The Ad Hoc Patient and Physician Coalition August 8, 2019

About the Ad Hoc Patient and Physician Coalition: The Ad Hoc Patient and Physician Coalition consists of patients and physicians who are concerned that the proposed Lyme disease guidelines of the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR) will further restrict access to care and harm patients by leaving them undiagnosed and undertreated. The coalition consists of over 35 patient groups, (including LymeDisease.org, the national Lyme Disease Association, Bay Area Lyme Foundation among others) and the International Lyme and Associated Diseases Society, which represents clinicians who treat Lyme disease nationwide.

These were authored by Lorraine Johnson, JD|MBA, CEO LymeDisease.org and Dr. Elizabeth Maloney, who represents the International Lyme and Associated Diseases Society. The comments were filed on August 8, 2019 and may be revised.

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General Comments

Lack of Process Integrity and Transparency

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The IDSA posted its newly proposed guidelines on its website on the eve of July 4th and provided 45 days for comments. The guidelines alone are over 100 pages and the supplemental materials are more than 200 pages. Yet those who would like to comment can neither download nor print these materials for review. This poses an extraordinary barrier to review given the length of the materials. Imposing these types of barriers to comments makes it extremely difficult to review the guidelines or comment on them and undermines process integrity.

We would also point out that while this comment system seems designed to insure anonymity, the comments of patient organizations and the International Lyme and Associated Diseases Society (ILADS) should be given a considerable amount of weight by the panel because these patients and their treating physicians, who are the ones most affected by the guidelines, were not meaningfully represented on the panel, and will bear the adverse consequences of guidelines that do not adequately provide for the exercise of clinical judgment and patient values. The panel excluded patients who represent the community and the physicians who treat them.

In accordance with the National Academy of Medicine [(NAM), previously the Institute of Medicine (IOM)] requirements, this panel should "consider all external reviewer comments and keep a written record of the rationale for modifying or not modifying a CPG in response to reviewers' comments." (IOM 2011)

The panel should review the previous GRADE assessments developed by NICE, ILADS, and Hayes and Mead (CDC) and reconsider the questions it has posed (or omitted), the outcomes it has selected, its evaluation of evidence, and its recommendations. (Hayes 2003, Cameron 2014, NICE 2018). These proposed IDSA guidelines are inordinately restrictive compared to the IDSA previous guidelines and to those of NICE and ILADS, which also used GRADE, in terms of diagnosis, treatment durations, retreatment options, and persistent manifestations of Lyme disease. In addition, the outcomes evaluated as well as evidence assessment and translation into recommendations are remarkably incongruent with the all other Lyme disease GRADE assessments conducted to date. The panel should reconcile its evidence assessment with those of NICE and ILADS.

The guidelines overstate the evidence base and fail to acknowledge that the science in Lyme disease is emerging and evolving. In persistent Lyme disease, there are only four randomized treatment trials. (Klempner 2001, Krupp 2003, Fallon 2008) The few clinical trials in Lyme disease that the NIH has funded utilized very small samples (ranging from 37 to 129) and screened out between 89% and 99% of those who applied, resulting in study samples that were not representative of the overall population of chronic Lyme disease patients. By failing to acknowledge the emergent evidence base, these guidelines give a false appearance of settled science and prematurely close the door on research. This is an ethical violation that misrepresents the state of the research in Lyme and may diminish research funding. It is an unprofessional and irresponsible response to a growing crisis that the CDC estimates has more than 300,000 cases a year. Lyme disease is a research-disadvantaged disease that already has less clinical research conducted than leprosy, which has an incidence of 200 cases a year. (Goswami 2013)

In addition, the guidelines have significant omissions vital to those assessing the quality and transparency of these guidelines. These omissions were raised in previous comments on behalf of patient groups to the guidelines plan, which indicates that their omission here would not simply be an oversight, but rather an intentional attempt to mislead those using the guidelines. Fundamental transparency requires disclosure of the following: (a) the existence of a controversy in the treatment of Lyme disease, (b) the existence of competing guidelines by another medical society, (c) the fact that the IDSA guidelines have been subject to multiple antitrust actions, and (d) that the lack of process integrity and transparency in previous guidelines caused the NAM to publicly admonish the IDSA and recommend that it remedy these problems in its future guidelines.

The guidelines need to acknowledge that there is a divergence of opinion in both the physician and researcher communities regarding the diagnosis and treatment of Lyme disease so that readers are not misled into believing that the IDSA guidelines are unchallenged or that alternative standards of care in the treatment of Lyme disease do not exist. The guidelines also should disclose the existence of conflicting guidelines by a competing medical society, the International Lyme and Associated Diseases Society (ILADS).

