Antibiotic Prophylaxis for Lyme Disease: How the Way of Reporting a Clinical Trial Can Alter the Perception of Effectiveness

Urbà González, MD, PhD; Department of Dermatology, Clinica Plató, Barcelona, Spain

Commentary on: Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite
Nadelman RB, Nowakowski J, Fish D, Falco RC, Freeman K, McKenna D, Welch P, Marcus R, Agüero-Rosenfeld, Dennis DT, Wormser GP

Question: Is a single 200-mg dose of doxycycline effective for preventing Lyme disease after an *Ixodes scapularis* tick bite?

Design: Nadelman et al conducted a randomized, double-blind (patients and study personnel), placebo-controlled clinical trial over a period of 9.5 years (May 1987 to December 1996) to determine the effect of a single dose of doxycycline on prevention of Lyme disease after a tick bite. Some patients were included twice during this time. At baseline and at 3 weeks' and 6 weeks' follow-up, patients were interviewed and examined, and serum antibody tests were performed and blood cultures done for *Borrelia burgdorferi*. A randomization list was used to maintain a 1:1 ratio. Patients swallowed the pills under direct observation of study personnel. Sample size calculations were clearly defined. The trial included 506 patients with 482 meeting the inclusion parameters (235 doxycycline, 247 placebo) and who had removed identifiable *I scapularis* ticks from their bodies. Twenty-eight had removed multiple ticks at the time of the enrollment bite. Species, sex, and stage of 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 tick's attachment time to the subject was estimated on the basis of a measurement of the tick body. Specific questions regarding the adverse effects of doxycycline use were added to a questionnaire. Additional subjects were enrolled after it was discovered that the risk of erythema migrans was limited to subjects who had been bitten by nymphal ticks (to obtain a sample size with enough statistical power).

Setting: The evaluations occurred at Westchester Medical Center (461 patients [91%]) or at a nearby community hospital (45 patients [8.9%]) in Westchester County, New York.

Patients: Patients were older than 12 years. Inclusion and exclusion criteria were clearly defined. All patients recruited had removed an attached *I scapularis* tick from their bodies within the preceding 72 hours and had been bitten in Westchester County where Lyme disease is hyperendemic. Excluded patients had clinical signs of Lyme disease (eg, 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 the tick that bit them. The demographic characteristics were similar in both the doxycycline and placebo groups. In 482 patients (median age, 41 years; 53% men), the ticks were confirmed to be *I scapularis* ticks. Patients who had tick bites identified as something other than scapularis were included only in the analysis of safety.

Interventions: A single 200-mg dose of doxycycline (2 capsules, 100 mg each) or matched placebo (lactose).

Main Outcome Measures: The primary outcome was the development of erythema migrans at the site of the tick bite. Secondary outcomes were erythema migrans occurring at a different site from that of the identified tick bite and laboratory evidence of *B burgdorferi* infection (positive skin culture or seroconversion) in the absence of erythema migrans.

Results: End points and follow-up data were available for 431 subjects (89.4%), 235 in the doxycycline group and 247 in the placebo group. One patient (1/235, 0.4%) in the doxycycline group and 8 patients (8/247, 3.2%) in the placebo group developed erythema migrans at the site of the tick bite. The authors reported the efficacy of prophylaxis as the relative risk reduction (using an indirect formula: 1 – relative risk, where relative risk is the ratio of the risk in the experimental group in relation to the risk in the control group) that for the primary outcome was 87% (95% confidence interval [CI], 14%-160%). The risk difference was 2.8% (95% CI, 0.5%-5.2%) and the number needed to treat was 36 (95% CI, 19-220). One patient in the doxycycline group and one in the placebo group developed erythema migrans at a different site from that of the identified tick bite. One patient in the doxycycline group and 2 patients in the placebo group had laboratory evidence of *B burgdorferi* infection. The rela-

