Efficacy of Antibiotic Prophylaxis for Prevention of Lyme Disease

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OBJECTIVE: **To determine if antibiotic prophylaxis following a deer tick bite is effective in reducing the risk of developing Lyme disease.**

DESIGN: **Meta-analysis of published trials.**

DATA IDENTIFICATION: **Clinical trials were identified by a computerized literature search of MEDLINE and by an assessment of the bibliographies of published studies.**

STUDY SELECTION: **Trials were included in the analysis if their patients were randomly allocated to a treatment or control group, enrolled within 72 hours following an *Ixodes* tick bite, and had no clinical evidence of Lyme disease at enrollment. Three trials were selected for review after inclusion criteria were applied.**

DATA EXTRACTION: **Data were extracted for details of study design, patient characteristics, interventions, duration of therapy, and number of adverse events in each arm of therapy.**

RESULTS OF DATA SYNTHESIS: **Among the 600 patients with *Ixodes* tick bites, the rate of infection in the placebo group was 1.4%. In contrast, patients who received antibiotic prophylaxis had a 0% infection rate. The pooled odds ratio, comparing prophylaxis to placebo, was 0.0 (95% confidence interval 0.0, 1.5) ($p = .12$).**

CONCLUSIONS: **The available evidence to date suggests that the routine use of antibiotic prophylaxis for the prevention of Lyme disease remains uncertain. Meta-analysis of the controlled trials failed to establish definitive treatment efficacy owing to the small sample size of the combined trials and the low rates of infection following a deer tick bite. A larger randomized trial is needed to demonstrate definitively that prophylaxis is more effective than placebo in reducing the risk of early Lyme disease in endemic areas.**

KEY WORDS: **Lyme disease; prevention; tick bite; meta-analysis; antibiotic prophylaxis.**
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Lyme disease is the most common vector-borne disease in the United States, with more than 50,000 cases reported to the Centers for Disease Control and Prevention (CDC) since 1982.[1] Clinical manifestations range from an expanding rash, erythema migrans, to a multisystem disorder with prominent neurologic and rheumatologic involvement. In an effort to prevent the morbidity associated with *Borrelia burgdorferi* infection, several trials of antimicrobial prophylaxis following *Ixodes* tick bites have been conducted in endemic areas.[2–4] Although all trials have demonstrated an effect in favor of prophylactic treatment with antibiotics, no trial to date has demonstrated, with statistical significance, that administering prophylactic antibiotics is effective in preventing Lyme borreliosis after an *Ixodes scapularis* bite. Because the risk of infection appears to be low (1.0% to 3.5%), the trials' investigators believed the inability to establish treatment efficacy in individual studies was due to small sample size.

In this study we perform a meta-analysis of published data to determine if antibiotic prophylaxis following *Ixodes* tick bites is effective in reducing the risk of developing Lyme disease. This technique allows us to improve the ability to detect small differences in infection rates between antibiotic and placebo groups. We can also estimate more precisely the magnitude of benefit derived from antimicrobial prophylaxis.

METHODS

Selection of Trials and Acquisition of Data

We conducted a MEDLINE search from 1983 to 1995 to identify all published trials of antibiotic prophylaxis for the prevention of Lyme disease using the combinations: "Lyme disease and Prevention," "Lyme disease and Prophylaxis," and "Lyme disease and Trial." Bibliographies from retrieved articles were examined to identify any other relevant trials. Trials were included in the analysis if they were published in the English language and if their patients were randomly allocated to a treatment group, enrolled within 72 hours following an *Ixodes* tick bite, and had no clinical evidence of Lyme disease at enrollment.

We extracted data from the eligible trials including their year of publication, patient demographics, the number of patients enrolled in and completing the trial, inclusion criteria, the antimicrobial agent used (including dose, schedule, and duration of therapy), and the duration of patient follow-up. We also extracted from the included trials the number of subjects that experienced an adverse event in each arm of therapy. An adverse event was defined as the development of erythema migrans at the site of the tick bite, or symptoms compatible with

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early disseminated disease (e.g., seventh cranial nerve palsy) or late Lyme disease (e.g., arthritis) confirmed by seroconversion. An asymptomatic infection was considered an adverse event only if seroconversion was confirmed by an immunoblot assay or by strong evidence of Lyme disease on follow-up. Disagreements regarding the number of adverse events in each trial were resolved by discussion and consensus.