Until recently, when its funding was subjected to budget cuts, the quality of guidelines was determined by the National Guidelines Clearinghouse (NGC) of the Agency for Healthcare Research and Quality. While the NGC was operational, it posted the 2014 ILADS guidelines under its updated standards requiring that guidelines comply with the NAM standards for creating trustworthy guidelines, including the rigorous GRADE evidence assessment requirements. (Cameron 2014, IOM 2011, Wormser 2006) During this same period, the IDSA guidelines were delisted from the NGC as being outdated. Disclosing this information is a critical component to transparency. It alerts patients and practitioners that there are alternative treatment options and approaches to consider when making treatment decisions.

The ILADS guidelines are patient-centered and included a patient on the working team who had substantial subject matter expertise and was an officer in a widely trusted 501(c)(3) organization that had represented the patient community for over 25 years. (Cameron 2014) These guidelines provide a careful analysis of the roles of patient preferences and outcomes that patients deem important and have been endorsed by a major Lyme disease organization, LymeDisease.org. Reconciling these guidelines with those reflected in the ILADS guidelines should be a fundamental to transparency in these new guidelines.

Antitrust law is concerned with abuses of power. When organizations use their power in the marketplace to “sit in judgment of their competitors” by enforcing their guidelines against their competitors, antitrust issues arise. (Johnson 2010) This occurs when organizations, like the IDSA, have substantial market power to influence the ability of patients to access care by impeding the ability of physicians to provide care due to fear of legal retribution. The fact that the previous guidelines have been the subject of two antitrust actions should be expressly stated so that the readers have an understanding that these guidelines are controversial, have been and continue to be legally challenged, and arise in the context of a professional turf war between two medical societies.

The first antitrust action was an investigation by the Connecticut Attorney General (AG) who stated that the IDSA's 2006 Lyme disease guideline panel undercut its credibility by allowing the individuals developing its guidelines to hold financial interests (in vaccine companies, Lyme disease diagnostic tests, patents and consulting arrangements with insurance companies) and by excluding divergent medical evidence and opinion. (Johnson 2010, State of Connecticut Attorney General 2008) This antitrust action implicated all three organizational sponsors of the current Lyme guidelines development process [the IDSA, the American Academy of Neurology (AAN), and American College of Rheumatology (ACR)]. Key members from all three organizations who sat on the panel of the 2006 IDSA Lyme guidelines as well as two of the organizations, the AAN and IDSA, were subject to the investigation by the AG in connection with the development of the 2006 IDSA Lyme guidelines. The second action is an on-going RICO action that maintains that the IDSA has conspired with insurers to deny patients access to care. (Torrey et al vs IDSA et al).

The AG ultimately required the IDSA to review its own guidelines by a panel of the IDSA’s choosing that did not have clinical conflicts of interests. Although this newly seated panel, which consisted primarily of members of the IDSA, confirmed the guidelines previously adopted by their medical society, it did not address the antitrust concerns raised by the AG. (Johnson 2009) A year later, the NAM took the highly unusual step of publicly admonishing the IDSA in its landmark report, “Clinical Practice Guidelines We Can Trust,” in 2011.

“The 2006 lawsuit by Connecticut’s Attorney General against the Infectious Diseases Society of America’s Lyme Disease Guidelines highlights the need for standardization and transparency in all aspects of systemic data collection and review, committee administration, and guideline development, so that questions about these issues do not detract from the

science. GDGs must be aware of the many, varied observers who will consider their development processes, particularly when their recommendations are likely to be controversial." (IOM 2011)

The fact that the IDSA has failed to do heed the NAM's warning in the development of these proposed guidelines is unfortunate for all those who rely on guidelines to be unbiased, scientifically valid, and trustworthy.

Physicians, patients and the medical community need to understand the highly controversial context in which these guidelines were developed. More specifically, they need to understand that competing ILADS guidelines exist and that the sponsoring members of these guidelines have been subject to antitrust actions. Finally, they need to understand that the science in Lyme disease treatment is emergent and developing. The proposed guidelines should disclose these facts.

It is critical that readers understand the remarkable differences between the proposed guidelines and the two existing GRADE assessments of ILADS and of NICE. This would require that the panel reconcile its guidelines evidence assessments and recommendations with those of the two other Lyme disease GRADE assessments by ILADS and NICE and explain why its assessment and recommendations differ. Because it has failed to do so, the recommendations fail to comply with Standard 5 of the NAM Standards for Developing Trustworthy Clinical Practice Guidelines which requires a description and explanation of any differences of opinion regarding the recommendation.

