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Insufficient evidence to deny antibiotic treatment to chronic Lyme disease patients

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SUMMARY

Background: The severity, length of illness, and cost of chronic Lyme disease (CLD) have been well described. A number of oral, intravenous, and intramuscular antibiotics have been prescribed for CLD. Surprisingly few antibiotic schedules prescribed for the treatment of CLD have been evaluated in randomized double-blind placebo-controlled clinical trials (RCTs). Physicians have increasingly turned to clinical treatment guideline (CPG) panels to judge the mixed results of the evidence. Two CPG panels have looked at the evidence only to reach opposite conclusions: (1) antibiotic therapy for CLD is not effective and (2) antibiotic therapy for CLD is effective. Physicians have been advised by guideline developers to use clinical discretion in diagnosing and treating CLD. Nevertheless, many health insurers – relying exclusively upon only one CPG – have a policy of automatically denying antibiotics to CLD patients regardless of the specifics of each case or the recommendations of the patient's physician.

Hypotheses: This paper examined the eight limitations of the evidence used to conclude that antibiotics therapy for CLD is not effective in forming the following hypothesis: insufficient evidence to deny antibiotic treatment to CLD patients.

Evidence for the Hypothesis: There are eight limitations that support the hypothesis: (1) the power of the evidence is inadequate to draw definite conclusions, (2) the evidence is too heterogeneous to make strong recommendations, (3) the risk to an individual of facing a long-term debilitating illness has not been considered, (4) the risk to society of a growing chronically ill population has not been considered, (5) treatment delay has not been considered as a confounder, (6) co-infections have not been considered as a confounder, (7) the design of RCTs did not address the range of treatment options in an actual practice, and (8) the findings cannot be generalized to actual practice.

Implications of the hypotheses: This hypothesis suggests that physicians should consider the limitations of the evidence before denying antibiotic treatment for CLD. Physicians who deny antibiotic treatment to CLD patients might inform their patients that there are some clinicians who disagree with that position, and then offer to refer them for a second opinion to a doctor who could potentially present a different point of view. The hypothesis also suggests that health care insurers should consider the limitations of the evidence before adopting policies that routinely deny antibiotic treatment for CLD patients and should expand coverage of CLD to include clinical discretion for specific clinical situations.

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Introduction

The number of individuals with Lyme disease (LD) continues to grow worldwide [1–3]. The number of LD cases reported each year in the US alone to the Centers for Disease Control and Prevention (CDC) nearly tripled from 1992 to 2007 to more than 27,000 [3]. The actual number of LD cases in the US has been estimated to be more than 270,000 per year assuming a 10-fold underreporting to the CDC [4]. The estimated incidence of 34,000 LD cases in Connecticut alone in 2004 was 24× the number reported to the CDC [5].

The severity, length of illness, and cost of chronic Lyme disease (CLD) have been well described. For patients who contract Lyme disease, the risk of developing CLD has been reported to be as high

as 34–62% years in two cohorts after antibiotic treatment [6,7]. Onsets of illness of CLD averaged 4.7–9 years in National Institutes of Health (NIH) sponsored double-blind randomized placebo-controlled clinical trials (RCTs) [8,9]. The symptoms of CLD enrolled in RCTs were severe on all 22 standardized measures of fatigue [8,10], pain [8,11], psychopathology [8,11], cognition [8,10,11], role function [11,12], and quality of life [8,11]. The annual, average per-patient cost for CLD patients in the US has been estimated to be \$1872 for direct medical costs and \$14,327 for indirect medical costs, non-medical costs, and productivity losses [13].

A number of antibiotic treatments have been prescribed based on the evidence from non-placebo and comparator trials and case series for CLD including the following: (1) oral doxycycline, amoxicillin, cefuroxime, azithromycin, clarithromycin, penicillin VK [14,15], (2) intravenous ceftriaxone, cefotaxime, penicillin G [14,15], and (3) intramuscular benzathine penicillin [16]. These antibiotics have

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been used singly or in combinations [14] or with antibiotics for co-infections such as atovaquone with azithromycin for *Babesia microti* [17]. Antibiotics have been prescribed for more than 30 days – and months if necessary – until CLD has resolved [8,14,18,19].