Statistical Methods

An exact stratified analysis, using EGRET computer software[5] was used to estimate the odds ratio and its 95% confidence interval (CI) for each trial, estimate the common odds ratio and its 95% CI for all trials combined, and compute a test of homogeneity to observe the consistency between trial results. Because of the low sensitivity of tests of homogeneity to detect significant heterogeneity among trial results, a value of $p < .10$ was used to define heterogeneity.[6]

The overall infection rates for the antibiotic prophylaxis and placebo groups were determined as the sum of the adverse events divided by the total number of subjects in the group. The 95% CI was computed using an exact method.[7]

A sensitivity analysis was performed by including a retrospective cohort study,[8] which was initially excluded from the study selection.

RESULTS

Study Selection

Of 225 references (from MEDLINE) examined in abstract form, 15 clinical trials were identified and examined.[2-4, 8-19] Three trials met all our inclusion criteria.[2-4] Ten trials were excluded because they examined the effect of antibiotic therapy in patients with established Lyme disease.[9-18] One trial was excluded because it was a retrospective observational study that compared the effect of antibiotic prophylaxis within 2 weeks of an *Ixodes* bite with that of no therapy.[8] One trial was excluded because it was a duplication of trial results reported in abstract form 2 years prior to its full-length publication.[19] One trial was excluded because it was still in progress and had not been unblinded.[20] No other trials identified from the bibliographies of retrieved articles were included into the meta-analysis.

Study Characteristics and Methodologic Issues

Table 1 summarizes study characteristics of the three trials included for analysis.[2-4] All three were conducted in areas where Lyme disease is endemic: Madison, Connecticut,[2] northern Westchester County, New York,[3] and Middletown, Connecticut.[4] A total of 639 patients were enrolled in the trials. The total number completing the studies was 600: 308 in the antibiotic prophylaxis group and 292 in the placebo group. All trials enrolled patients with an *Ixodes* tick bite within the preceding 72 hours. Both adults and children were enrolled in two of the three trials,[2,4] while one trial enrolled only children between the ages of 3 and 19.[3] The percentage of males in the trial varied from 36%[4] to 49%.[3] Patients were excluded from the trials if they were pregnant,[2,4] were allergic to penicillin,[2,4] were undergoing antimicrobial therapy,[2-4] were less than 5 years of age,[4] had IgG antibodies to *B burgdorferi* at the time of enrollment,[2] were bitten by a tick other than an *Ixodes* species,[2-4] were already symptomatic with Lyme disease,[4] or were potentially infected with *B burgdorferi* by a previous tick bite between 72 hours and 6 weeks before enrollment.[2]

In two of the three trials the method of randomization was reported.[2,3] In one trial a table of random numbers

Table 1. Study Characteristics of Included Trials

Trial Source, Year	State	Patients Enrolled (Completed)	Patient Characteristics	Antibiotics Used	Daily Dose (mg/d)	Duration of Therapy (d)	Duration of Follow-up (yr)
Shapiro et al.,[2] 1992	Conn.	387 (365)	Adults and children enrolled at one site*	Amoxicillin	750	10	1
Agre and Schwartz,[3] 1993	NY	184 (179)	Children enrolled at one pediatric practice†	Penicillin or tetracycline	1,000	10	1–3
Costello et al.,[4] 1989	Conn.	68 (56)	Adults and children enrolled at multiple practice sites‡	Penicillin	1,000	10	0.5–1

Of the patients enrolled, 51% were adults and 49% were children. The mean age was 47 years for adults and 6 years for children.

†*The ages of the children ranged from 3 to 19 years. The median age was 6 years.*

‡*The mean age of the patients who completed the study was 37 years (range 5 to 85 years). The percentage of adults or children was not reported.*

was used to assign patients to a treatment group,[2] and in the other trial the result of a coin flip recorded in advance on cards selected "blindly" by a third person was used.[3] In all three trials, the blinding of patients was performed by giving them identical-looking tablets, capsules, or liquid suspensions. The success of patient blinding was assessed in only one study.[2] In all three trials, physicians were reported to be blinded to the treatment allocation; however, no trial reported how physician blinding was assessed. One trial measured compliance to the antibiotic regimen by assessing the antimicrobial activity of the urine.[2] Only 42% of the specimens from the amoxicillin-treated group exhibited antimicrobial activity.[2]

Dosages and preparations of antibiotics tested varied among trials. One trial used amoxicillin tablets for adults and a liquid suspension of amoxicillin for children.[2] One trial used a liquid suspension of penicillin for children less than 9 years of age (59 patients) and tetracycline capsules for children 9 years or older (30 patients).[3] One trial used penicillin tablets for all patients, both children and adults.[4] Penicillin or tetracycline was administered 4 times a day, and amoxicillin 3 times a day.