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Acceptability, Equity, and Ethical Principles

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The IDSA Clinical Practice Guideline development resources provide: “To ensure the production of trustworthy, evidence-based guidelines, IDSA requires that guideline developers adhere to a) The IDSA Handbook for Clinical Practice Guidelines Development (Draft 3/2018), b) The Institute of Medicine's (IOM) practice standards and c) the GRADE approach”. (IDSA, CPG Training and Resources) The IDSA further states that it “considers the application of its content as mandatory at all levels of the guideline development process. This handbook thereby serves as a tacit agreement between the IDSA SPGC and panelists.” (IDSA Handbook) The handbook incorporates some generally accepted equitable principals for the development of guidelines, including equity (the greater impact an intervention has on health inequities, the less likely a strong recommendation is warranted), acceptability (the less acceptable an intervention is for stakeholders, the less likely a strong recommendation is warranted).

When translating evidence to recommendations, one of the key issues the IDSA Handbook raises concerns the acceptability of the recommendation by stakeholders. “Are key stakeholders likely to find the option acceptable (given the relative importance they attach to the desirable and undesirable consequences of the option; the timing of the benefits, harms and costs; and their moral values)?” (IDSA Handbook) A number of the recommendations in the proposed guidelines will be regarded as completely unacceptable to the stakeholders most affected by these guidelines, the patients and the physicians who treat them. Chief among these are a) the decision to exclude from the panel representative patients and their treating physicians, b) the failure to consider patient-important outcomes, values and preferences, c) the failure to provide for the exercise of clinical judgment and consideration of patient values and circumstances or individualized care for patients, d) the failure to diagnose patients who do not live in endemic areas, e) the failure to diagnose patients with non-specific symptoms, e) the failure to provide an adequate duration of treatment for those diagnosed early to assure cure, f) the failure to provide any opportunity for retreatment for patients who fail an initial course of antibiotic treatment, and g) the failure to consider the devastating consequences to patient lives the these guidelines will cause.

Patients are the ones affected by these guidelines. Appointing token patients to the panel who are not known, nominated, or regarded as representatives of the community is unacceptable. Yet neither representative patients nor their physicians were included on the panel. Accordingly, any patient participation on the panel is regarded as token by the Lyme disease community. As NAM recognizes, it is a fundamental rule of equity that “those affected” should participate in the guidelines developments that affect their health. (IOM 2011) Here, representative patients were intentionally excluded along with their treating physicians.

As the NAM notes, the opportunity for harm in treatment guidelines is enormous because they “set standards of care and criteria for insurance coverage [and] may affect millions of patients.” (IOM 2009) The consequence of “getting it wrong,” particularly when treatment options (and patient autonomy) are restricted as these guidelines do, may have devastating effects on the patient’s quality of life. Further, there is no institutional accountability for guideline developers and no regulatory oversight of the process.

Guidelines can be proscriptive, prescriptive or permissive. Guidelines, like those proposed, which unduly restrict the exercise of clinical judgment, the provision of individualized care, and the ability of patients to choose among treatment options based on their circumstances and values, may be viewed as legal mandates by medical boards, quality control standards, hospitalization practices, and courts and may provide insurers with legal cover for denying reimbursement for treatment and to exclude physicians from participating in insurance networks. (Johnson 2010) This is true notwithstanding the existence of a boiler plate disclaimer—such as the one proposed for these guidelines.

Guideline panels of a dominant medical society have the authority to set the rules for patient care but are not accountable to those patients when care fails. It is all too easy to turn a blind eye on treatment failures and patient

suffering when one never sees or treats the patient. The medical society is not responsible for the consequences of failure and neglect, and has no obligation to the individual. Meanwhile, the patient alone bears the ultimate consequences of missed diagnosis, treatment failure or being deprived of the only treatment option available. Abandoning patients who have a quality of life worse than that of those with congestive heart failure is unacceptable. This fundamental inequity—that patients who are suffering a profound quality of life impairment—are denied any treatment options by a medical society that is not accountable for the consequences of this suffering—will be made far worse by these guidelines, which remarkably limit care even more than the previous guidelines do. This is unacceptable to patients and widens the inequities in Lyme disease treatment.

