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PROPHYLAXIS WITH SINGLE-DOSE DOXYCYCLINE FOR THE PREVENTION OF LYME DISEASE AFTER AN *IXODES SCAPULARIS* TICK BITE

ROBERT B. NADELMAN, M.D., JOHN NOWAKOWSKI, M.D., DURLAND FISH, PH.D., RICHARD C. FALCO, PH.D., KATHERINE FREEMAN, DR.P.H., DONNA MCKENNA, R.N., PETER WELCH, M.D., ROBERT MARCUS, M.D., MARIA E. AGÜERO-ROSENFELD, M.D., DAVID T. DENNIS, M.D., AND GARY P. WORMSER, M.D., FOR THE TICK BITE STUDY GROUP*

ABSTRACT

Background It is unclear whether antimicrobial treatment after an *Ixodes scapularis* tick bite will prevent Lyme disease.

Methods In an area of New York where Lyme disease is hyperendemic, we conducted a randomized, double-blind, placebo-controlled trial of treatment with a single 200-mg dose of doxycycline in 482 subjects who had removed attached *I. scapularis* ticks from their bodies within the previous 72 hours. At base line, three weeks, and six weeks, subjects were interviewed and examined, and serum antibody tests were performed, along with blood cultures for *Borrelia burgdorferi*.

Results Erythema migrans developed at the site of the tick bite in a significantly smaller proportion of the subjects in the doxycycline group than of those in the placebo group (1 of 235 subjects [0.4 percent] vs. 8 of 247 subjects [3.2 percent], $P<0.04$). The efficacy of treatment was 87 percent (95 percent confidence interval, 25 to 98 percent). Objective extracutaneous signs of Lyme disease did not develop in any subject, and there were no asymptomatic seroconversions. Treatment with doxycycline was associated with more frequent adverse effects (in 30.1 percent of subjects, as compared with 11.1 percent of those assigned to placebo; $P<0.001$), primarily nausea (15.4 percent vs. 2.6 percent) and vomiting (5.8 percent vs. 1.3 percent). Erythema migrans developed more frequently after untreated bites from nymphal ticks than after bites from adult female ticks (8 of 142 bites [5.6 percent] vs. 0 of 97 bites [0 percent], $P=0.02$).

Conclusions A single 200-mg dose of doxycycline given within 72 hours after an *I. scapularis* tick bite can prevent the development of Lyme disease. (N Engl J Med 2001;345:79-84.)

LYME disease is transmitted by the bite of an *Ixodes scapularis* tick and is the most common vector-borne disease in the United States.[1] This infection may be prevented by vaccination.[2,3] However, the vaccine's general acceptance is likely to be limited by its cost (a cost to the pharmacist of $61.25 per dose) and the need for multiple doses to achieve and maintain protection.[2,3] In addition, the vaccine is less than 100 percent effective and is currently approved only for persons 15 to 70 years of age.[3]

Antimicrobial prophylaxis for persons with *I. scapularis* tick bites may be a way to prevent Lyme disease. However, it is not known whether antimicrobial agents can effectively cure incubating *Borrelia burgdorferi* infection. In an animal model of another tick-borne disease, Rocky Mountain spotted fever, antibiotic prophylaxis appeared to delay but not prevent infection.[4] Antimicrobial therapy for the prevention of Lyme disease after *I. scapularis* tick bites has not been shown to be effective in controlled treatment trials.[5-9] In these studies, as well as in a model of cost effectiveness,[10] the drug regimens consisted of courses of antibiotics lasting 10 to 14 days, similar to those typically recommended for the treatment of clinical-

From the Department of Medicine, Division of Infectious Diseases (R.B.N., J.N., R.C.F., D.M., G.P.W.), and the Department of Pathology (M.E.A.-R.), New York Medical College; and the Lyme Disease Diagnostic Center, Westchester Medical Center (R.B.N., J.N., D.M., G.P.W.) — both in Valhalla, N.Y.; the Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Conn. (D.F.); the Vector Ecology Laboratory, Louis Calder Center, Fordham University, Armonk, N.Y. (R.C.F.); the Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, N.Y. (K.F.); Northern Westchester Hospital Center, Mt. Kisco, N.Y. (P.W., R.M.); and the Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, Colo. (D.T.D.). Address reprint requests to Dr. Nadelman at the Division of Infectious Diseases, Westchester Medical Center, Macy Pavilion 209 Southeast, Valhalla, NY 10595.