Adverse reactions to antibiotics were reported in all three trials. In the groups receiving antibiotics, one study reported that 2 (1%) of 205 patients developed a rash to amoxicillin,[2] another trial found 1 (4%) of 27 patients developed a rash attributable to penicillin,[4] while no adverse reactions to antibiotics were reported in the third trial.[3] Serious adverse reactions such as anaphylaxis were not reported from any of the trials.

Dropout and exclusion rates of patients were generally low. In one trial 15 patients, 9 (4.4%) in the amoxicillin group and 6 (3.3%) in the placebo group, dropped out primarily by refusing follow-up venipuncture.[2] In the same trial, 7 patients (1.9%) were excluded from statistical analysis because they had serologic evidence (IgG enzyme-linked immunosorbent assay [ELISA]) of past infection with *B burgdorferi* at the time of enrollment.[2] In another trial, 5 patients (2.7%) were excluded from analysis, 4 because an intercurrent illness required antibiotic therapy and 1 because the patient refused follow-up venipuncture.[3] In the third trial, 12 patients (18%) were excluded from analysis, 5 (16%) in the penicillin group and 7 (19%) in the placebo, for failure to return for follow-up venipuncture.[4]

In two of three trials the ticks that were presented to or removed by the physician were tested for the presence of *B burgdorferi* by immunofluorescence or polymerase chain reaction.[2,4] The overall percentage of infected ticks was 15% in one trial,[2] and 29% in the other trial.[4] Shapiro et al. reported that 30 (16%) of 185 ticks submitted from the amoxicillin group and 23 (14%) of 159 ticks from the placebo group were infected with *B burgdorferi*.[2] Costello et al. found 6 (29%) of 21 evaluable ticks infected; 3 each in the placebo and antibiotic groups.[4] The percentage infected in each group, however, was not reported. All trials measured serum antibodies against *B burgdorferi* at presentation and on follow-up. Two trials used an ELISA method,[2,4] and one used an immunofluorescence assay.[3] One trial confirmed positive ELISA results with immunoblotting.[2] Although protocols varied among the trials, patients were periodically examined for clinical signs of Lyme disease by direct patient visits, monitored by periodic telephone calls, and instructed to return for a follow-up visit if symptoms or signs of Lyme disease developed.

Meta-analysis

Study results of included trials are summarized in Table 2. The rate of acquiring Lyme disease among subjects who received antibiotic prophylaxis was 0% in all three trials, while the rate of infection among the placebo groups ranged from 1.1% to 3.4%. The overall weighted rate of infection with Lyme disease following an *Ixodes* tick bite in the placebo group was estimated at 1.4% (95% CI 0.4%, 3.5%), and the overall weighted rate of infection with Lyme disease in the prophylaxis group was estimated at 0.0% (95% CI 0.0%, 1.2%). For each trial the

Table 2. Study Results of Included Trials

Trial Source	Patients (*n*)	Infection Rate* (%)		Odds Ratio† (95% CI)	*p* Value
		Treatment	Placebo		
Shapiro et al.[2]	365	0/192 (0.0)	2/173 (1.2)	0.0 (0.0, 4.8)	0.45
Agre and Schwartz[3]	179	0/89 (0.0)	1/90 (1.1)	0.0 (0.0, 39.4)	1.00
Costello et al.[4]	56	0/27 (0.0)	1/29 (3.4)	0.0 (0.0, 41.9)	1.00
Falco and Fish[8,‡]	71	0/31 (0.0)	2/40 (5.0)	0.0 (0.0, 6.9)	0.63
Pooled results[§]	600	0/308 (0.0)[‖]	4/292 (1.4)[¶]	0.0 (0.0, 1.5)	0.12

**Defined as the number (n) of Lyme disease cases that developed in the total number (N) of study patients allocated to treatment or placebo.*

†Value reflects the ratio of the odds of having an infection on prophylaxis to the odds of having an infection on placebo therapy. OR < 1 implies that prophylaxis is more effective than placebo; OR > 1 implies that prophylaxis is less effective than placebo; OR = 1 implies equal effectiveness for both therapies.

‡Trial[8] included only in the sensitivity analysis.

