

ORIGINAL ARTICLE

Postexposure Treatment with Doxycycline for the Prevention of Tick-Borne Relapsing Fever

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ABSTRACT

BACKGROUND

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Tick-borne relapsing fever (TBRF) is an acute febrile illness. In Israel, TBRF is caused by *Borrelia persica* and is transmitted by *Ornithodoros tholozani* ticks. We examined the safety and efficacy of postexposure treatment to prevent TBRF.

METHODS

In a double-blind, placebo-controlled trial, 93 healthy subjects with suspected tick exposure (52 with signs of tick bites and 41 close contacts — those without signs but with a similar risk of contact with ticks) were randomly assigned to receive either doxycycline (Dexxon, in a dose of 200 mg the first day and then 100 mg per day for four days) or placebo after presumed exposure to TBRF. Cases of TBRF were defined by fever and a positive blood smear. Serologic analysis for cross-reactivity to *Borrelia burgdorferi* and polymerase chain reaction (PCR) for the borrelia *glpQ* gene were also performed.

RESULTS

After randomization, 47 subjects (26 with signs of tick bites and 21 close contacts) received doxycycline. Forty-six other subjects (26 with signs of tick bites and 20 close contacts) received placebo. All 10 cases of TBRF identified by a positive blood smear were in the placebo group of subjects with signs of a tick bite ($P < 0.001$). These findings suggested a 100 percent efficacy of preemptive treatment (95 percent confidence interval, 46 to 100 percent). PCR for the borrelia *glpQ* gene was negative at baseline for all subjects and subsequently positive in all subjects with fever and a positive blood smear. Seroconversion was detected in eight of nine cases of TBRF. PCR and serum samples were negative for all of the other subjects tested. No major treatment-associated adverse effects were identified.

CONCLUSIONS

Treatment with doxycycline is safe and efficacious in preventing TBRF after suspected exposure to ticks in a high-risk environment. (ClinicalTrials.gov number, NCT00237016.)

N Engl J Med 2006;355:148-55.
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TICK-BORNE RELAPSING FEVER (TBRF), AN acute febrile illness characterized by a pattern of remissions and relapses, is transmitted by several types of soft ticks.¹ TBRF in Israel is caused by *Borrelia persica* associated with *Ornithodoros tholozani* ticks.²⁻⁴ Humans are infected during the blood meal of an infected tick. In contrast to bites from hard ticks, bites from soft ticks are usually unnoticed by humans during the tick's blood meal. The estimated rate of transmission of infection from a tick bite is 50 percent, with an incubation period of 2 to 18 days.^{1,5,6} *Borrelia* are typically found in the person's bloodstream during his or her febrile periods.^{5,7} People with infection typically present with high temperatures, dizziness, headaches, and muscle and joint pain.⁴⁻⁶ In the absence of treatment, fever can recur up to 15 times. Myocarditis accompanied by arrhythmia, cerebral bleeding, and liver dysfunction are rare fatal complications.^{3,8}

Direct visualization of borrelia spirochetes in a blood smear is the gold standard for the diagnosis of TBRF.¹ Polymerase chain reaction (PCR) and serologic analysis have occasionally been used as additional diagnostic tools.⁹⁻¹¹ *Borrelia* are sensitive to a wide range of antibiotics^{5,6,12}; however, therapy with antimicrobial agents can trigger a Jarisch–Herxheimer reaction with sudden fever, rigors, and hemodynamic instability.^{5,6,13-15}

Antimicrobial prophylaxis for persons with tick bites or persons who have stayed in areas (such as caves) where there is risk of infection may prevent TBRF. Short courses of treatment with doxycycline have been shown to be effective in post-exposure prevention of other spirochetal infections such as Lyme disease.^{16,17} Observations from uncontrolled studies suggest that prophylactic treatment after exposure to ticks may be effective for TBRF,¹⁸ but to our knowledge a controlled study has not been published.¹⁹

In this study, we examined the efficacy of a short course of doxycycline in preventing TBRF after high-risk activities in an area where TBRF is endemic. PCR and serologic analysis were used for the diagnosis in addition to evaluation of blood smears.