*Other investigators in the Tick Bite Study Group are listed in the Appendix.

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ly evident early Lyme disease. On the basis of the experience with syphilis[11] and leptospirosis,[12] it might be anticipated, however, that a much shorter course of antimicrobial therapy would be effective in treating an incubating (but inapparent) spirochetal infection. We studied the efficacy and safety of a single 200-mg dose of doxycycline in preventing Lyme disease after an *I. scapularis* tick bite.

METHODS

Subjects

Between May 1987 and December 1996, we recruited subjects who had removed an attached *I. scapularis* tick from their bodies within the preceding 72 hours and had been bitten in Westchester County, New York, where Lyme disease is hyperendemic.[13] Eligible subjects 12 years old or older were enrolled after they had given written informed consent. Parental consent was obtained for those who were younger than 18 years old. Subjects were excluded if they had clinical signs of Lyme disease (e.g., erythema migrans) at the time of enrollment, were taking or had just completed a course of antibiotics effective against *B. burgdorferi,* were pregnant or lactating, had been vaccinated against Lyme disease, or did not submit to study personnel the tick that bit them. Enrolled subjects whose ticks were later identified as something other than *I. scapularis* were included only in the analysis of safety. Subjects were evaluated at Westchester Medical Center, a university medical center (461 of the 506 subjects [91.1 percent]), or at a nearby community hospital (45 subjects [8.9 percent]).

Ticks

The species, sex, and stage of the ticks were determined by a medical entomologist. Ticks were initially classified as unfed (flat) or partly fed (partially engorged) on the basis of a visual inspection. When possible, the duration of the tick's attachment to the subject was estimated on the basis of a measurement of the tick scutal index. This determination (the ratio of tick body length to scutal width) was calculated as reported previously.[14]

Clinical Evaluation

At enrollment, at three weeks, and at six weeks, participants were examined and interviewed with the use of a written questionnaire. During the course of the study, specific questions regarding adverse effects of the study medication were added to the questionnaire. The analysis of adverse events was therefore restricted to the 309 subjects for whom this information was available. Subjects were encouraged to contact study personnel if clinical symptoms occurred between the scheduled visits or in the period immediately after the final visit. They were also counseled on ways to prevent tick bites. Blood was collected at each visit for antibody testing and for culture for *B. burgdorferi*.

Study Medication

After clinical evaluation and phlebotomy, subjects were given two pills from a vial that contained either two 100-mg capsules of doxycycline or two identical-appearing placebo pills containing lactose. Capsules were prepared by the hospital pharmacy and distributed according to a randomization list that maintained a 1:1 ratio between subjects in the doxycycline group and those in the placebo group. Both subjects and study personnel were unaware of the contents of the vials. Subjects swallowed the pills under direct observation by study personnel.

Laboratory Tests

Urine pregnancy tests (Clearview HCG II, Wampole Laboratories, Cranbury, N.J.) were performed at the initial encounter for all women of childbearing potential. Serum antibodies to *B. burgdorferi* were measured by polyvalent fluorescence immunoassay (FIAX, Whittaker Bioproducts, Walkersville, Md.) from 1987 through 1990, and by polyvalent enzyme-linked immunosorbent assay (ELISA) (WhittakerStat, Whittaker Bioproducts) after 1990. Specimens with equivocal or positive assay results were retested by separate immunoblot assays for IgM and IgG antibodies to *B. burgdorferi* (MarDx Diagnostics, Carlsbad, Calif.). All tests were performed and interpreted according to the manufacturers' instructions. Assays on specimens from the same patient were run in parallel. Heparinized whole blood (0.3 ml) or, in some cases, serum (0.3 ml) was cultured for *B. burgdorferi* in modified Barbour–Stoenner–Kelly medium by means of previously described techniques.[15]

Primary End Point

The primary end point was the development of erythema migrans at the site of the tick bite. Erythema migrans occurring at a different site from that of the identified tick bite and laboratory evidence of *B. burgdorferi* infection in the absence of erythema migrans were analyzed as secondary end points. Seroconversion was defined as a change from a negative result on ELISA to an equivocal or positive result in association with the presence of IgM bands on immunoblotting that met the recommended criteria for seropositivity.[16]