This situation has created a crisis in patient access to care. Barriers to care may be geographic, financial, or systemic structural factors that result in failure to provide needed services. Key factors include insurance coverage, healthcare costs, travel time and distance to obtain care, and availability of care. Here, the barriers to care are structural and are created solely by the IDSA guidelines constraints that leave patient undiagnosed, undertreated, and make many physicians fearful of legal retribution through medical board action if they provide services to patients. IDSA guidelines allow insurers to deny coverage for care and exclude physicians who treat from their networks.

Most patients with persistent disease see many doctors before diagnosis, are diagnosed late in the course of their disease, and travel significant distances to receive care. (Johnson 2011) Most patients see more than four physicians before they are diagnosed, creating delays that may profoundly impact their quality of life. To obtain care, 49% must travel more than 50 miles. (Johnson 2011) The cost, inconvenience, and work-related impact of traveling these distances may result in many patients foregoing care all together. 84% of Lyme patients were not diagnosed within the first 4 months of illness. 36% of Lyme patients were unable to receive a diagnosis before at least six years of illness. (Johnson 2011) For Lyme patients, there are no treatment alternatives to antibiotics. Guidelines that place inordinate restrictions on patient's ability to obtain a diagnosis and be treated, and if treatment fails, to be retreated, deny these patients the quality of life that they hold dear.

These proposed guidelines will impose even more stringent mandates on patients affected and their treating physicians (who were excluded from the process). Patients can expect to have their diagnosis delayed or denied for arbitrary reasons (e.g. lack of an EM rash, failure to reside in an endemic area, non-specific symptoms). They can expect increased treatment failures due to shortened treatment duration. Finally, they can expect treatment to be routinely withheld if they have persistent Lyme disease or simply require retreatment for treatment failure.

The investigators of the four NIH-sponsored retreatment trials documented that the patients' quality of life was consistently worse than that of control populations and equivalent to that of patients with congestive heart failure; pain levels were similar to those of post-surgical patients and fatigue was on par with that seen in multiple sclerosis. (Krupp, 2003; Klempner 2001; Fallon 2008). The proposed guidelines will have a profound effect on patient quality of life and make the access to care situation worse.

The diagnostic and treatment restrictions will justifiably spark outrage in the patient community. There is no guesswork involved here as two antitrust actions have been launched to protect those affected: one by the Connecticut Attorney General and one in civil court as a RICO action. In addition, the NAM spotlighted the IDSA Lyme guidelines in its report on creating trustworthy guidelines as one of the most acrimonious battle of guidelines. (IOM 2011) Patients, meanwhile do not choose to be treated under infectious disease guidelines. Almost all patients with persistent Lyme disease choose to be treated under the ILADS GRADE protocol.

More specifically, very few Lyme patients (6%) choose infectious disease physicians to treat their illness. (Johnson 2018) LymeDisease.org conducted a patient survey in 2011 of over 5,000 patients asking patients whether the treatment guidelines used by clinicians affected their choice of clinicians. (LymeDisease.org 2011) Most patients (75%) said that they "select a physician who follow the guidelines of ILADS", while less than 2% said they selected a physician who

follows the guidelines of IDSA. These patients are choosing clinicians based on the standard of care their guidelines support. The main difference between the two guidelines is that in the face of uncertainty the ILADS guidelines embrace clinical judgment, individualized treatment, and shared medical decision making, which the IDSA guidelines restrict. This makes it all the more inequitable that patients who do not elected to be treated under the IDSA guidelines and who were not allowed to participate in this process, will be the ones most deeply affected by these guidelines which will both further restrict their access to care and which disregard the quality of life hardships these guidelines impose on them.

The most egregious thing that the IDSA guidelines do is to provide inordinate restrictions on the exercise of clinical judgment and the consideration of patient values, particularly in diagnosis and in the treatment restrictions for both early treatment failures as well as for persistent Lyme disease. They do this by imposing strong recommendations in the face of low quality evidence and by artificially inflating the quality of evidence by ignoring patient-important outcomes. This limits the patient's ability to obtain a diagnosis for a disease that has serious quality of life implications. It also limits treatment options for these patients. The panel's decision to value potential treatment side effects over potential treatment benefits does not align with patient values. This increases the degree of health inequities in Lyme disease and could be remedied by modifying the guidelines to provide more clinical judgment reflecting the individual circumstances for diagnosis and treatment.

