majority (62.5%) were males (15/24) and 22 (91.7%) were Caucasian. One-third (8/24) had multiple erythema migrans skin lesions. Seventeen (70.8%) had 1 or more concomitant subjective symptoms attributed to Lyme disease. All 24 subjects had laboratory evidence of *B. burgdorferi* infection. Eighteen subjects (75%) had a positive blood or skin biopsy culture for *B. burgdorferi*, and the remaining 6 subjects were either C6 Lyme enzyme immunoassay reactive at baseline ($n = 4$) or seroconverted ($n = 2$) by the first follow-up visit. The first follow-up visit occurred at a mean ± SD of 14.0 ± 6.0 days after the baseline visit (median 13.5 days, range 5–31 days). Nine patients had 2 follow-up visits within the first 30 days. Nineteen patients (79.2%) had a follow-up visit between 3 and approximately 6 months, averaging 155.2 ± 39.3 days after the baseline visit (median 161 days). The final assessment occurred at or after 9 months in 100% of subjects and at or after 12 months in 22 (91.7%) patients.

Erythema migrans resolved in all patients, and no patient (0/24; 95% CI: 0% to 13.8%) developed an objective neurologic, cardiac, or rheumatologic manifestation of Lyme disease. The treatment course of 1 subject was extended beyond 14 days by the subject's primary care physician for unclear reasons. For this subject, another course of amoxicillin was prescribed 3 days after completion of the first course but had to be discontinued on day 13 of therapy due to the development of neutropenia. No other subject had a recognized adverse effect of amoxicillin. Twenty-two subjects were 100% adherent with taking the 14-day amoxicillin treatment regimen, 1 subject only missed 2 doses, and for 1 subject, data on adherence were unavailable. Intercurrent antibiotics active against *B. burgdorferi* were prescribed for only 1 subject within 6 months of the baseline visit. PTLDS occurred in 4 subjects. Two subjects (8.3%) developed another episode of erythema migrans during the following summer, precluding an unequivocal assessment of PTLDS at that time point.

3. Discussion

In this study, a 14-day course of amoxicillin was uniformly successful in resolving the erythema migrans skin lesion and in preventing the development of an objective neurologic, cardiac, or rheumatologic manifestation. The only noteworthy adverse event was the development of neutropenia in the single subject during retreatment with another 14-day course of amoxicillin prescribed by the primary care physician. Neutropenia is a recognized but infrequent adverse effect of amoxicillin and other beta-lactam antibiotics (Andres et al., 2017; Walbroehl and John, 1992). Compliance with taking the 3 times daily amoxicillin dosing was excellent. A 2-week course of amoxicillin was similarly highly successful and comparably effective to comparators in prospective studies of patients with erythema migrans conducted in Europe (Arnez and Ruzic-Sabljic, 2015; Eliassen et al., 2017, 2018; Nizic et al., 2012). Although 1 study in the United States had evaluated a 10-day course of amoxicillin, in conjunction with probenecid, for treatment of patients with erythema migrans (Massarotti et al., 1992), no studies from the United States on the efficacy of a 14-day course of amoxicillin have been reported to date. This may seem surprising since a 14-day course of amoxicillin has been in wide clinical usage for many years (Sanchez et al., 2016; Wormser et al., 2000, 2006).

Although evidence of PTLDS was found for 16.7% of the 24 subjects in our study, this rate is comparable to that observed in other treatment trials in the United States, irrespective of the antibiotic regimen prescribed (Cerar et al., 2010; Nowakowski et al., 2003; Weitzner et al., 2015). Limitations of this study include that the exact number of days until full resolution of the erythema migrans skin lesion was not routinely recorded. In addition, the study was relatively small and only involved a single center rather than a large multicenter, prospective, randomized trial.

In conclusion, available data indicate that a 14-day course of 500 mg amoxicillin given 3 times per day to adults with erythema migrans is highly effective therapy.

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Conflicts of interest

The authors declare no conflicts of interest.

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