Challenge to the Recommendation on the Prophylaxis of Lyme Disease

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This challenge is to Recommendation #2 in the 2006 IDSA guidelines regarding the prophylaxis of Lyme disease. The recommendation on page 1100 states:

> "*For prevention of Lyme disease after a recognized tick bite, routine use of antimicrobial prophylaxis or serologic testing is not recommended (E-III). A single dose of doxycycline may be offered to adult patients (200 mg dose) and to children >8 years of age (4 mg/kg, up to a maximum dose of 200 mg) (B-I) when all of the following circumstances exist: (a) the attached tick can be reliably identified as an adult or nymphal I. scapularis tick that is estimated to have been attached for >36 h on the basis of the degree of engorgement of the tick with blood or on certainty about the time of exposure to the tick, (b) prophylaxis can be started within 72 h of the time that the tick was removed, (c) ecologic information indicates that the local rate of infection of these ticks with B. burgdorferi is >20%, and (d) doxycycline is not contraindicated.*

This challenge is based on the feasibility of meeting required circumstances a, b and c, on the scientific evidence regarding prophylaxis and on flaws in the panel's processes for grading the quality of evidence and assigning strength of recommendation categories.

The application of the required circumstances to primary care practices in endemic areas may be problematic. The panel recommends that medical professionals acquire the ability to identify ticks and assess engorgement; however, there is no assurance that physicians will do so. Recommendation 3 suggests that practitioners only need to learn "to differentiate ticks that are at least partially engorged with blood", a task requiring much less precision than recommendation 2 calls for. Recommendation 2 also requires physicians to be aware of the infection rate for *B. burgdorferi* in their local tick population. In many areas this data is not immediately available. Tick infection rates vary significantly in the same general locale which may lead to inaccurate risk assessments.[1] A patient's ability to receive appropriate care for a tick bite should not depend on whether or not the treating physician has acquired entomology skills and stays abreast of the *B. burgdorferi* infection rates in ticks of various locales. And what should be done in situations where ticks were identified by non-medical personnel and then discarded or were damaged during removal such that they are unrecognizable? Withholding treatment solely on those grounds exposes patients to the risk of infection. The stated circumstances in the recommendation are impractical to impose on community medical practitioners and patients. According to the US Preventive Services Task Force: *"External validity is rated "poor" if: the study differs from the US primary care population / situation / providers in many way that have a high likelihood of affecting the clinical outcomes; the probability is low (<50%) that the clinical experience with the intervention observed in the study will be attained in the US primary care setting."*[2] The study employed a medical entomologist to assess the ticks and this assessment included measurement of the tick scutal index; community physicians are not likely to have, or develop, this level of expertise. Thus, the external validity of the study is poor. On this basis, the recommendation should be rejected.

What evidence is there that the recommended prophylaxis strategy offers sufficient protection against a *Borrelia burgdorferi* infection? The 2006 IDSA guideline panel primarily based its recommendations for the management of a known tick bite on a single prophylaxis study by Nadelman et al. This treatment trial purportedly demonstrated that administering a single 200 mg dose of oral doxycycline within 72 hours of an *I. scapularis* bite prevented the development of Lyme disease.[3] The treatment efficacy rate was reported to be 87%. Due to the import accorded it by the IDSA panel, this study deserves detailed scrutiny.

The conclusion reached by Nadelman et al. is not sufficiently supported by the study. The study's design does not permit any claim regarding the prevention of Lyme disease. Lyme disease is a multi-systemic illness having both early and late manifestations.[4-9] Patients may be asymptomatic early in the infection only to develop symptoms of late disease after a latent period lasting months to years.[10-12] The study employed a 6 week follow-up period, too short a time frame to allow for the development of late Lyme disease. Thus, the claim that a single 200 mg dose of oral doxycycline prevents Lyme disease following a tick bite was not proven by Nadelman et al.