Calculation and Comparison of Different Efficacy Measures

Tabulation of Results

Development of Erythema Migrans at the Site of the Tick Bite	Placebo Group	Doxycycline Group	Total
Yes	8 (a)	1 (b)	**9**
No	239 (c)	234 (d)	**473**
Total	**247**	**235**	**482**

Quantifying the Risk of Developing the Outcome in Each Group

Risk in control group (Rc)	a/(a + c)	0.032 (3.2%)
Risk in experimental group (Re)	b/(b + d)	0.004 (0.4%)

Different Forms of Measuring the Effect of Treatment

Metric	Formula	Nadelman Value	95% Confidence Interval
ARR*	Rc–Re	0.028 (2.8%)	0.5%-5.2%
No. needed to treat	1/(Rc–Re)	36	19-220
Relative risk reduction	(Rc–Re)/Rc	0.869 (86.9%)	14.0%-159.7%
Relative risk†	Re/Rc	0.13	0.02-1.04
OR‡	(b × c)/(a × d)	0.13	0.02-1.03

*Ranges from –1 (–100%) to 1 (100%). If there is no relationship between the intervention and the outcome, the absolute risk reduction (ARR) will be exactly 0. The ARR will be >0 when the intervention is associated with less occurrence of the outcome and <0 when the intervention is associated with an increased occurrence of the outcome.

†When the baseline risk is low, as in this trial, the relative risk and the odds ratio (OR) are similar.

‡Ranges from 0 to infinite. The odds of an event (eg, an outcome) are the probability of it occurring compared with the probability of it not occurring. If the experimental group has lower odds, the OR will be <1; if the control group has lower odds, the OR will be >1; and if there is no difference between the 2 groups, the OR will be 1.

tive risk reduction for all outcomes was 71% (95% CI, 5%-138%), the risk difference was 3.2% (95% CI, 0.2%-6.1%), and the number needed to treat was 31 (95% CI, 16-433). Information for the adverse events was provided for 309 of the 506 original subjects. Adverse events occurred more in the doxycycline group (30.1%) than in the placebo group (11.1%). The complaints were primarily nausea (15.4% vs 2.6%, respectively) and vomiting (5.8% vs 1.3%, respectively). It was not stated if any patient had to leave the study due to adverse effects, only that no serious adverse events occurred.

Authors' Conclusion: A single 200-mg dose of doxycycline given within 72 hours after an *I scapularis* tick bite is highly effective in preventing the development of Lyme disease.

Comment

I recommend the complementary reading of other commentaries about the applicability of this study. Shapiro, in an accompanying editorial,[1] pointed out the difficulty in clinical practice to know the species, stage, degree of engorgement of the tick, and even the difficulty to determine if the "tick" is actually a tick; the side effects of therapy; and the importance of other effective strategies for prevention such as educating the population in

endemic areas to check carefully for ticks and to remove them promptly and correctly. In another commentary by Meyerhoff,[2] attention was drawn to the fact that an adequate follow-up period is needed to allow for the development of Lyme disease.

This randomized trial appears to be valid and well designed. However, the authors provided no description of how the randomization sequence was generated or about concealment of allocation. Patients and investigators were blinded for interventions, there was an evaluation of compliance and only 51 (10.6%) of 482 people were lost to follow-up. The outcome measures and end points were clearly defined and explained and the analysis of results was by intention to treat.

The results of this trial contrasted with those of previous studies, which showed no clear protection attributable to antibiotic prophylaxis given after a tick bite. These earlier studies failed to establish definitive treatment efficacy because of small sample size and the very low risk of infection even in endemic areas.[3] Although, in the study of Nadelman et al the authors concluded that "doxycycline is highly effective in preventing Lyme disease," they were equally clear that the relative risk reduction (87%) should be interpreted cautiously because of the small number of patients who developed the outcome and the wide 95% CI.