Early diagnosis is essential. The heavy burden of illness associated with late Lyme disease highlights the need for earlier diagnosis of Lyme disease to avoid progression of the disease. A study of over 3,000 patients with persistent Lyme disease showed that the percentage of patients who reported their health quality as poor increased from 23% of those with Lyme disease for less than six months to 56% at one year and 72% at 5–10 years. (Johnson 2014) Few who have had Lyme disease for longer than six months were diagnosed early; most were diagnosed late (78%). (Johnson 2014) Approximately half (50.5%) of the sample reported having Lyme disease for more than 10 years. These proposed guidelines are not equitable because they deny patients who are ill access to care in diagnosis and in treatment. It is agreed by all that early diagnosis and treatment is essential for Lyme disease patients to be restored to their pre-morbid quality of life. Yet these guidelines create barriers to diagnosis that can be expected to have profound consequences on patients and their quality of life because they permit the window of therapeutic effectiveness to diminish or close entirely.

Patients with an EM rash who happen to live in an endemic area may receive a diagnosis, while those who do not happen live in an endemic area are not likely to. Yet it is clear that every state has ticks that carry the bacteria that causes Lyme disease and is now in over half of the counties in the US. (Asher 2016) The geographic reach of the disease is ever expanding and so-called "low incidence" states have much higher rates of Lyme disease when measured by other independent big data sources. (Sonenshine 2018) Some states, like California, have hot spots where Lyme is highly endemic, although the rest of the state is low incidence. (Lane 1992) Two recent studies, one by Quest Diagnostics and the other by FAIR Health insurance claims database, demonstrate that the incidence of Lyme disease in so-called "low incidence" states is much higher than CDC surveillance statistics suggest. (Quest 2018, McGinty 2018, Gelburd 2017) For example, in California the CDC surveillance cases are around 90, yet Quest diagnostics alone reports nearly 500 positive tests in the state annually (and that is only one lab), and FAIR Health reports nearly 47,000 insurance claims in California. These types of disparities are also reported in other low incidence states like Florida, Texas, and North Carolina. A Wall Street Journal article included both North Carolina and California among the top five in the nation for insurance claims. (McGinty 2017) Under equitable principles, these patients deserve to be diagnosed just as much as patients in endemic areas deserve diagnosis. Even where Lyme disease is less common in a state, the panel should not deny that patient the diagnosis that is necessary to restore health. Other guidelines, such as NICE and ILADS, provide no geographic restrictions. Yet under the proposed IDSA guidelines, these patients would not be diagnosed. This will increase health disparities and inequity in Lyme disease.

It is also well known that many patients do not have an EM rash. Estimates on the percentage of patients without a rash vary, but at least 20% and perhaps as many as 31% by CDC standards do not have the rash. (CDC 2008) Under the proposed guidelines, these patients will also not be diagnosed through any means. Patients with non-specific manifestations of Lyme disease and those with Lyme encephalopathy clearly exist and denying them the opportunity to be diagnosed and treated to wellness is not justifiable as a matter of equity. These patients may be more difficult to diagnose and may require the exercise of clinical judgment to ascertain exposure, symptoms, duration, quality of life impairment, etc. However, the diagnosis of the summertime flu or a constellation of symptoms that raise a high clinical suspicion of Lyme disease with non-specific symptoms should be included within the diagnostic standard.

The previous IDSA guidelines dealt with patients with non-specific symptoms by using laboratory testing to confirm diagnosis. Here, the IDSA seems to acknowledge the poor state of the testing (its antitrust guidelines panel hung on the issue of whether positive serology should be required for a diagnosis.) However, it is fundamentally inequitable to simply exclude these patients from diagnosis altogether. NICE guidelines recognize this saying "Non-specific symptoms could be an indication of an acute infection without the involvement of specific organ systems. The committee agreed that people with a positive test result for Lyme disease and non-specific symptoms should be treated in the same way as people with an erythema migrans rash." (NICE 2018) NICE the acknowledges that tests merely play a supportive role in the clinical diagnostic process. Its guidelines provide, "Do not rule out diagnosis if tests are negative but there is high clinical suspicion of Lyme disease. .... If there is a clinical suspicion of Lyme disease in people without erythema migrans: offer an enzyme-linked immunosorbent assay (ELISA) test for Lyme disease and consider starting treatment with antibiotics while waiting for the results if there is a high clinical suspicion."

