Single-dose doxycycline prevented Lyme disease after an *Ixodes scapularis* tick bite

Nadelman RB, Nowakowski J, Fish D, et al., for the Tick Bite Study Group. **Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite.** N Engl J Med. 2001 Jul 12;345:79-84.

QUESTION

In patients with *Ixodes scapularis* tick bites, does single-dose doxycycline prevent Lyme disease?

DESIGN

Randomized (unclear allocation concealment*), blinded (patients and study personnel),* placebo-controlled trial with 6-week follow-up.

SETTING

A university hospital and a community hospital in Westchester County, New York, United States.

PATIENTS

506 patients who were ≥ 12 years of age; had removed an attached *I. scapularis* tick from their bodies in the previous 72 hours; and were bitten in Westchester County, New York. Exclusion criteria were clinical signs of Lyme disease, current or recent completion of an antibiotic course that is effective against *Borrelia burgdorferi*, vaccination against Lyme disease, nonsubmission of the removed tick, or pregnancy or lactation. In 482 patients (median age 41 y, 53% men), the ticks were confirmed to be *I. scapularis* ticks. 85% of these patients completed follow-up.

INTERVENTION

Patients were allocated to doxycycline, two 100-mg capsules (n = 235), or placebo (n = 247).

MAIN OUTCOME MEASURES

Development of erythema migrans at the site of the tick bite. Secondary outcomes were erythema migrans at a different site and laboratory evidence (positive skin culture or seroconversion) of *B. burgdorferi* infection in the absence of erythema migrans.

MAIN RESULTS

Fewer patients in the doxycycline group than the placebo group developed erythema migrans at the site of the tick bite ($P < 0.04$) (Table). The groups did not differ for secondary outcomes (Table). More patients in the doxycycline group than the placebo group had adverse events (30% vs 11%, $P < 0.001$), which were mainly nausea and vomiting; these adverse events were not serious and were self-limited.

CONCLUSION

In patients with *Ixodes scapularis* tick bites, single-dose doxycycline was effective in preventing Lyme disease.

Sources of funding: Tick-Borne Diseases Institute of the New York State Department of Health and Centers for Disease Control and Prevention.

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*See Glossary.

Doxycycline vs placebo after an *Ixodes scapularis* tick bite†

Outcomes at 6 wk	Doxycycline	Placebo	RRR (95% CI)	NNT (CI)
Erythema migrans at tick site	0.4%	3.2%	87% (20 to 98)	36 (17 to 195)
Laboratory-confirmed *Borrelia burgdorferi* in absence of erythema migrans	0.4%	0.8%	47% (–299 to 93)	Not significant
			RRI (CI)	**NNH**
Erythema migrans elsewhere	0.4%	0.4%	5.1% (–89 to 903)	Not significant

†Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY

The studies by Nadelman and Klempner and their colleagues address 2 important controversies about the treatment of Lyme disease: prophylaxis for tick bites and treatment of persistent symptoms after acute Lyme disease.

The possibility of a patient developing chronic symptoms despite treatment for acute Lyme disease creates pressure on physicians to give antibiotics for tick exposures. Prophylactic antibiotics for tick bites, however, have not previously been shown to be effective in preventing Lyme disease (1–5). The success of the trial by Nadelman and colleagues may have resulted from the regimen chosen or from the fact that the size of the trial allowed small differences in treatment effect to be detected. Since patients were followed for only 6 weeks, we cannot know whether post–Lyme-disease symptoms were prevented, either in patients who developed erythema migrans or in those who may have developed asymptomatic infection. However, in an endemic area with probable re-exposure (18% of the patients reported a subsequent tick bite in the 6-week trial period), it would be impossible to know whether post–Lyme-disease symptoms resulted from the tick bite that was treated or from previous or subsequent exposure.

For patients in endemic areas, feasibly implementing prophylaxis would require that a supply of doxycycline be kept and taken after each tick bite, without contacting a health care provider each time. For patients with only occasional tick bites in endemic areas, a single-dose regimen may be practical. For those with chronic exposure, given the risks for side effects and the public health issues of bacterial resistance, vaccination is probably indicated, although the duration of efficacy is not known (6). Because the vaccine for Lyme disease is not approved for children < 15 years of age (although it appears to be effective) (7) and doxycycline is contraindicated in children < 9 years of age, prevention in children (and in adults unwilling to take the vaccine) continues to be based on avoidance of high-risk areas and daily tick checks.