Besides relative risk reduction (RRR), there are other measures for quantifying the benefit of an intervention in a clinical trial. Although they are derived from the same data, they may lead to different inferences with regard to the efficacy level. The other commonly used measures of the benefits of an intervention are absolute risk reduction or risk difference (ARR), its inverse (1/AAR), the number needed to treat (NNT), the relative risk (RR), and the odds ratio (OR). The **Table** shows how these measures can be calculated from tabulated results of controlled clinical trials comparing 2 interventions and with binary (yes or no) outcomes. In the Nadelman et al study, the efficacy of prophylaxis was expressed as RRR. But this measure is not the best way of expressing the overall efficacy of doxycycline in this trial. As with the RR, the RRR does not tell anything about the absolute baseline risk and therefore the real benefit to be gained. In addition, with these relative measures the impact of an intervention can be overestimated or underestimated if the risk in the control group is very low or very high, respectively. In the calculation of RRR for the primary outcome in this study, a small absolute difference in risk (2.8%) can seem rather high (87%) when compared with a fairly low (3.2%) baseline (control group) risk of developing erythema migrans. In this case, the absolute difference between the risk in the control and the experimental group (AAR) and the NNT are more clinically relevant and useful measures of benefit to use than RRR. The NNT tells us the number of patients who need to be treated to prevent one bad outcome. In this trial, the NNT was 36; in other words, 36 patients need to be treated to prevent 1 case of erythema migrans. Once the effect has been quantified, the CI measures the precision of the estimate of the treatment effect. A wide CI indicates that the estimate of the treatment effect is imprecise. In the trial by Nadelman et al the 95% CIs are wide and con-

sequently the efficacy measures should be interpreted cautiously.

Bottom Line: It is important that clinicians be familiar with all these measures, as they are often used indistinctly in analysis of clinical trials. Furthermore, there is some empirical evidence that the perception of effectiveness by the readers of clinical trials depends on the outcome metric used.[4,5] Clearly, the study of Nadelman et al is more impressive expressed with an efficacy (RRR) of 87% than an ARR of 2.8%. It is known that most patients consulting physicians for tick bites in endemic areas receive prophylactic antibiotic therapy.[6] The type of reporting used in this trial can predispose more to the routine use of antibiotic therapy for prophylaxis of Lyme disease, even when the value of this intervention is still controversial.

Corresponding author: Urbà González, MD, PhD, Department of Dermatology, Clinica Plató, C/Plató 21, 08006 Barcelona, Spain (e-mail: 24998ugc@comb.es).

1. Shapiro ED. Doxycycline for tick bites: not for everyone [editorial]. *N Engl J Med.* 2001;345:133-134.
2. Meyerhoff J. Single-dose doxycycline prevented Lyme disease after an *Ixodes scapularis* tick bite [commentary]. *ACP Journal Club.* 2002;136:56-57.
3. Poland G. Prevention of Lyme disease: a review of the evidence. *Mayo Clin Proc.* 2001;76:713-724.
4. Bobbio M, Demichelis B, Giustetto G. Completeness of reporting trial results: effect on physicians' willingness to prescribe. *Lancet.* 1994;343:1209-1211.
5. Naylor CD, Chen E, Strauss B. Measured enthusiasm: does the method of reporting trial results alter perceptions of therapeutic effectiveness? *Ann Intern Med.* 1992;117:916-921.
6. Fix AD, Strickland GT, Grant J. Tick bites and Lyme disease in an endemic setting: problematic use of serologic testing and prophylactic antibiotic therapy. *JAMA.* 1998;279:206-210.

News and Notes

T he 24th Arcachon Annual Course of Pediatric Dermatology will be held from April 22 to April 25, 2003, at the Palais des Congres, Boulevard Veyrier Montagnères, F-33120 Arcachon, France. Topics will include cutaneous tumors in children; the eye in pediatric dermatology; immunomodulation in pediatric dermatology; and the umbilicus/clinical cases from Bordeaux Children's Hospital. For more information and registration, contact Gisèle Latournerie, Unitè Dermatologie Pédiatrique, Hôpital Pellegrin Enfants, 33076 Bordeaux Cedex, France (phone: 33 5 56 79 565 42; fax: 33 5 57 82 14 50; e-mail: gisele.latournerie@chu-bordeaux.fr).