§Data pooled from three trials.[2,3,4]

‖The 95% CI of the overall infection rate on antibiotic therapy was 0.0%, to 1.2%.

¶The 95% CI of the overall infection rate on placebo therapy was 0.4% to 3.5%.

odds ratio (OR) estimated was 0.0 (in favor of therapy), and it was not statistically significant in all three trials. The pooled OR, which included 600 patients, was estimated at 0.0 (95% CI 0.0, 1.5; $p = .12$). The test of homogeneity of the ORs failed to detect any significant heterogeneity of the ORs among the three trials ($p = 1.00$).

Sensitivity Analysis

The inclusion of a trial with weaker methodologic standards did not alter the pooled OR estimate with the exception of improving the precision of our results (narrowing of the CIs). The trial by Falco et al. had an infection rate of 5% among untreated patients,[8] which was substantially larger than that for the prospective trials. Our pooled OR estimate was 0.0 (95% CI 0.0, 0.9) and achieved statistical significance ($p = .04$).

DISCUSSION

The available evidence to date does not show conclusively that the routine use of antibiotic prophylaxis for the prevention of Lyme disease after *Ixodes* tick bites is warranted. Although patients treated with antibiotics from each of the three trials demonstrated a large but nonsignificant reduction in the risk of acquiring Lyme disease, meta-analysis of the controlled trials could not exclude the possibility that prophylaxis is not more effective than placebo (OR 0.0; 95% CI 0.0, 1.5; $p = .12$). Further, the upper limit of our CI indicates that the data are consistent with a 50% increase in risk of infection in patients on prophylaxis. In contradistinction, our point estimate and the lower limit of the CI (OR 0.0) did not exclude a net beneficial effect in favor of prophylaxis.

Our point estimate, in conjunction with the biological plausibility of Lyme disease prevention using prophylaxis, the consistency of the individual trial results, and the fact that no patient developed Lyme disease on prophylactic therapy, gives weight to the hypothesis that prophylaxis is effective. To improve the precision of the overall evidence, however, future trials of Lyme prophylaxis must be much larger. We estimate that a trial of 864 patients in each group is required to be 80% certain of showing a significant difference between the groups at the $p = .05$ level, when the infection rate in the placebo and prophylaxis groups are 1.4% and 0.2%, respectively.[21] This expresses a conservative relative risk reduction of 86%. To date only 600 patients in total have been randomized.

Despite the lack of precision of the results, if prophylaxis is truly effective, what would the magnitude of the clinical benefit be and would the benefits of therapy outweigh its risks? Given the low observed risk of acquiring Lyme disease infection while on placebo (1.4%) and assuming an 86% reduction in risk on prophylaxis, 1 case of Lyme disease is prevented for every 83 patients given antibiotics following an *Ixodes* tick bite. If the rate of developing a rash while on amoxicillin is 1%, then for every 10 cases of Lyme disease prevented, 8 cases of rash are produced. If the rate of developing minor adverse side effects of amoxicillin is 4%, then for every case of Lyme disease prevented, three individuals will develop minor side effects. In fact, if we assume the rate of anaphylaxis following amoxicillin administration is 0.1%,[22] then for every 10 cases of early Lyme disease prevented, 1 severe life-threatening reaction would be expected.

Because the chance of missing early Lyme disease following a recognized tick bite is very small, it may be argued that the more realistic benefit of prophylaxis to be measured is the number of patients needed to treat to prevent serious sequelae of Lyme disease (cardiac, neurologic, and rheumatologic). As no cases of disseminated or late disease developed in persons on placebo therapy during the follow-up period in this analysis, it may appear futile, causing more harm than good, to provide prophylaxis to all patients bitten by an *Ixodes* tick even in endemic areas. Owing to the small trial sizes, however, no precise estimates can be made regarding the incidence rates of major sequelae from patients who did not develop erythema migrans from these three trials or the true incidence rate of anaphylaxis.

In summary, a larger randomized trial of antibiotic prophylaxis for the prevention of Lyme disease after an *Ixodes* tick bite is needed to estimate more precisely the magnitude of the benefits and risks, in particular the risks of acquiring late sequelae of the disease if it goes undetected, and to demonstrate definitively that prophylaxis is more effective than placebo in reducing the risk of acquiring early Lyme disease in endemic areas. For the present, even in highly endemic areas, too much uncertainty exists about the benefits and risks of antimicrobial prophylaxis to prevent Lyme disease after a tick bite to warrant its routine use in all patients.

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