In addition, despite known treatment failures, which a Wormser study pegged at 17% and an Aucott study using quality of life and resolution of symptoms as endpoints found to be 36%, these guidelines reduce treatment times from 10-21 days to 10-14 days which may increase treatment failures. (Wormser 2003, Aucott 2013) It does so by valuing avoidance of adverse side effects from commonly used antibiotics over potential benefit of higher cure rates. This is not what patients would value and does not conform to the requirements of GRADE. NICE also considered this issue and adopted 20 days as its standard course of antibiotic treatment commenting that that "in the absence of good quality evidence for treatment duration, the committee opted for the longer duration to be cautious, due to concern at the low cure rates in some of the studies and the lack of additional adverse events with a longer course (20 versus 10 days)." (NICE 2018)

The treatment limitations in these proposed guidelines are also unacceptable because patient who fail the first round of treatment are simply abandoned because diagnostic tests cannot determine active infection. Equitable approaches to this problem would provide for retreatment. NICE, for example, provides ""If Lyme disease is treated early, most people recover completely, but studies show that some people have ongoing symptoms following antibiotic treatment. It is not known whether these symptoms are due to persisting infection, tissue damage, autoimmune reaction or some other process. There is currently no test that helps determine this. It is important to assess whether repeat or longer courses of antibiotics might help ..... Consider a second course of antibiotics for people with ongoing symptoms if treatment may have failed." (NICE 2018) Although NICE recommends against providing more than two courses of antibiotics "routinely," it does not tie the clinician's hands should additional treatment be necessary. In the case of Lyme disease, the magnitude of the risk of terminating treatment prematurely can be severe, permitting a serious systemic condition to progress with the risk of irreparable injury or even death.

The increased burden from these guidelines on patient access to care cannot be justified equitably. It is telling that NICE, which operates in the context as the insurer in England, has guidelines that are far more responsive to the interests of patients. NICE guidelines provide for greater flexibility in diagnosis, recognize that Lyme may present with non-specific symptoms, provides for a longer initial treatment to reduce treatment failures, and by provides for retreatment. The IDSA guidelines have left patients marginalized in the health care system. Insurance networks use them to exclude non-conforming clinicians, medical boards use them to justify actions against clinicians who treat, and insurance companies

use them to deny patient coverage for medical care. These guidelines have in short created an extreme access to care issue that has become a matter of civil rights. They are profoundly inequitable, placing all of the burdens on patients who were not permitted to participate in the process and who will bear the health consequences of what amounts to medical neglect under these guidelines. Because these guidelines use strong recommendations where they should use weak recommendations, they unduly restrict clinical judgment. They will make the access to care crises worse by making it more difficult for physicians who do not comply with these guidelines to provide care to patients under threat of losing their medical license.

They also do not comply with the IDSA Handbook, which provides: "The less acceptable an option is to key stakeholders, the less likely it is that it should be recommended, or if it is recommended, the more likely it is that the recommendation should include an implementation strategy to address concerns about acceptability." (IDSA Handbook) We call upon this panel to redress the inequities detailed above in the proposed guidelines.

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Authors

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Methodology

Pages 4-9, Lines 87-222

There are a number of critical issues in the methodology used to develop the clinical questions and evidence review:

The outcomes used for the evidence evaluation were not patient-important outcomes as required by GRADE. Important subgroups of the populations of interest were not identified and evaluated separately. Unless remedied, the omission of these subgroups and incorporation into clinical review questions will result in an extraordinary access to care issue, leaving patients undiagnosed and treated. The recommendations fail to comply with Standard 5 of the NAM Standards for Developing Trustworthy Clinical Practice Guidelines which requires an explanation of the part played by values, opinion, theory, and clinical experience in deriving the recommendation. In particular, the panel has failed to differentiates between its values, opinions, and theories from those of other stakeholders including patients values and patient important outcomes as well as the role of clinical judgment. The recommendations fail to comply with Standard 5 of the NAM Standards for Developing Trustworthy Clinical Practice Guidelines which requires a description and explanation of any differences of opinion regarding the recommendation. This would include an obligation to reconcile its guidelines evidence assessments and recommendations with those of the two other Lyme disease GRADE assessments by ILADS and NICE.

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NICE guideline [NG95], Lyme disease (Published date: April 2018). https://www.nice.org.uk/guidance/ng95

Lack of Transparency

Page 6-7 Lines 137-156

The proposed guidelines need greater transparency about their process. In particular, they need to provide detailed information regarding their “predefined inclusion and exclusion criteria”, together with a listing of all included studies and all excluded studies. The term “sufficiently peer-reviewed” requires further explanation—what criteria were used to determine whether studies were “sufficiently peer-reviewed”. This criterion appears to simply allow cherry picking exclusions of studies. Further clarification regarding the “rereview . . . necessary to ensure proper final selection of studies” is essential as this again would seem to permit further cherry picking of studies. For example, what criteria were used in the rereview? What studies were excluded as a result of the rereview?

