Patient Centered Care Advocacy Group

Information Quality Appeal

Antimicrobial prophylaxis for prevention of Lyme disease

July 12, 2019

On February 15, 2019, the Patient Centered Care Advocacy Group submitted an information quality request for correction (case #64) regarding information disseminated by the Centers for Disease Control and Prevention (CDC) about antimicrobial prophylaxis for the prevention of Lyme disease. On June 12, 2019 Lyle Petersen, MD, MPH, Director, CDC Division of Vector-Borne Diseases issued a response denying our request. Attached is a copy of our request and Dr. Peterson's response.

We believe Dr. Peterson's response is inadequate for the following reasons:

1. The response fails to address shortcomings of the integrity and utility of the contested information.
2. The contested information has potential to harm patients.
3. The response fails to provide necessary relief.

Therefore, we are appealing the decision and submitting this amended complaint.

Description of Information

The CDC publication, *Tick-Borne Diseases of the United States, 5th Edition*[1], includes the following statement on page 49:

> *"The Infectious Disease[sic] Society of America (IDSA) does not generally recommend antimicrobial prophylaxis for prevention of Lyme disease after a recognized tick bite. However, in areas that are highly endemic for Lyme disease, a single dose of doxycycline may be offered to adult patients (200 mg) who are not pregnant and to children older than 8 years of age (4 mg/kg up to a maximum dose of 200 mg) when all of the following circumstances exist:*
>
> 1. *Doxycycline is not contraindicated.*
> 2. *The attached tick can be identified as an adult or nymphal I. scapularis tick.*
> 3. *The estimated time of attachment is ≥36 h based on the degree of tick engorgement with blood or likely time of exposure to the tick.*
> 4. *Prophylaxis can be started within 72 h of tick removal.*
> 5. *Lyme disease is common in the county or state where the patient lives or has recently traveled, (i.e., CT, DE, MA, MD, ME, MN, NH, NJ, NY, PA, RI, VA, VT, WI)."*

This recommendation for tick bite prophylaxis is from the Infectious Diseases Society of America (IDSA) 2006 guidelines for diagnosis and treatment of Lyme disease.[2]

The CDC publication *Guidance for Clinicians: Recommendations for Patients after a Tick Bite* includes a similar recommendation.[3]

Problems with Quality

The CDC and IDSA recommendations for prophylaxis of Lyme disease are based on a study published in the New England Journal of Medicine in 2001.[4]

The study evaluated the efficacy of a single dose of doxycycline for preventing Lyme disease after a tick bite. Endpoints in the study included erythema migrans (EM), isolation of *Borrelia burgdorferi* in culture, or seroconversion. The study design was randomized, double-blind, and involved over 450 subjects. The end points used to determine if subjects were infected with *B. burgdorferi* and developed Lyme disease are shown below:

> "The primary end point was the development of erythema migrans at the site of the tick bite. Erythema migrans occurring at a different site from that of the identified tick bite and laboratory evidence of *B. burgdorferi* infection in the absence of erythema migrans were analyzed as secondary end points. Seroconversion was defined as a change from a negative result on ELISA to an equivocal or positive result in association with the presence of IgM bands on immunoblotting that met the recommended criteria for seropositivity."

The conclusion of this study that the prophylaxis "prevented Lyme disease" is inadequately supported by the data presented in the paper. The study design is based on "end points" for Lyme disease which rule out subjects who did not develop an EM rash or seroconvert during the 6-week study period. As noted in the HHS Tick-Borne Disease Working Group 2018 report to Congress[5], the clinical observations of acute viral-like illness without EM, disseminated EMs, asymptomatic seroconversion, and febrile episodes are, in fact, symptoms associated with *Borrelia burgdorferi* infection (Lyme disease), and in some cases these symptoms may not occur for weeks to months after infection.

Use of EM as a primary end point for Lyme disease

CDC surveillance data from 1992-2006 documented that 31% of surveillance cases lacked an EM rash.[6] Patient-derived data from the MyLymeData patient registry (a project by LymeDisease.org)[7] noted that only 34% of 3,903 patients recalled having an EM rash. More commonly reported early symptoms were flu-like symptoms (64%) and severe headache or stiff neck (44%).

In a comprehensive study of the pathobiology of infection with *B. burgdorferi* in outbred non-human primates (NHPs), the rate of EM in NHPs infected by nymph tick bite and confirmed to be infected by culture or PCR, was only 10%. It is noted by the NHP researchers that more than half of infected NHPs do not develop any erythematous rash (personal communication with the study authors) following infection. NHP studies convincingly demonstrate that the macaque model most closely resembles human borreliosis and provides the best experimental model to study Lyme disease.[8] In this animal model, the rate of association between EM and *B. burgdorferi* infection is low.

Since the association between EM and *B. burgdorferi* infection (Lyme disease) is actually quite low (40-70%), the number of subjects who developed Lyme disease cannot be determined from the data. The data shows only that there was a statistical difference in the rate of EM, but not Lyme disease, between the prophylaxis and placebo groups.