Nor can the authors claim that a single dose of oral doxycycline prevents early Lyme disease. The study's primary endpoint was strictly limited to the development of an erythema migrans rash at the bite site. It is estimated that 20 to 40% of all Lyme disease patients do not exhibit an erythema migrans rash in the course of their illness.[13] In the Nadelman study, 3 patients (1 in the doxycycline group and 2 in the placebo group) had acute viral-like illnesses accompanied by laboratory evidence of *B. burgdorferi* infection without developing an erythema migrans rash. Despite symptoms and laboratory evidence consistent with early Lyme disease, these patients were not considered as "disease positives" when the efficacy of treatment was calculated because they did not meet the narrowly defined end point criteria. In clinical practice, failure to recognize early Lyme disease in patients lacking the characteristic erythema migrans rash continues to occur.[14] In their discussion, the authors acknowledged a theoretical problem with their chosen endpoint. *"Our use of a restrictive primary end point (erythema migrans at the site of the tick bite) could have resulted in underestimation of the actual incidence of B. burgdorferi infection attributable to the bite of an identified I. scapularis tick."* Excluding those 3 patients from the disease positive group resulted in the underestimation of the incidence of post-bite infection and the overestimation of treatment efficacy. Their exclusion further limits the study's ability to draw a broad conclusion. Instead of demonstrating that a single 200mg dose of oral doxycycline prevented all clinical manifestations of Lyme disease or that it specifically prevented early Lyme disease, the study, with its restrictive endpoint, demonstrated that this prophylaxis regimen may have prevented the development of erythema migrans at the bite site.

It is worthwhile to note that the median duration of tick attachment in this study was estimated to be 30 hours for nymphs and 10 hours for adult ticks. Thus, at least half of the subjects would have had shorter duration attachments than the 36 hour attachment time criteria set forth by the IDSA panel in its 2006 guidelines. Finally, the authors should have realized that subjects bitten solely by a larval stage tick were not at risk for disease. They should have been excluded; doing so would have increased the stated risk in the placebo group.

While the prophylaxis recommendations advanced by the IDSA panel rely heavily on the study by Nadelman et al., the panel also draws support from other sources. A mouse study is offered as additional evidence that a single dose of doxycycline prevents Lyme disease. In this study the effectiveness of a single dose of oral doxycycline hyclate was compared to that of a subcutaneous injection of sustained-release doxycycline.[15] The specific oral dose chosen by Zeidner et al. in the mouse study accounted for the differences between the pharmacodynamics of doxycycline in humans and mice and was intended to yield plasma levels similar to those in the Nadelman study. The oral dose in the mouse study was 43% effective in preventing Lyme. In their discussion, Zeidner et al. stated, *"[O]ur protection data for a single oral administration of doxycycline compare favorably with those reported for humans by Nadelman et al. [6], in whose study the 95% confidence interval varied widely (from 25 to 98%) and true protection efficacy approached 50%."* Instead of supporting the

efficacy claimed by Nadelman, the Zeidner study refuted it, estimating that a single dose of oral doxycycline prevented Lyme disease only 50% of the time in mice and humans. Zeidner's data also undermine the panel's theory that T>MIC is what determines efficacy.(IDSA, page 1097) *"We conclude that the enhanced prophylactic efficacy of sustained-release doxycycline hyclate in this animal model is due to the sustained-release effect over a 19-day period after administration. Interestingly, concentrations of doxycycline in plasma after the administration of sustained-release doxycycline hyclate (0.1 to 0.5 μg/ml) were lower than those reported as the MIC in vitro for B. burgdorferi (1.6 μg/ml).*"[15]

A subsequent study by Zeidner investigated the use of doxycycline in mice to prevent the simultaneous transmission of *B. burgdorferi* and *A. phagocytophilum*.[16] This study demonstrated that single-dose oral doxycycline provides little prophylaxis against acquiring *B. burgdorferi* in the presence of *A. phagocytophilum*. In this second study, only 20% of the mice given single-dose oral doxycycline were protected from *B. burgdorferi* infection.