Clinical Practice Guidelines

Page 4, lines 89-94

Shared medical decision-making

Although this section states that guidelines are “intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health”, the proposed guidelines do not in fact provide for the exercise of clinical judgment or shared medical decision making in several key recommendations. For example, the diagnosis or treatment of EM rash or prolonged symptoms following treatment of Lyme disease do not provide for shared medical decision making. It also does not consider treatment trade-offs between the benefits and risks of different treatment options or provide patients with treatment options or individualized care in the context of shared medical decision-making. These proposed guidelines focus on “objective measures of disease” and fail to consider symptoms and

outcomes important to patients or even provide for decision making in the context of a given patient's quality of life or functional impairment.

Guideline Panel Composition

Pages 4-5, lines 96-115

The NAM states that "[t]o be trustworthy, clinical practice guidelines should: (a) be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups; (b) consider important patient subgroups and patient preferences, as appropriate; and (c) be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest." (IOM Report Brief 2011) The NAM explains that the ability of the guidelines development group to perform seemingly technical assessments, "depends on the composition of the group (whether the right participants have been brought to the table) and group processes (whether the process allows all participants to be involved in a constructive way)." (IOM 2011) As the NAM notes, "the aim is to ensure that group processes fundamentally encourage inclusion of all opinions and grant adequate hearing to all arguments." (IOM 2011)

NAM Standard 3.1 provides that the guideline development panel should include populations expected to be affected by the guidelines. However, this panel has excluded those most deeply affected by these guidelines patients and their treating clinicians.

It is unacceptable that this panel does not have any meaningful representation of the interests of patients with persistent Lyme disease given that these patients will suffer the consequences of under-diagnosis, under-treatment, and failure to retreat under these guidelines. The NAM requires that guidelines "be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups." (IOM Brief 2011) This section of the proposed guidelines states that the panel includes three patient representatives and one healthcare representative. Three of these patients are not identified and Jane Rips, who by her own admission knows nothing about Lyme disease, is not considered a patient representative. The only information we are given on the three unidentified patients is that they were "treated for Lyme disease and one parent of a pediatric patient treated for Lyme disease". These patients likely were treated early and restored to health. They cannot represent patients who did not have this good fortune. Moreover, there are well established non-profits who are trusted by the community to represent their interests who should have been on this panel. Patients who are not known and recognized by the affected community as being capable of representing the community's interests are simply tokens. The use of a consumer representative (presumably Jane Rips) is inappropriate in a disease where a patient community exists. What group of consumers does she purport to represent? It is analogous to selecting someone who has previously had a cold or the flu to sit on an HIV/AIDs panel.

The NAM notes that in evidence-based medicine "clinical expertise and patient preferences remain vital to clinical decision making." (IOM 2011) Yet, this panel does not include physicians who treat chronic Lyme disease – another population that will be deeply affected by these guidelines. Clinicians who do not comply with the guidelines are targeted by medical boards. Insurance companies do not cover the treatments they order. Members of the IDSA testify against them. (Johnson 2009) Essentially, this allows the IDSA to develop the rules and standard of care and use them as a sword against their competitors who are not permitted in the room.

According to the NAM, the aim of including a broad spectrum of opinions and viewpoints of those affected is to ensure that "group processes fundamentally encourage inclusion of all opinions and grant adequate hearing to all arguments." This panel, however, consists of two groups of people: those who have strongly held polemic viewpoints and biases against the diagnosis and treatment of patients with Lyme disease, the remainder have no apparent knowledge of Lyme disease. Patients and their treating physicians were deliberately excluded from the process.

The NAM also warns against dysfunctional group processes, which include "minority influence (a single member or minority of group members sway the majority, often by capitalizing on small divisions in the group), group polarization

(group dynamic leads to more extreme decisions than members would make individually), and 'groupthink' (members' desire for unanimity trumps objective appraisal of the evidence)". They caution that multidisciplinary groups are particularly at risk because members vary in "professional status, in the nature or depth of their specialist knowledge, and in their appreciation of roles and modus operandi of professional colleagues." (IOM 2011)

Key panel members (Lantos, Auwaerter, Halperin, Sood, Steere, Wormser, Strle, Aguero-Rosenfeld, Bockenstedt, Krause, and Zemel) routinely publish with each other and sit on grant peer review study groups together. They support each other's careers, which are predicated on the view that Lyme disease is "hard to catch and easy to diagnose and cure". Many in this group hold laboratory interests in Lyme diagnostic tests. These COIs are both commercial and intellectual.