Use of antibiotics for persistent symptoms after Lyme disease is also controversial. Symptoms that are similar to fibromyalgia may develop in some patients after Lyme disease despite appropriate early treatment

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Prolonged antibiotic treatment did not relieve chronic symptoms in Lyme disease

Klempner MS, Hu LT, Evans J, et al. **Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease.** N Engl J Med. 2001 Jul 12;345:85-92.

QUESTION

In patients with chronic symptoms after treatment for Lyme disease, does prolonged antibiotic treatment relieve symptoms?

DESIGN

2 randomized {allocation concealed*}†, blinded {patients, physicians, nurses, study coordinators, statisticians, and outcome assessors}†,* placebo-controlled trials with 180-day follow-up.

SETTING

{New York, Connecticut, Rhode Island, and Massachusetts, USA.}†

PATIENTS

129 patients who were ≥ 18 years of age (mean age 54 y, 53% men); had a history of acute Lyme disease acquired in the United States; had ≥ 1 of history of single or multiple erythema migrans skin lesions, early neurologic or cardiac symptoms of Lyme disease, radiculoneuropathy, or Lyme arthritis; had been previously treated for acute Lyme disease with antibiotics; and had ≥ 1 symptom (widespread musculoskeletal pain, cognitive impairment, radicular pain, paresthesias, or dysthesias) that interfered with functioning, beginning within 6 months of the initial infection and continuing for ≥ 6 months but < 1 year. Exclusion criteria included use of parenteral antibiotics for ≥ 60 days and coexisting conditions that could account for symptoms. Follow-up was 89%.

INTERVENTION

Patients were allocated to antibiotics (n = 64) or placebo (n = 65). Antibiotics were intravenous (IV) ceftriaxone, 2 g/d for 30 days, followed by oral doxycycline, 100 mg twice daily for 60 days.

MAIN OUTCOME MEASURE

Improvement in patients' health-related quality of life (Medical Outcomes Study 36-item Short-Form General Health Survey [SF-36]).

MAIN RESULTS

The studies were stopped early because of lack of efficacy. Analysis was by intention to treat for the 115 patients who had enrolled ≥ 180 days before enrollment was stopped. The groups did not differ for improvement on the SF-36 at 180 days (Table).

CONCLUSION

In patients with chronic symptoms after treatment for Lyme disease, prolonged treatment with antibiotics was not better than placebo for relieving symptoms.

Source of funding: National Institutes of Health.

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*See Glossary.

†Information provided by author.

Antibiotics vs placebo for chronic symptoms in Lyme disease at 180 days‡

SF-36 outcome category	Antibiotics	Placebo	RBI (95% CI)	NNT
Improved by > 2 SE	40%	36%	11% (–30 to 78)	Not significant
			RRR (CI)	
Unchanged	28%	29%	4.2% (–69 to 46)	Not significant
Worse (decline by > 2 SE)	32%	34%	8.4% (–54 to 46)	Not significant

‡SE = standard error; SF-36 = Medical Outcomes Study 36-item Short-Form General Health Survey. Other abbreviations defined in Glossary; RBI, RRR, NNT, and CI calculated from data in article.

COMMENTARY *(continued from page 56)*

(usually 3 to 4 wk of doxycycline or ceftriaxone) of acute symptoms (erythema migrans, Bell palsy, or acute arthritis). The study by Klempner and colleagues shows that prolonged antibiotic treatment in these patients is no better than placebo. No evidence of persistent *Borrelia burgdorferi* infection was found in study patients.

Unfortunately, this study may not convince proponents of long-term therapy who believe post–Lyme-disease symptoms may represent concurrent symptoms of ehrlichiosis and babesiosis (8), both of which should be treated with antibiotics. Part of the controversy results from the limitations in diagnostic testing for these infections. For patients with post–Lyme-disease symptoms, the best recommendation is referral to a rheumatologist or infectious-disease specialist knowledgeable about Lyme disease and experienced in fibromyalgia.

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