By contrast, the injectable sustained-release preparation of doxycycline was 100% effective in both studies.[15,16] Tissue studies in the mice treated with sustained-release doxycycline were consistently negative for infection.[15,16] Therefore, Zeidner's work does support a single dose approach for prophylaxis but that support is not for the oral form studied by Nadelman and advanced by the IDSA panel. Rather, Zeidner reached this conclusion*: "Thus,* ***a single injection of a sustained-release-formulation antibiotic*** *may offer a viable option for prophylactic treatment of Lyme borreliosis for patients presenting with B. burgdorferi-infected tick bites."*[15] (italics added)

Given Zeidner's estimation that the oral single dose doxycycline strategy is likely to fail 50-80% of the time, clinicians must consider what that failure may mean to patients. Dattwyler et al. demonstrated that administering antibiotics early in the course of the infection alters the immune response and may subsequently alter the results of serologic testing; giving rise to Lyme disease patients who are seronegative.[17] Seronegative patients have also been described by others.[18-21] Thus, patients who remain infected after a single dose of doxycycline may develop manifestations of Lyme disease yet remain seronegative. Proof of this potential outcome is found in the Nadelman study. Erythema migrans developed in 9 patients, and as the authors noted: *"An additional subject (in the doxycycline group) who remained seronegative by ELISA was positive for IgM antibody on immunoblotting."* Some may argue that, despite the negative ELISA, the patient was not truly seronegative because the IgM immunoblot was positive. However, throughout the guidelines, the panel repeatedly endorses the two-tier testing algorithm recommended by the CDC. In that testing scheme, patients with negative ELISA results would not receive immunoblotting; instead they would be classified as disease negative and testing would cease.[22] Such patients would likely experience a delay or denial of appropriate treatment for their infections; treatment delays have been associated with poorer outcomes.[23,24]

In selecting a prophylaxis regimen, clinicians must determine which antibiotics are best suited for individual patients. Antibiotic selection must consider patient factors — age, pregnancy status, allergic history and medication tolerance. This process should also address risks for other tick-borne pathogens. In some regions, *A. phagocytophilum* is a frequently encountered pathogen.[25,26] Ticks can transmit *A. phagocytophilum* to humans in less than 24 hours and may simultaneously transmit *B. burgdorferi* and *A. phagocytophilum*.[27,28] In a dual infection model, single-dose oral doxycycline was only 30% effective in preventing infection by *A. phagocytophilum* while a single injectable dose of sustained-release doxycycline was 100% effective.[16] Clearly, a single oral dose of doxycycline will not provide adequate prophylaxis against *A. phagocytophilum* and it is not known what effect this dose may have on serologic testing for HGA. Treatment for HGA requires a minimum of 10 days of doxycycline; amoxicillin is not effective therapy.

In making its prohibitive recommendations for the prophylaxis of Lyme disease, the IDSA panel noted that it *"weighed both the risks and consequences of developing Lyme disease (including the risk of late complications) in persons bitten by I. scapularis or I. pacificus ticks against the economic costs and adverse effects of prophylactic anti-microbials."* How individual risks, consequences, costs and adverse effects were weighted by the panel is not easily understood.

The panel reportedly considered the risk of late complications yet the recommendation for a single oral dose of doxycycline was based primarily on a study which could not assess this risk. The panel was aware of the study's limitation in this regard, stating: *"The single dose doxycycline chemoprophylaxis trial had a six-week follow-up period and was not designed to detect long-term outcomes."*[29] Lacking long-term outcome data from this trial makes it impossible to predict the risk of developing late Lyme disease when single-dose oral doxycycline prophylaxis fails. Attempting to minimize this evidentiary gap, Wormser et al., in a letter to Lancet, asserted, based on outcomes from earlier prophylaxis studies, that the risk of developing late Lyme disease was minimal.[30] However, there is no evidence to support this conclusion.

The prophylaxis studies cited by Wormser et al. employed treatment regimens which were markedly different from the single-dose oral doxycycline regimen.[31-33] These 3 studies employed 10 days of antibiotic treatment (principally amoxicillin) and followed patients beyond the acute stage (and up to 3 years in the Agre trial). The individual studies were smaller than the Nadelman study and lacked sufficient power to demonstrate treatment efficacy. Given Zeidner's conclusion that prophylactic efficacy is dependent on treatment duration, it is scientifically unsound to suggest that single-dose oral doxycycline prophylaxis would yield long-term outcomes similar to those seen in trials using antibiotic prophylaxis regimens of significantly longer duration. Thus, the treatment efficacy of single-dose oral doxycycline for the prevention of late Lyme disease cannot be assumed and remains unknown.