Sample Size

The frequency of Lyme disease (characterized by erythema migrans) among untreated subjects who had been bitten by an *I. scapularis* tick in Westchester County was initially estimated to be approximately 5 percent. The smallest clinically important reduction in this rate was considered to be a reduction from 5 percent to 1 percent. Since it was expected that doxycycline would be at least as effective as placebo in preventing the occurrence of disease, the hypothesis was considered one-tailed. Because the frequency (incidence) in each group was expected to be quite small, an arc-sine transformation was performed in conjunction with the binomial test for two independent samples to derive the required sample sizes. On the basis of an alpha level of 0.05 and a power of 80 percent, the planned sample size was 129 subjects in each treatment group. At the time the projected number of subjects had been enrolled, it appeared that the risk of erythema migrans was limited to subjects who had been bitten by nymphal *I. scapularis* ticks. Thus, it became important to continue to enroll subjects until sufficient statistical power could be achieved in the subgroup of subjects bitten by nymphal ticks.

Statistical Analysis

Categorical variables were compared by means of the two-tailed Fisher's exact test or the two-tailed chi-square test. The final analysis for the primary end point was also two-tailed, in order to be more conservative. Student's t-test was used for continuous variables. Statistical analyses were performed with the use of SAS software (version 6.12, SAS Institute, Cary, N.C.). Because an interim analysis was performed in September 1992, the determination of the alpha level was based on the O'Brien–Fleming criteria.[17] A P value of 0.0475 or lower was considered to indicate statistical significance in the final analysis. The efficacy of prophylaxis was calculated as follows: (1−[the risk of infection among the doxycycline-treated subjects ÷ the risk among subjects receiving placebo])×100 percent.[8] A 95 percent confidence interval was computed around the efficacy rate with the use of the test-based method.[18]

RESULTS

A total of 506 subjects were randomly assigned to receive either doxycycline or placebo; this total included 6 persons who were enrolled twice in different years. The primary (intention-to-treat) analysis was restricted to the 482 subjects who had removed identifiable *I. scapularis* ticks from their bodies (Table 1).

TABLE 1. CHARACTERISTICS OF 482 SUBJECTS WHO HAD REMOVED *IXODES SCAPULARIS* TICKS FROM THEIR BODIES AFTER BITES.*

CHARACTERISTIC	DOXYCYCLINE GROUP (N=235)	PLACEBO GROUP (N=247)
Subjects		
Age — yr		
Median	41	41
Range	12–82	17–77
Male sex — no. (%)	127 (54.0)	130 (52.6)
History of Lyme disease — no. (%)	22 (9.4)	24 (9.8)†
Multiple tick bites at enrollment — no. (%)	13 (5.5)	15 (6.1)
Seropositive at base line — no. (%)‡	16 (6.9)	18 (7.3)
Follow-up — no. (%)		
Completed all 3 visits	209 (88.9)	222 (89.9)
Completed 2 visits	223 (94.9)	226 (91.5)
Additional unscheduled visit	9 (3.8)	6 (2.4)
Ticks		
Nymphal§		
Engorgement status — no. (%)	124 (52.8)	142 (57.5)
Partially engorged	78 (62.9)	81 (57.0)
Unfed (flat)	43 (34.7)	59 (41.5)
Unknown	3 (2.4)	2 (1.4)
Estimated duration of attachment — hr		
Median	30	31
Range	4–125	4–123
Adult female		
Engorgement status — no. (%)	100 (42.6)	97 (39.3)
Partially engorged	28 (28.0)	36 (37.1)
Unfed (flat)	66 (66.0)	57 (58.8)
Unknown	6 (6.0)	4 (4.1)
Estimated duration of attachment — hr		
Median	10	16
Range	0–148	0–110
Larval — no. (%)	10 (4.3)	8 (3.2)
Adult male — no. (%)	1 (0.4)	0

*Data are based on an intention-to-treat analysis. An additional 24 subjects underwent randomization (12 to each treatment group) but were excluded from this analysis because they had been bitten by ticks other than *I. scapularis,* including dermacentor species (4 subjects), amblyomma species (7 subjects), *I. cookei* (1 subject), and ticks of unknown species or no identifiable tick (12 subjects). The classification of engorgement status was based on the tick's macroscopic appearance. The estimation of the duration of attachment was based on the scutal index obtained for 115 nymphal ticks (55 from the doxycycline group and 60 from the placebo group) and 76 adult ticks (37 from the doxycycline group and 39 from the placebo group).