Surprisingly few antibiotic schedules described for the treatment of CLD have been evaluated in RCTs. The Krupp RCT concluded that 4 week of intravenous (IV) ceftriaxone was significantly more effective than placebo for fatigue (69% vs. 23%, $p = 0.001$) but not more effective for cognitive function and for an Outer surface protein A (OspA) laboratory measure of infection [10]. The Klempler RCTs concluded that 4 weeks of IV ceftriaxone followed by 8 weeks of oral doxycycline was not more effective than placebo for improving quality of life (QOL) [9]. The Fallon RCT concluded that 10 weeks of intravenous ceftriaxone was more effective than placebo for fatigue (67 vs. 25, $p = 0.05$) [8]. The Fallon RCT also concluded that the significant benefits in cognitive function after 10 weeks of intravenous ceftriaxone were not sustained 3 months after the end of antibiotic therapy [8]. I authored a RCT that concluded that oral amoxicillin for 3 months was significantly more effective than placebo (46 vs. 18, $p = 0.007$) [20].

Clinical practice guidelines (CPG) panels have looked at the evidence from these RCTs only to reach different conclusions. The Infectious Diseases Society of America (IDSA) [15] CPG panel concluded: antibiotic therapy for CLD is not effective [15]. The American Academy of Neurology (AAN) CPG panel [15] and the Ad Hoc International Lyme Disease Group echoed that recommendation [21]. The International Lyme and Associated Diseases (ILADS) CPG concluded: antibiotic therapy for CLD is effective. The opposing recommendations have been characterized as two standards of care [22] and clinical equipoise [23]. Clinical equipoise has been defined as the absence of consensus within the clinical community.

Physicians have been advised by guideline developers to use clinical discretion for particular patient or special clinical circumstances. IDSA's *Guide to the development of practice guidelines* advised the following: "Clinical discretion is of the utmost importance in the application of a guideline to individual patients, because no guideline can ever be specific enough to be applied in all situations" [24]. In a disclaimer, the IDSA CPG for LD advised caution in applying their CPG to individual patients: "It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations" [25].

Nevertheless, health care insurers have published policies that deny antibiotics to CLD patients without taking into account specific clinical discretion for specific clinical situations. United-Healthcare [26], Cigna [27], Aetna [28], and BlueCross BlueShield of Wisconsin [29] are examples of insurers who have cited the IDSA CPG to deny more than 4 weeks of intravenous antibiotics without taking into account clinical judgment for specific clinical situations and IDSA CPG's own disclaimer [30].

Hypotheses

This paper examines the eight limitations of the evidence used to conclude that antibiotics therapy for CLD is not effective. The limitations lead to the following hypothesis: insufficient evidence to deny antibiotic treatment to CLD patients.

Evidence for the hypothesis

The power of the evidence is inadequate to draw definite conclusions

Only the Krupp RCT enrolled enough subjects to have sufficient power to draw definite conclusions on the treatment of CLD. The

Krupp RCT [10] found 4 weeks of ceftriaxone was more effective than placebo for the primary outcome, fatigue (64% vs. 18.5%, $p < 0.001$). The Krupp RCT [10] was not able to demonstrate a treatment effect for cognition in part due to a differing power concern: "although the patients with Lyme disease showed cognitive slowing compared to healthy controls, these deficits were relatively mild, which may have contributed to the lack of a treatment effect on cognition" ([10], p. 1928). The Krupp RCT [10] did not reach the sample size estimated for the OspA laboratory measure of infection as there were only nine of 55 LD subjects (16%) that had an abnormal OspA at baseline. The actual sample sizes of 51, 78, 37, and 86 for the two Klempler [11], Fallon [8], and Cameron [20] RCTs, respectively, were less than the 194, 194, 45, and 118 recommended by power analysis to draw definite conclusions. The actual number of subjects in the treatment arms for all five trials combined equaled only 167 subjects [8,10,11].