The panel's discussion on the adverse effects of antibiotics cited prophylaxis studies by Shapiro and Costello. Using the data from these trials, the panel wrote: *"… the risk of acquiring Lyme disease after a tick bite among placebo recipients was approximately the same as the risk of developing a rash from the prophylactic antibiotic."* The risks for developing Lyme disease and an antibiotic-induced rash may have been equal but the conditions themselves are not; a simple drug eruption and Lyme disease differ significantly in their potential to harm patients. There is substantial evidence on the outstanding clinical safety of both amoxicillin and doxycycline.[34,35] These antibiotics are inexpensive and readily available. And there is substantial evidence detailing the consequences of late Lyme disease which can be quite severe and irreversible.[36-40]

Clinical guidelines are intended to assist physicians in managing the medical needs of their patients.[41] Guidelines are written to provide a concise review of the scientific literature and an assessment of available therapeutic options. In this context, it is appropriate for the panel to evaluate and report the risks and benefits associated with individual prophylaxis strategies. Such a discussion would rightly consider the cost of antibiotics and the potential for adverse reactions, balancing these against the benefits patients may achieve with treatment and the risks of withholding therapy. Information of this nature alerts clinicians to the potential consequences of their management decisions and allows them to more fully inform their patients of these considerations. Guideline committees are not in a position to perform risk-benefit analyses for specific patients. Those analyses are dependent on facts not accessible to the committee; unrelated co-morbidities and patient values, resources and preferences all factor into the equation. Patient-specific risk-benefit analyses form the essence of clinical judgment. Such judgments are the domain of individual treating physicians; guideline committees may inform judgments through their evaluation of therapeutic options but they may not substitute their judgments for those of the treating physicians. In the case of Lyme disease prophylaxis, patients and their physicians may determine that treatment is warranted under a much wider array of circumstances than those outlined by the panel.

With regards to the construction of treatment guidelines, it is undesirable to propose recommendations which limit treatment options based on limited evidence.[42] Such an occurrence is especially troubling here because withholding prophylaxis or providing inadequate prophylaxis may lead to treatment delays and poorer outcomes for some. As noted previously, in selecting a 6-week follow-up period, the Nadelman study was improperly designed to address whether or not single-dose oral doxycycline prevents late Lyme disease. This flaw significantly decreases the quality of the trial's evidence.[42]

The lack of independent reviews of guidelines raises the potential for bias.[41] Those charged with establishing evidence-based guidelines must carefully review and appraise each study pertaining to

the topic at hand yet it appears that the panel disregarded a significant design flaw in the Nadelman study. The fact that this study was co-authored by 3 members of the guidelines panel raises concerns regarding the panel's objectivity and its ability to critically analyze this specific material.

In summary, the recommendation for Lyme disease prophylaxis should be rejected. The panel set forth conditions which many patients and clinicians will find difficult to meet. Furthermore, the only study investigating single-dose oral doxycycline prophylaxis: 1) employed a design which was specific for evaluating the prevention of erythema migrans and does not permit any scientific conclusion regarding the prevention of late Lyme disease, 2) overstated the treatment's true effectiveness for erythema migrans prevention, 3) understated the probability of infection, 4) failed to investigate what effects such treatment may have on the development and diagnosis of late Lyme disease, 5) is at odds with well designed animal studies on single-dose regimens and 6) was authored by 3 panel members, which may have unduly influenced the panel's analysis of the study's quality.

Alternative recommendations for Lyme disease prophylaxis following a known *I. scapularis* bite need to be constructed; excessive restrictions limiting the use of prophylaxis have not been substantiated. Available evidence is limited but findings from 2 mouse studies suggest that the duration of antibiotic treatment is critical to the prevention of Lyme disease. The optimum treatment duration remains unknown; clinicians may consider using regimens which mimic the duration of coverage seen in the mouse studies. Recognizing the potential for the transmission of *A. phagocytophilum* alone or in tandem with *B. burgdorferi*, it is reasonable to recommend doxycycline as the preferred agent in appropriate patient populations. Taking doxycycline with food and administering probiotics should significantly reduce or eliminate many of the minor adverse effects (nausea, vomiting, abdominal pain and diarrhea) encountered in the Nadelman study.[43] Given their effectiveness in early Lyme disease and contra-indications for the use of doxycycline in children and pregnant women, amoxicillin and cefuroxime may be appropriate alternatives in some circumstances.[20,44,45]

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