†It was unknown whether 2 of the 247 subjects in the placebo group had a history of Lyme disease.

‡Seropositivity was determined by fluorescence immunoassay or enzyme-linked immunosorbent assay. An additional 21 subjects had equivocal titers (10 in the doxycycline group and 11 in the placebo group). Base-line serologic testing was not performed in three subjects in the doxycycline group and two subjects in the placebo group.

§The subgroup with bites from nymphal ticks includes three subjects who removed both a nymphal and a larval tick and two subjects who removed both an adult and a nymphal tick.

Of those subjects, 28 had removed multiple ticks at the time of the bite that led to enrollment, including 23 who had removed at least two ticks of the same stage, 3 who had removed both a nymphal and a larval *I. scapularis* tick, and 2 who had removed both a nymphal and an adult *I. scapularis* tick. (For certain analyses, the latter five subjects were included in the subgroup of subjects who had removed only nymphal ticks.) The demographic characteristics of the 235 subjects in the doxycycline group were similar to those of the 247 subjects in the placebo group (Table 1). A total of 431 subjects (89.4 percent) completed all three visits (enrollment, three weeks, and six weeks).

Erythema migrans occurred at the site of the tick bite in 8 of the 247 subjects in the placebo group (3.2 percent), as compared with 1 of the 235 subjects in the doxycycline group (0.4 percent, $P<0.04$). Seven of these nine subjects also had laboratory evidence of Lyme disease, including skin cultures positive for *B. burgdorferi* in all four subjects who underwent a skin biopsy. Seroconversion determined by ELISA occurred in seven subjects. An additional subject (in the doxycycline group) who remained seronegative by ELISA was positive for IgM antibody on immunoblotting. The last of the nine subjects with erythema migrans had an equivocal result on ELISA and negative results for IgM and IgG antibodies on immunoblotting and did not return for serologic testing during the convalescent phase.

Erythema migrans developed at the site of the tick bite a median of 12 days (range, 4 to 17) after the removal of nymphal *I. scapularis* ticks that showed visual evidence of partial engorgement with blood (Table 2). In untreated subjects, bites from nymphal ticks were significantly more likely than bites from adult ticks to be associated with erythema migrans (8 of 142 [5.6 percent] vs. 0 of 97 [0 percent], $P=0.02$).

In the two groups combined, nymphal ticks were nearly twice as likely as adult ticks to be partially engorged (159 of 266 ticks [59.8 percent] vs. 64 of 197 ticks [32.5 percent], $P<0.001$). The estimated median duration of attachment, based on the tick scutal index for the 115 nymphal ticks that were measured, was 30 hours (range, 4 to 125), as compared with 10 hours (range, 0 to 148) for 76 adult ticks ($P<0.001$). Untreated bites from nymphal ticks that had been attached to subjects for an estimated 72 hours or longer were more likely to result in erythema migrans than were untreated bites from nymphal ticks that had been feeding for less than 72 hours (3 of 12 bites [25 percent; 95 percent confidence interval, 7 to 57 percent] vs. 0 of 48, $P=0.006$).

Objective extracutaneous manifestations of Lyme disease (e.g., facial-nerve palsy, meningitis, heart block, and oligoarthritis) were not observed during the study period, nor was asymptomatic seroconversion (the development of antibody to *B. burgdorferi)*. However, in addition to the nine subjects in whom erythema migrans developed at the identified site of the tick bite, solitary erythema migrans lesions developed in two subjects (one in each group) at other sites. In three other subjects (one in the doxycycline group and two in the placebo group), transient viral-like illnesses developed, with laboratory evidence of *B. burgdorferi* infection (Table 3).

TABLE 2. ERYTHEMA MIGRANS AT THE SITE OF AN *IXODES SCAPULARIS* TICK BITE IN 482 SUBJECTS.