METHODS

SUBJECTS

As part of special military training, subjects underwent a five-day camouflage and survival exer-

cise in an area where TBRF is endemic. During the exercise, subjects remained hidden in small niches and caves, in close proximity to the ground during the day. Subjects conducted the exercise in pairs. After all subjects completed the exercise, a physician examined them meticulously for signs of tick bites. A typical sign of a tick bite is a central erythematous area surrounded by a bluish-purple area. Subjects with signs of tick bites and their close contacts (the other subjects who were paired with them) were eligible for recruitment for the study. Subjects with fever, those with known sensitivity to doxycycline, and those with suspected TBRF in the three weeks before randomization were not recruited. Written informed consent was obtained, and subjects were randomly assigned to placebo or doxycycline. All subjects with a tick bite were treated. Subjects who declined to participate in the study were treated with doxycycline according to current Israel Defense Force (IDF) policy.

TREATMENT PROTOCOL

Subjects received either placebo pills or 200 mg of doxycycline immediately after randomization and 100 mg per day for the subsequent four consecutive days in a double-blind fashion. The rationale for a five-day treatment was based on the common treatment practice in the IDF and a previous report on postexposure treatment.¹⁸ The randomization was stratified for subjects with signs of tick bites and for their contacts (for a detailed randomization protocol, see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

Subjects were given the pills under direct observation. Subjects with suspected illness stopped the blinded medication and were treated by their attending physician. The research protocol was approved by the IDF ethics committee.

CLINICAL EVALUATION

Before undergoing randomization, subjects completed a questionnaire that included personal data and information about prior episodes of TBRF as well as details regarding previous and current potential exposures and preventive measures adopted.

During the first week after randomization, an appointed supervisor monitored subjects daily for fever. He or she also completed written questionnaires concerning subjects' symptoms and pos-

sible adverse effects including nausea, vomiting, heartburn, dysphagia, photophobia, headache, diarrhea, and rash. A member of the study personnel also examined and interviewed subjects one week and three weeks after randomization. A written questionnaire concerning compliance with treatment, adverse effects, and symptoms of TBRF was completed during an interview by the study physician. Subjects were not in a setting where they could be exposed to TBRF again during the three-week intensive follow-up period. Passive surveillance of subjects continued for the duration of their remaining military service (details regarding the passive surveillance are available in the Supplementary Appendix).

During randomization, blood samples were collected for blood smear, PCR, and serologic analysis. An additional blood sample was obtained from the study subjects 15 to 21 days later.

Subjects were instructed to contact the study personnel immediately if symptoms of TBRF (such as high fever, headache, and malaise) occurred. Subjects with suspected illness consistent with TBRF were interviewed and examined, and blood was drawn for diagnosis (blood smear), PCR, and serologic analysis. Subjects with fever were treated with doxycycline by their attending physician and monitored for the occurrence of a Jarisch-Herxheimer reaction (sudden fever, rigors, and hemodynamic instability). Serum samples from these patients were obtained two weeks later. A case of TBRF was defined by fever and a positive blood smear. The interval from the suspected tick encounter to onset of fever was defined as the incubation period.

BLOOD SMEARS

Thick and thin blood smears were prepared from tubes containing EDTA and from fresh blood. Blood smears were stained with rapid Giemsa's stain. A laboratory technician examined all blood smears according to a previously described method.^{20,21} Detection of *B. persica* by blood smear is highly specific, because to our knowledge there is no evidence of other tick-borne spirochete diseases in Israel.

PCR

A new PCR assay for the *glpQ* gene was developed and established in our laboratory for the detection of TBRF.²² The *glpQ* gene, encoding the enzyme glycerophosphodiester phosphodiesterase,

is conserved among spirochetes that cause relapsing fever. These spirochetes include *B. persica*, *B. hermsii*, *B. recurrentis*, and *B. crocidurae*, but the *glpQ* gene is absent from *B. burgdorferi*, the causative agent of Lyme disease.^{22,23} Detailed information about the PCR protocol is provided in the Supplementary Appendix.

SEROLOGIC ANALYSIS

A commercial enzyme-linked immunosorbent assay (ELISA) kit for detection of human IgM antibodies against *B. burgdorferi* (Euroimmun) was used. The antigen in the kit consisted of a mixture of antigen extracts of *B. burgdorferi* and *B. afzelii*. It is thought that an appreciable cross-reacting antigen homology exists between *B. burgdorferi* and *B. persica*. The tests were performed according to the manufacturer's instructions. Detailed information about the method of serologic analysis is provided in the Supplementary Appendix.