The evidence is too heterogeneous to make strong recommendations

The success rates for the RCTs [8,10,11] were too heterogeneous to make strong recommendations. The success rates varied from as low as 37% and 41% for the two Klempler RCTs [11] on a QOL scale to as high as 64% and 67% for the Krupp and Fallon RCTs on a fatigue severity scale [8,10]. The Fallon RCT also reported moderate improvements on a cognitive index for both treatment and placebo. Antibiotics were more effective than placebo in improving cognitive function in the Fallon RCT at 3 months but the difference was not significant at 6 months [8]. The Cameron RCT concluded that oral amoxicillin for 3 months was significantly more effective than placebo (46 vs. 18, $p = 0.007$) [20]. The 37–67% success rates for the RCTs were also heterogeneous compared with the 63–100% success rates for comparator [31] and case series [18,19,32–34].

The risk to an individual of facing a long-term debilitating illness has not been considered

The 4% risk of a serious adverse event to an individual because of antibiotic treatment of CLD has not been weighed against the risk to an individual of facing a long-term debilitating illness. There were six serious adverse events for the 167 subjects in the treatment arms of the RCTs [8,10,11]. Four individuals developed serious events known to be related to antibiotics consisting of anaphylaxis [10], allergic reaction [8], and two cases of thrombus. Two individuals developed serious events that are not established events related to antibiotics – one individual with life-threatening pulmonary embolism [11] and a second with fever, anemia, and gastrointestinal bleeding [11]. The Cameron RCT concluded that a significant gain in the QOL for subjects randomized to amoxicillin without serious adverse events is consistent with the goal of improving patient's QOL and consequently worthy of further study. The risk of facing a long-term debilitating illness without antibiotic treatment was demonstrated by the two Klempler RCTs where subjects were ill an average of 4.7 years with a QOL "equivalent to those observed in patients with congestive heart failure or osteoarthritis and were more than 0.5 SD greater than the impairment observed in patients with type 2 diabetes or a recent myocardial infarction" ([11], p. 89). The risk of facing a long-term debilitating illness was confirmed in the Fallon RCT where subjects were ill an average of 9 years with a QOL as poor as subjects entering the two Klempler RCTs, severe fatigue, and pain "similar to those of postsurgery patients" ([35], p. 1127). The severity of the symptoms of CLD was validated in a review of four of the RCTs as determined by 22 standardized measures of QOL, including fatigue, pain, role function, psychopathology, and cognition [12].

The risk to society of a growing chronically ill population has not been considered

The risk to society of emerging resistant organisms has not been weighed against the risk to society of an emerging population saddled with CLD. The risk to society of overuse of antibiotics and emergence of multi-resistant infectious disease organisms [36] has received considerable attention. The risk to society of the emerging population of CLD has received less attention. The risk of developing CLD has been downplayed following reports that 88–95% of LD cases exhibiting an erythema migrans and Bell's palsy were successfully treated. Cohort studies of consecutively treated LD patients have shown that long-term outcomes were not nearly so successful. Thirty-four percent of a population-based, retrospective cohort study in Massachusetts had long-term sequelae from Lyme disease (arthritis or recurrent arthralgias, neurocognitive impairments, and neuropathy or myelopathy) a mean of 6.2 years after treatment [7]. Sixty-two percent of a cohort of 215 consecutively treated LD patients in Westchester County remained ill a mean of 3.2 years after treatment [6]. Mean durations of illness of 4.7–9 years for the two Klempner [11] and Fallon RCT [8] validate the risk to society of a growing chronically ill population [6,7].

The cost of a growing CLD population was significant using a Centers for Disease Control and Prevention (CDC) economic cost study of 'clinically defined late-stage LD' in Maryland's Eastern Shore. The average annual economic impact of LD was estimated to be \$16,199 per patient, per year [13]. Ninety-five percent of the cost was indirect medical costs, non-medical costs, and productivity losses. The authors estimated the annual economic impact of LD to be ≈\$203 million (in 2002 dollars) in the US based on the 23,763 cases reported to the CDC. The actual annual economic cost of LD could be as much as ≈\$2 billion (in 2002 dollars) in the US based on CDC estimates that the actual number of LD cases is 10× higher than reported.