TICK STAGE AND ENGORGEMENT STATUS	DOXYCYCLINE GROUP (N=235)	PLACEBO GROUP (N=247)	P VALUE*
	no. with erythema migrans/total no. (%)		
Nymphal	1/124 (0.8)	8/142 (5.6)	<0.04
Partially engorged	1/78 (1.3)	8/81 (9.9)	0.03
Unfed (flat)	0/43	0/59	1.00
Adult female	0/100	0/97	1.00
Partially engorged	0/28	0/36	1.00
Unfed (flat)	0/66	0/57	1.00
Larval	0/10	0/8	1.00
Adult male	0/1	0/0	1.00
All	1/235 (0.4)	8/247 (3.2)	<0.04

*P values were derived by the two-tailed Fisher's exact test.

TABLE 3. OTHER CLINICAL EVENTS AFTER A BITE FROM AN *IXODES SCAPULARIS* TICK.

EVENT	DOXYCYCLINE GROUP (N=235)	PLACEBO GROUP (N=247)	P VALUE*
	no. (%)		
Erythema migrans not at site of tick bite	1 (0.4)	1 (0.4)	1.00
Acute viral-like illness without erythema migrans†	1 (0.4)‡	2 (0.8)§	1.00
Asymptomatic seroconversion	0	0	1.00
Febrile episodes¶	5 (2.1)	4 (1.6)	0.75
Subsequent tick bites‖	29 (18.0)	30 (17.2)	0.97

*P values were derived by the two-tailed Fisher's exact test.

†These subjects also had laboratory evidence of *Borrelia burgdorferi* infection.

‡Seroconversion was documented in this subject by enzyme-linked immunosorbent assay (ELISA) but not by IgM blotting.

§One subject had a change from negative to equivocal results on ELISA and from negative to reactive results on IgM blotting; the other subject had a negative serologic test but a positive blood culture for *B. burgdorferi*.

¶These subjects did not have erythema migrans or laboratory evidence of *B. burgdorferi* infection.

‖Information was available for 161 subjects in the doxycycline group and 174 subjects in the placebo group.

Nine additional subjects (five in the doxycycline group and four in the placebo group) reported febrile episodes after removing *I. scapularis* ticks during the six-week study period but had no laboratory evidence of *B. burgdorferi* infection. A total of 59 of the 325 subjects questioned (18.2 percent) recognized additional tick bites after enrollment but during the six-week study period.

Adverse events (primarily nausea and vomiting) were more frequent in the doxycycline group than in the placebo group ($P<0.001$) (Table 4). However, these events were not serious and were self-limited. No subject reported photosensitivity or a rash attributable to the study medication.

TABLE 4. ADVERSE EVENTS.*

EVENT	DOXYCYCLINE GROUP (N=156)	PLACEBO GROUP (N=153)	P VALUE†
	no. of subjects (%)		
Any adverse event	47 (30.1)	17 (11.1)	<0.001
Nausea	24 (15.4)	4 (2.6)	<0.001
Vomiting	9 (5.8)	2 (1.3)	0.06
Abdominal discomfort	11 (7.1)	6 (3.9)	0.34
Diarrhea	6 (3.8)	6 (3.9)	0.79
Dizziness	4 (2.6)	1 (0.7)	0.37
Other‡	6 (3.8)	1 (0.7)	0.12

*Data are from 309 subjects with recorded answers to specific questions about adverse events; some subjects had more than one such event.

†P values were derived by the two-tailed Fisher's exact test or the two-tailed chi-square test.

‡Other adverse events included headache (in 2 subjects), stiff neck (1), fatigue (1), weakness (1), decreased appetite (1), feeling "feverish" (1), and having "flushes" (1).

DISCUSSION

This randomized, controlled trial shows that antimicrobial prophylaxis with a single 200-mg dose of doxycycline, given after a recognized bite from an *I. scapularis* tick, is highly effective in preventing the development of Lyme disease. Prophylaxis with doxycycline had an efficacy of 87 percent, which compares favorably with the 95 percent efficacy rate of doxycycline given once weekly to prevent leptospirosis.[12] The efficacy rate found in our study should be interpreted cautiously, however, because of the relatively small number of subjects in whom Lyme disease developed and the resultant wide 95 percent confidence interval (25 to 98 percent).