TICKS

An effort was made to trace suspected locations of exposure by a detailed interview of infected subjects. Ticks were collected from the indicated locations with the use of dig-in plastic traps containing dry ice. These ticks were identified by entomologists from the Israeli Ministry of Health.

STATISTICAL ANALYSIS

The sample size was determined according to the primary end point: efficacy of doxycycline as preventive treatment for TBRF. Assuming an α (two tailed) value of 0.05, a statistical power of 90 percent, a ratio of doxycycline treatment to placebo of 1:1, a proportion of disease in the treated group of 1 percent, and a proportion of disease in the placebo group of 15 percent, we determined that 140 subjects would need to be enrolled: 70 in the treatment group and 70 in the placebo group. An interim analysis by an external inspector was planned after 10 subjects received a diagnosis of TBRF. According to a prespecified stopping rule, the external inspector was to examine the distribution of TBRF cases between the study groups and order the trial to be stopped if there was a treatment advantage of more than eight to two. The results were conclusive in favor of treatment, so the study was stopped after 93 subjects underwent randomization.

The t-test was used to compare continuous variables between the treatment and placebo groups.

Chi-square or Fisher's exact tests were used to examine the statistical significance of differences between the treatment and placebo groups. These differences included categorical variables such as the presence of TBRF and occurrence of adverse events after treatment. All tests used were two-tailed, and a P value of <0.05 was considered to indicate statistical significance.

RESULTS

During the study period (April 2002 to April 2003), 582 subjects in 17 cohorts were screened after returning from field exercises (Fig. 1). Among

them, 81 subjects (14 percent) had typical signs of tick bites and 44 subjects (8 percent) were close contacts of subjects who had tick bites. A total of 125 subjects (21 percent) were eligible to receive postexposure prophylaxis. In all, 93 subjects (16 percent) volunteered to be included in the study; this number included 52 of 81 (64 percent) with signs of tick bites and 41 of 44 (93 percent) close contacts.

The characteristics of the study population are shown in Table 1. There were no significant differences between the doxycycline and placebo groups in sex, age, prior exposure, prior antibiotic treatment, prior reported illness with TBRF, per-



Table 1. Characteristics of the Two Groups.*

Characteristic	Doxycycline Group (N=47)	Placebo Group (N=46)
Male sex — no.	47	46
Age — yr	20±1.1	19.9±1.2
Antibiotics taken 3 wk before study — no./total no. (%)†	2/41 (5)	4/44 (9)
Prior illness (relapsing fever) — no./total no. (%)	1/44 (2)	0/45
Prior possible exposure — no./total no. (%)	26/45 (58)	25/44 (57)
Signs of tick bites — no./total no. (%)	26/47 (55)	26/46 (57)
Time from presumed tick bite (day)	2.00±1.34	1.87±0.82
Body cover — no./total no. (%)‡	28/46 (61)	28/45 (62)
Use of insect repellent — no./total no. (%)	8/46 (17)	8/45 (18)

* Plus-minus values are means ±SD. There were no significant differences between groups. Data were not available for all participants.

† Antibiotics taken for other reasons were recorded because this treatment may have influenced susceptibility to infection from and treatment for tick bites.

‡ Body cover pertains to the maximal coverage of body surface by rolling down sleeves and buttoning shirts.

sonal preventive behavior, or number of visible signs of tick bites. In view of the lower recruitment rate among subjects with tick bites, we compared the characteristics of the subjects who participated in the study with those of the subjects who declined; these characteristics included the number of visible signs of tick bite. No statistically significant differences between these groups were observed.

We evaluated the number of signs of tick bites in 47 of the 52 subjects with signs of bites, 22 of 26 subjects in the placebo group, and 8 of 10 subjects with TBRF diagnosed by a positive blood smear. The discrimination of individual tick bites among subjects with many signs of bites was of limited accuracy, so comparisons were made between subjects with TBRF and healthy subjects. These comparisons categorized the number of bites in two groups: one to three bite signs and four or more bite signs. We did not find an association between the number of signs of tick bites and disease for all subjects ($P=0.69$) or for the subjects in the placebo group ($P=1.00$ by Fisher's exact test).

Of the 81 subjects with signs of tick bites, only 46 (57 percent) saw ticks during the exposure period and 53 (65 percent) noticed the signs of bites after finishing the field exercise. There was no appreciable difference in personal preventive behavior between subjects with tick bites and their

close contacts. Subjects who remembered a tick bite were recruited a mean (\pm SD) of 1.93 ± 1.08 days after being bitten. None of the subjects were ill or had fever at recruitment into the study.

