Single dose of doxy after tick bite only prevents rash—not Lyme disease

by Daniel J. Cameron, MD MPH

The Journal of Emergency Medicine recently published an article entitled "Lyme Disease: Emergency Department Considerations." The authors recommend using a one-time, single dose of doxycycline after a tick bite to prevent the onset of Lyme disease, despite the fact that there has been only one study exploring the effectiveness of such a limited dosage. The article also neglects to mention that there are doctors who take a different approach and advise against a one-time, single dose. The following is republished from the All Things Lyme blog.

The authors cite the 2006 Infectious Diseases Society of America (IDSA) guidelines when making their recommendation that "individuals be treated with a single dose of doxycycline (4 mg/kg in children ≥8 years of age to a maximum 200 mg and 200 mg in adults)." [1]

Their recommendation applies only to patients meeting the following criteria,

(1) the attached tick is clearly identified as a nymph or adult I. scapularis;
(2) the tick has been attached ≥36 hours;
(3) local infection rates of ticks with B. burgdorferi is ≥20%; and
(4) there are no contraindications to doxycycline." [3]

The IDSA guidelines adopted the single, 200 mg dose of doxycycline despite the fact that three previous prophylactic antibiotic trials for a tick bite had failed.

The authors fail to mention that the IDSA single dose of doxycycline approach is based on a single study, which only found a reduction in the number of erythema migrans (EM) rashes. "A study by Nadelman et al. found that patients treated with a single dose of doxycycline developed EM manifestation at a lower rate than the placebo group (0.4% compared to 3.2%, respectively)," according to Applegren from the School of Medicine, University of Missouri.

The review also does not mention the evidence, as put forth by the International Lyme and Associated Diseases Society (ILADS), which finds that a single dose is ineffective in warding off Lyme disease. Such evidence was easily accessible via open access, peer-reviewed journals in PubMed [2], the Journal's website, [4] and the National Guideline Clearing House. [5]

ILADS 2014 guidelines used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to conclude that the evidence for a single, 200 mg dose of doxycycline was "sparse, coming from a single study with few events, and, thus, imprecise." [2]

There were only nine EM rashes in the Nadelman study. Nadelman and colleagues were able to reduce the number of rashes from eight to one by prescribing a single 200 mg dose of doxycycline. The "p" value was barely significant at 0.04.

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Nadelman's study had several other limitations:

1. It was not designed to detect Lyme disease if the rash were absent.
2. The six-week observation period was not designed to detect chronic or late manifestations of Lyme disease.
3. It was not designed to assess whether a single dose of doxycycline might be effective for preventing other tick-borne illnesses such as Ehrlichia, Anaplasmosis, or Borrelia miyamotoi.

Today, patients expect to be informed of their treatment options. The recent review in the Journal of Emergency Medicine [1] would have been stronger if the authors had disclosed the evidence against using a single, 200 mg dose of doxycycline for prophylactic treatment of a tick bite.

Ticks Tick Borne Dis. 2012 Jun;3(3):193-6. doi: 10.1016/j.ttbdis.2012.01.001. Epub 2012 Mar 13.

Protective value of prophylactic antibiotic treatment of tick bite for Lyme disease prevention: an animal model.

Piesman J[1], Hojgaard A.

Clinical studies have demonstrated that prophylactic antibiotic treatment of tick bites by Ixodes scapularis in Lyme disease hyperendemic regions in the northeastern United States can be effective in preventing infection with Borrelia burgdorferi sensu stricto, the Lyme disease spirochete. A large clinical trial in Westchester County, NY (USA), demonstrated that treatment of tick bite with 200mg of oral doxycycline was 87% effective in preventing Lyme disease in tick-bite victims (Nadelman, R.B., Nowakowski, J., Fish, D., Falco, R.C., Freeman, K., McKenna, D., Welch, P., Marcus, R., Agúero-Rosenfeld, M.E., Dennis, D.T., Wormser, G.P., 2001. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. N. Engl. J. Med. 345, 79-84.). Although this excellent clinical trial provided much needed information, the authors enrolled subjects if the tick bite occurred within 3 days of their clinical visit, but did not analyze the data based on the exact time between tick removal and delivery of prophylaxis. An animal model allows for controlled experiments designed to determine the point in time after tick bite when delivery of oral antibiotics would be too late to prevent infection with B. burgdorferi. Accordingly, we developed a tick-bite prophylaxis model in mice that gave a level of prophylactic protection similar to what had been observed in clinical trials and then varied the time post tick bite of antibiotic delivery. We found that two treatments of doxycycline delivered by oral gavage to mice on the day of removal of a single potentially infectious nymphal I. scapularis protected 74% of test mice compared to controls. When treatment was delayed until 24 h after tick removal, only 47% of mice were protected; prophylactic treatment was totally ineffective when delivered ≥2 days after tick removal. Although the dynamics of antibiotic treatment in mice may differ from humans, and translation of animal studies to patient management must be approached with caution, we believe our results emphasize the point that antibiotic prophylactic treatment of tick bite to prevent Lyme disease is more likely to be efficacious if delivered promptly after potentially infectious ticks are removed from patients. There is only a very narrow window for prophylactic treatment to be effective post tick removal.

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Single-Dose Antibiotic Prophylaxis of Lyme Disease: Too Little Too Late?

Over the years since the article by Nadelman et al. was published in 2001 (1), doctors have been using single-dose doxycycline prophylaxis to treat patients following a tickbite. Newer research in animals and humans suggests that this prophylaxis may be ineffective.

The study by Nadelman et al. forms the basis for the Lyme prophylactic treatment guidelines of the Infectious Diseases Society of America (IDSA), and the IDSA guidelines recommend starting prophylaxis "within 72 hours of the time that the tick was removed." However in 2004 Zeidner et al. noted that a single dose of doxycycline prevented infection in only 43% of mice exposed to Borrelia burgdorferi, the agent of Lyme disease, and a follow-up study in 2008 showed that only 20-30% of mice were protected from combined infection with B. burgdorferi and Anaplasma phagocytophilum following single-dose doxycycline prophylaxis (2). To explain prophylactic treatment failure, Piesman and Hojgaard recently published a mouse study showing the importance of the time interval between tick removal and prophylactic treatment (3).

In commenting on the study by Nadelman et al., Piesman and Hojgaard state: "The authors enrolled subjects if the tickbite occurred within 3 days of their clinical visit, but did not analyze the data based on the exact time between tick removal and delivery of prophylaxis….We found that two treatments of doxycycline delivered by oral gavage to mice on the day of removal of a single potentially infectious nymphal I. scapularis tick protected 74% of test mice compared to controls. When treatment was delayed until 24h after tick removal, only 47% of mice were protected; prophylactic treatment was totally ineffective when delivered ≥2 days after tick removal." The loss of prophylactic efficacy over this time interval is supported by well-documented observations of rapid transmission of Lyme disease within 24 hours of a tickbite in humans (4). A review of the pertinent literature revealed that the risk of B. burgdorferi transmission within 24 hours of a tickbite was 7% under experimental conditions in mice and up to 25% in clinical studies involving humans (5).

In summary, animal and human studies of exposure to B. burgdorferi suggest that there may be a very narrow window for prophylactic treatment following tick removal. In failing to take this narrow prophylactic window into account, the study by Nadelman et al. appears to put patients at risk of developing Lyme disease following antibiotic prophylaxis that may be too little too late.

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