Our results contrast with those of previous studies,[6-8] which showed no clear protection attributable to antimicrobial prophylaxis given after a tick bite. We observed a beneficial effect of prophylactic doxycycline despite a fairly low infection rate in the placebo group (3.2 percent) — a rate similar to that in other studies (range, 1.1 to 3.4 percent). The fact that our study demonstrated the efficacy of antimicrobial prophylaxis is probably related to its size (482 subjects, as compared with 56 subjects,[6] 184 subjects,[7] and 387 subjects[8] in the other randomized studies), which provided the study with greater statistical power to show relatively small differences.

Our use of a restrictive primary end point (erythema migrans at the site of the tick bite) could have resulted in underestimation of the actual incidence of *B. burgdorferi* infection attributable to the bite of an identified *I. scapularis* tick. However, this end point was chosen deliberately. Erythema migrans at the site of the bite is the most common clinical manifestation associated with *B. burgdorferi* infection and is the only reliable marker of infection caused by that specific bite. As shown in our study, subsequent tick bites are common (reported by 59 of the 325 subjects we questioned [18.2 percent]), even over a period as short as six weeks. Indeed, solitary erythema migrans developed in two of the study subjects at a site other than that of the initial tick bite, suggesting the occurrence of an additional, unrecognized bite. The follow-up was limited to six weeks in order to reduce confounding associated with illnesses that might result from subsequent tick bites.

A theoretical risk associated with prophylactic antimicrobial treatment is that it might alter the disease presentation so that the characteristic erythema migrans rash might not be manifested in treated subjects, in whom a more subtle, nonspecific illness might develop or asymptomatic seroconversion might occur. In such circumstances, an unrecognized latent infection might eventually result in arthritis or neurologic disease. We believe that this is unlikely for several reasons. First, nonspecific febrile illnesses were not disproportionately common in the doxycycline group. Furthermore, there was no asymptomatic seroconversion (suggesting the occurrence of subclinical infection) in subjects in the doxycycline group (or in the placebo group). In addition, there was no delayed onset of erythema migrans at the original site of the tick bite in any subject during the six weeks of observation — a period four times the average incubation period for this rash.[19] Finally, objective extracutaneous manifestations of Lyme disease did not develop in any of the subjects in our study or in the three other prospective trials of antimicrobial prophylaxis (with follow-up lasting between six months and three years).[6-8]

Our finding that only ticks that are partially engorged with blood are associated with the development of erythema migrans at the site of the bite is consistent with studies in animals, which have demonstrated that *B. burgdorferi* is infrequently transmitted before the tick has been attached for 48 hours.[20] Our results also confirm those of Sood et al.,[21] who found a significantly increased risk of *B. burgdorferi* infection in humans after tick bites involving an estimated duration of attachment of 72 hours or longer. In addition, our findings support those of previous epidemiologic studies that have shown a temporal association between the development of erythema migrans and exposure to nymphal rather than adult ticks.[13] One possible explanation for this is that adult ticks (which are considerably larger than nymphal ticks) are detected and removed earlier in the feeding process than nymphal ticks; in our study, the estimated median duration of attachment for adult ticks in both groups (10 hours) was one third as long as that for nymphal ticks (30 hours).

Although no serious adverse events were noted, 30.1 percent of those who received doxycycline had medication-related problems, as compared with 11.1 percent with placebo. The events reported were primarily nausea (15.4 percent with doxycycline vs. 2.6 percent with placebo, $P<0.001$) and vomiting (5.8 percent vs. 1.3 percent, $P=0.06$). Taking doxycycline with food may improve its tolerability, with only a minimal decrease in peak serum levels.[12]

The ticks in our study were identified by medical entomologists. Patients and clinicians may have difficulty in distinguishing *I. scapularis* from other ticks and arthropods, and even from scabs or debris.[22] Furthermore, the efficacy of doxycycline in the prevention of other infections transmitted by *I. scapularis* ticks (e.g., babesiosis and human granulocytic ehrlichiosis) is unknown and should not be assumed. Nor can it be assumed that other antimicrobial agents that are effective for the treatment of Lyme disease (e.g., amoxicillin) or even other regimens of doxycycline (e.g., 100 mg twice daily) would have similar efficacy when used for short-term prophylaxis.

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APPENDIX

Other investigators in the Tick Bite Study Group are as follows: Susan Bittker, Denise Cooper, Diane Holmgren, and Charles Pavia, from the Department of Medicine, Division of Infectious Diseases, and Ira Schwartz, from the Department of Biochemistry and Molecular Biology, New York Medical College, Valhalla.

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