Subjects received a mean of 4.9 ± 0.4 days of the 5-day treatment. Only 1 subject (1.1 percent) received three doses, and 10 (10.4 percent) received four doses. None of the subjects reported stopping medication because of adverse effects. There was no significant difference in compliance between groups. No other antimicrobial agents were used by the subjects during the three-week follow-up period.

There were no significant differences between the treatment and placebo groups in the rate of adverse effects on any of the three occasions when data were collected. Data on adverse effects recorded during the first week are shown in Table 2. None of the adverse effects were considered serious by the treating physician. Adverse effects such as fever, diaphoresis, and hemodynamic changes consistent with the Jarisch–Herxheimer reaction were not observed in subjects who received prophylactic treatment.

Ten subjects who had high fever and a positive blood smear for borrelia were categorized as having TBRF. All 10 were in the placebo group (10 of 46 cases), and none were in the doxycycline group (0 of 47). This difference was significant ($P<0.001$) and yielded a 100 percent efficacy rate of doxycycline prophylaxis (95 percent confidence interval, 46 to 100 percent). The characteristics of the 10 subjects with TBRF are shown in Table 3. Two more subjects with tick bites in the placebo group had a disease consistent with TBRF, but they were treated before blood samples could be obtained and thus were not confirmed as having TBRF. These two illnesses were not included in the statistical analysis.

The incubation period ranged from 5 to 10 days. All subjects with TBRF reported headache and malaise, and all had signs of tick bites. Subjects received doxycycline treatment under medical supervision and two subjects required hospitalization. After treatment, eight subjects had high fever, diaphoresis, and rigors typical of the Jarisch–Herxheimer reaction. After randomization, blood smears were performed from the blood samples of three subjects in whom TBRF subsequently developed and from the sample of a subject in whom a disease that was consistent with TBRF but not laboratory-proven by blood

smear developed. All four blood smears were negative. Blood smears were performed from the blood samples of only three subjects after randomization because our acquisition of blood samples for this purpose was incomplete.

All subjects with TBRF confirmed by positive blood smear had a positive PCR for *glpQ*. No other subjects from the placebo group or the treatment group had a positive PCR result.

The serum samples of eight of nine of the subjects with positive smears (89 percent) showed seroconversion. Findings were negative in all serum samples of subjects in the placebo group with signs of tick bites in whom fever did not develop (15 subjects) and in subjects with bite signs who received doxycycline (17 subjects). The baseline reactivity of the serologic test used was determined by the results of 10 serum samples from subjects who had no known previous exposure to *Borrelia* and were paired with subjects who had signs of tick bites.

Data on their remaining military service (for long-term surveillance) were available for 91 of 93 subjects. A total of 87 of 91 subjects (96 percent) were under surveillance for more than half a year, whereas 4 of 91 subjects (4 percent) were under surveillance for zero to three months. Long-term surveillance did not reveal latent cases of TBRF.

The estimated rate of TBRF infection among subjects with tick bites in our group was 39 percent (10 of 26 subjects with signs of tick bites in the control group). This finding, which is consistent with a previous report of a 50 percent infection rate from infected ticks,⁶ suggests that ticks in the studied zone were highly infected with *Borrelia*. A few dozen to hundreds of ticks were collected in each of four of six field sites in which infection was recognized. All ticks were identified as *O. tholozani*.

DISCUSSION

This study demonstrates that postexposure prophylaxis with a five-day course of the antimicrobial agent doxycycline is both safe and efficacious in preventing TBRF in a population at high risk of exposure to *B. persica*. These data support previous observations¹⁸ but were obtained from a randomized, placebo-controlled, double-blind trial. Since the rate of compliance with the five-day treatment was high, the efficacy of shorter treatment after exposure to ticks could not be assessed.

Table 2. Adverse Effects in the Study Groups during the First Week of Treatment.*

Adverse Effects	Doxycycline (N = 46)	Placebo (N = 46)	P Value
	no. (%)		
Nausea	2 (4)	8 (17)	0.09
Vomiting	1 (2)	4 (9)	0.18
Heartburn	4 (9)	5 (11)	0.73
Dysphagia	2 (4)	3 (7)	0.65
Headache	5 (11)	7 (15)	0.76
Diarrhea	3 (7)	6 (13)	0.48
Skin symptom	1 (2)	4 (9)	0.36
Any adverse effect	14 (30)	20 (43)	0.28

* One patient did not complete the daily report on which this analysis was based. On subsequent follow-up reports, he did not report any adverse effects.