Treatment delay has not been considered as a confounder

None of the RCTs was able to address whether or not treatment delay was a confounder to explain the heterogeneous outcomes. The Fallon RCT described delays of 1.8 years without discussing whether the delay affected the outcome [8]. A similar delay in treatment of 1.8 years was reported in a consecutive case series of LD patients confirmed by IgG Western blot testing [37]. Treatment delay was strongly associated with treatment failure [37]. The Klempner RCT did not discuss whether any of the average onset of illness of 4.7 years was due to delayed treatment [11]. The Krupp RCT [10] did not report whether delays in treatment occurred.

Coinfections have not been considered as a confounder

None of the RCTs were able to resolve whether co-infections could explain their mixed outcome. The ticks that carry LD also carry co-infections known to cause diseases such as babesiosis, anaplasmosis, and ehrlichiosis [38]. Krause reported an increased severity and duration of illness in patients co-infected with Lyme disease and babesiosis [17]. The Fallon RCT reported low positive IgG results for 10.8% of samples for of *Anaplasma phagocytophila* and an astonishing 27% for *B. microti*. The Klempner RCT actively excluded subjects with evidence of co-infections [8].

The design of RCTs did not address the range of treatment options in an actual practice

None of the RCTs assessed the range of treatment options available in actual practice. All four RCTs were limited to fixed

predefined interventions rather than the option to modify the antibiotic regimen as has been described in actual practice [14]. None of the RCTs incorporated symptomatic treatment into the protocol. CLD patients who are ill an average of 4.7–9 years with severe pain, fatigue, and a poor QOL might have benefited from symptomatic treatment combined with antibiotic therapy.[11] Fallon RCT's decision to drop a subject that required pain management illustrates the difficulty of designing RCTs to reflect the treatment options available in actual practice [8].

The findings cannot be generalized to actual practice

None of the RCTs discussed the difficulties encountered when attempting to generalize their data to actual practice. Following the Klempner RCT's report that, at the time of enrollment, study subjects had already been ill an average of 4.7 years and had already received an average of three courses of treatment, an analytical review by this author raised concerns about the generalizability of Klempner's conclusions, as follows: "Applying the findings to target populations with characteristics that differ from those included in these trials is inappropriate and may limit options for chronic Lyme disease patients who might benefit from antibiotic treatment" ([30], p. 12). The same generalizability issue could have been raised following the Fallon RCT wherein LD subjects had been symptomatic for an average of 9 years [8]. Fallon RCT raised an additional generalizability concern by noting that 3331 (99%) of the 3368 initial clinic contacts were excluded due to restrictive entrance criteria [8].

Test of the hypothesis

The hypothesis could be tested through new innovative trials of CLD that address the eight limitations discussed: the trials are better powered, the heterogeneity of results are reconciled, the risk to an individual of facing a long-term debilitating illness has been considered, the risk to society of a growing chronically ill population has been considered, treatment delays and co-infections have been considered as a confounder, trials are completed that address the range of treatment options in an actual practice, and findings can be generalized to actual practice.

Implications

This hypothesis suggests that physicians should consider the limitations of the evidence before denying antibiotic treatment for CLD. Physicians who continue to deny antibiotic treatment for CLD patients could let their patients know that there are clinicians and a professional society that consider the evidence insufficient to deny antibiotic treatment for this condition [14]. Shrier in a bioethical discussion of clinical equipoise came to the same conclusion as follows: "Rather than prohibiting the clinician from informing the patient of his or her personal beliefs, clinical equipoise simply asks the clinician to be honest, letting the patient know that a different but equally competent clinician might decide on a different course" [39].

The hypothesis also suggests that health care insurers consider the limitations of the evidence before adopting policies that deny antibiotic treatment for CLD patients. The hypothesis suggests that insurers should expand coverage of CLD to include clinical discretion for specific clinical situations.

Conflict of interest statement

The author is the President of ILADS, first author of the ILADS CPG, the principle investigator for one of the five RCTs, a clinician

who treats Lyme disease patients, and an advocate of better evidence. He has no interests that conflict with that goal.

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