Use of seroconversion as a secondary end point for Lyme disease

In a study which evaluated existing diagnostic tests for a "definitive diagnosis" of Lyme disease, the sensitivity of ELISA during the acute phase of infection is less than 50%.[9] Subjects in the single dose prophylaxis study were therefore equally likely to have Lyme disease, whether the ELISA was positive or negative.

As noted in the HHS Tick Borne Disease Working Group report to Congress, seroconversion, defined by the study authors as "a change from a negative result on ELISA to an equivocal or positive result in association with the presence of IgM bands on immunoblotting," may not occur during the first 4-6 weeks of infection. It was also noted that treatment of *B. burgdorferi* infection with an antibiotic, prophylactic or otherwise, is shown to prevent seroconversion, and that a proportion of people infected with *B. burgdorferi* do not seroconvert at all. As this study ended at 6 weeks, subjects who were infected but did not seroconvert or develop symptoms for weeks to months post infection, would not have been considered to have Lyme disease.

In Table 3 of the NEJM article, three subjects—one in the treatment group and two in the placebo group—had nonspecific symptoms and evidence of *B. burgdorferi* infection (secondary endpoints of the study). It should be noted for these characteristics – nonspecific symptoms and seroconversion – there appears to be no statistical difference between the treatment and placebo groups, which indicates that the prophylaxis does not prevent Lyme disease.

Since neither the primary or secondary end points used in this study will identify subjects with Lyme disease, the conclusion that the single dose prophylaxis prevents Lyme disease is invalid.

As shown in the following table from *Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease*, published by the International Lyme and Associated Diseases Society (ILADS) in 2014,[10] the quality of the evidence supporting the use of a single 200 mg dose of doxycycline following a tick bite is very low, implying that the true effectiveness of this prophylaxis is likely to be substantially different from the effectiveness rate reported in the NEJM article.

Table 2. Quality of the evidence, in aggregate, supporting single-dose doxycycline for Lyme disease prophylaxis.

No. of studies	Limitations	Imprecision	Inconsistency	Indirectness	Quality
1	Inappropriate surrogate (EM) Insufficient duration of observation Insufficient reporting of negative treatment-associated outcomes	Few events Wide CI Unsupported assumption regarding outcomes in dropouts	Non-replicated in humans Inconsistent with animal model	Not applicable to patients bitten by species other than *Ixodes scapularis* Not applicable to patients exposed to multiple tick-borne diseases Efficacy not applicable to other antibiotics Effectiveness findings applicable to prevention of EM only and not other, non-EM presentations	Very low

EM: Erythema migrans.

Furthermore, the ILADS publication, which adopted the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) system as the basis for evidence assessment and guidelines development, specifically recommends *against* a single dose of doxycycline for prevention of Lyme disease.

Instead, ILADS makes the following recommendation: *"Clinicians should promptly offer antibiotic prophylaxis for known Ixodes tick bites in which there is evidence of tick feeding,*

regardless of the degree of tick engorgement or the infection rate in the local tick population. The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days."

Finally, in the Discussion section of the NEJM article that is used to support the recommendation that a single dose doxycycline prophylaxis prevents Lyme disease, the authors note, "The efficacy rate found in our study should be interpreted cautiously, however, because of the relatively small number of subjects in whom Lyme disease developed and the resultant wide 95 percent confidence interval (25 to 98 percent)." They also concluded that "Our results contrast with those of previous studies,[6-8] which showed no clear protection attributable to antimicrobial prophylaxis given after a tick bite**.**"

Since there is contrasting evidence showing that antimicrobial prophylaxis does not prevent Lyme disease, the recommendation should be removed until such time that an unbiased study on tick bite prophylaxis can be completed.

Impact

CDC's recommendation of the single-dose antibiotic for tick-bite prophylaxis has the potential to cause serious harm to patients for whom the prophylaxis fails to prevent infection with *Borrelia burgdorferi*, the bacterium that causes Lyme disease.

Additionally, there have been no clinical trials to assess if this prophylaxis would also prevent infection by other strains of *Borrelia* such as *B. mayonii*, or any of the relapsing fever *Borrelia* (including *B. miyamatoi*) or any other tick-borne microbe. The antibiotic would not prevent infection with parasites, such as Babesia, or viruses.

With the current CDC-endorsed prophylaxis, patients and healthcare providers alike are given a false sense that a tick-borne disease has been prevented. Therefore, full treatment may be delayed or denied. Research shows that delayed treatment increases the rate of treatment failure.[11] In addition, this partial treatment has been shown to result in false negative blood test results for Lyme disease.[12, 13]

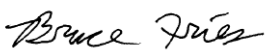
Requested Actions

We request that CDC take the following actions:

1. Remove recommendations for single-dose antimicrobial prophylaxis to prevent Lyme disease from all CDC publications, presentation materials, and websites.
2. Publish a notice in CDC's Morbidity and Mortality Weekly Report that CDC no longer recommends single-dose antimicrobial prophylaxis to prevent Lyme disease.

We look forward to your timely response.

Complainants



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