Adverse effects of prophylactic treatment were minor and did not differ significantly between the placebo and doxycycline groups. An important observation is that doxycycline prophylaxis did not cause a Jarisch–Herxheimer reaction in any of the subjects treated preemptively. In contrast, such a reaction was noted in 80 percent of the subjects treated after the onset of TBRF. We suspect that the prophylactic treatment given to the study subjects early after the presumed infection, before an appreciable bacterial load had accumulated, was the reason for the absence of a Jarisch–Herxheimer reaction after the preemptive treatment.

We did not find an association between the number of tick bites and illness. This may be the result of the small number of subjects in this analysis. Another explanation is that the main determinant of infectivity was the number of infectious locations the subject was exposed to (this assumes that most ticks in a specific location are infected because of vertical transmission to offspring ticks² and have a high rate of infectivity). In contrast to transmission of other spirochete pathogens such as *B. burgdorferi*, transmission of TBRF requires only a brief tick attachment. Many subjects probably failed to notice the tick bite.

Neither PCR nor serologic analysis yielded additional cases among the “healthy” subjects in the treatment and placebo groups, so these tests may not be more sensitive than the blood smear for detection of infection with *B. persica*. Another explanation is that the pathogenicity of TBRF is high and there were no subjects with subclinical infec-

Table 3. Characteristics of Subjects with TBRF.*

Subject No.	Signs of Bites Noticed (estimated)	Estimated Incubation days	Duration of Illness	Peak Temperature °C	JHR	Blood Smear	Sero-conversion	PCR Assay	Tick Found at Field Site
1	ND	6	3	38.4	Yes	+	Yes	+	Yes
2	10	7	2	39.0	No	+	Yes	+	Yes
3	1	6	1	38.6	Yes	+	Yes	+	No
4	2	5	1	38.8	Yes	+	No	+	No
5	ND	8	1	39.6	Yes	+	Yes	+	Yes
6	9	10	1	38.4	Yes	+	Yes	+	Yes
7	10	10	1	38.1	No	+	ND	+	ND
8	3	10	1	39.4	Yes	+	Yes	+	ND
9	2	7	1	38.2	Yes	+	Yes	+	ND
10	10	ND	1	38.2	Yes	+	Yes	+	ND

* JHR denotes Jarisch–Herxheimer reaction, plus signs positive results, and ND no data.

tion in the placebo group or among the subjects receiving the doxycycline prophylactic treatment.

In an environment with less frequent exposure to *B. persica*, a larger group of people (all with suspected exposure) may need to be treated. This treatment, for a limited benefit, would increase the risk of medication-associated adverse events. By meticulously examining people for signs of tick bites, this treatment group can be limited to those with the greatest likelihood of infection. Examination and treatment should be performed within a small window of opportunity, because the estimated incubation period among the subjects with TBRF in our study was 5 to 10 days (mean, 7.7±1.9); our findings were similar to those in previous reports.⁸ Self-examination by subjects would reduce and better target the group to be treated. However, in this study only 65 percent of subjects with tick bites noted them before examination. Another approach is to use sensitive labo-

ratory tests such as PCR to try to identify infection during the incubation period. However, none of the blood samples obtained from subjects after exposure but before the onset of disease yielded positive results by either PCR or blood smear. A theoretical risk of antibiotic prophylaxis might be a late relapse of TBRF or the alteration of the disease presentation. Relapses that occurred after treatment have been reported after a single dose²⁴ or 10 days of treatment with doxycycline.²⁵ In our study, no cases of late relapse were identified.

Supported by a grant (5648) from the Israeli Chief Scientist, Ministry of Health.

No potential conflict of interest relevant to this article was reported.

We are indebted to Dr. S. Pitlik (Rabin Medical Center, Beilinson Campus, Israel) for his help with the blinded interim analysis; to A. Wilamowski and Dr. H. Paner (Israeli Ministry of Health) for their help with the identification of captured ticks; and to R. Ambar (Medical Corps, Israel Defense Force, Military Post 02149) and D. Gutman (Haim Sheba Medical Center, Bacteriological Laboratory, Tel Hashomer, Israel) for their technical assistance in the detection of borrelia in blood smears.

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