This dynamic of having few in the know that have strong commercial and intellectual conflicts of interests "flock together" while the remainder of the group, who are largely not informed of the serious issues at stake play "follow the leader" permitted the guidelines to be dominated by the type of "groupthink" and minority influence that the NAM specifically warns guidelines panels to avoid.

The complete disregard evidenced in this process to the interests of those affected by these guidelines is unacceptable. It fails to comply with NAM Standard 3, which specifies that the guidelines process must include "populations expected to be affected by the guidelines." (IOM 2011) In addition, the constitution of the panel creates the type of process distortion that is subject to minority influence—a process dynamic the NAM advised panels to guard against.

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Disclosure and Management of Potential Conflicts of Interest (COI)

Pages 5-6, lines 117-131

The NAM stresses the importance of assessing institutional conflicts of interest. It states they should "be evaluated for the likelihood of undue influence and the seriousness of potential harms. . . , the extent of institutional accountability as well as the degree to which discretion is involved."(IOM 2009) For treatment guidelines, there is considerable discretion to fill evidence gaps with judgment. The NAM highlights the need for guideline panels to guard against organizational conflicts of interest (COIs): "The committee believes potential for COIs are great when funding for CPG development or for the supporting organization comes from stakeholders, particularly … specialty societies, which might benefit or whose members might gain from guideline recommendations." (IOM 2011) The sponsorship of this guideline development process by three organizations connected with the prior anti-trust action constitutes a classic COI where organizational interests may supersede the ethical mandate in medicine to hold patient interests paramount.

The first antitrust action was an investigation by the Connecticut Attorney General (AG) who stated that the IDSA's 2006 Lyme disease guideline panel undercut its credibility by allowing the individuals developing its guidelines to hold financial interests (in vaccine companies, Lyme disease diagnostic tests, patents and consulting arrangements with insurance companies) and by excluding divergent medical evidence and opinion. (State of Connecticut Attorney General 2008, Johnson 2010) This antitrust action implicated all three organizational sponsors of the current Lyme guidelines development process [the IDSA, the American Academy of Neurology (AAN), and American College of Rheumatology (ACR)] Key members from all three organizations who sat on the panel of the 2006 IDSA Lyme guidelines as well as two

of the organizations, the AAN and IDSA, were subject to the investigation by the AG in connection with the development of the 2006 IDSA Lyme guidelines. The second action is an on-going RICO action that maintains that the IDSA has conspired with insurers to deny patients access to care. (Torrey et al vs IDSA et al).

Developers of CPGs become 'promoters and defenders' of the guidelines produced under their auspices, particularly when their own guidelines have been legally challenged and criticized publicly. (Sniderman 2009) Validation of prior recommendations enables these societies to support their key opinion leaders, maintain their sphere of influence, suppress opposing viewpoints, and reduce potential litigation risk based on the guidelines.

Ten of the thirty panel members were either investigated for antitrust violations by the Connecticut Attorney General in connection with the IDSA 2006 guidelines, testified on behalf of the IDSA at the hearing, or sat on the IDSA hearing panel. These members have strong institutional as well as strong intellectual conflicts of interests and the guidelines appear to have been formulated to protect these interests.

Six of the panel members report financial COI related to Lyme diagnostic tests, having either received grants or commercial funding for Lyme tests. Four of the members of the panel have financial COI with Immunetics, the developer of the C6 Lyme test. One of the members, Dr. Wormser has financial COI with six diagnostic test companies. A number of questions posed by the panel relate to diagnostic test interests. Finally, there is a question regarding the use of "unvalidated" tests. This appears to be aimed at suppressing the development of innovative tests that may compete with the inferior tests in which panel members have conflicting interests. The participation by these panel members will ensure that the status quo which favors existing tests remains unchallenged by new entrants pursuing innovation in the market. The ultimate victims of these COIs and their impact on testing are the patients, whose physicians are instructed to use laboratory tests that miss more than 50% of Lyme cases. (Stricker 2007)

Although these conflicts may have been disclosed, the NAM standard 2.4 provides that "whenever possible CDG members should not have COI". (IOM 2011) Dr. Wormser, who has the most extensive conflicts of interests of anyone on the panel and who was the lead author of the previous guidelines and has been subject to many of the antitrust suits should have been excluded from this panel entirely as should the other panel members who were involved in the antitrust actions. Panel members who hold strong biases against patients, (including those associated with the Connecticut Attorney General antitrust investigation) and those with financial COIs (particularly those related to diagnostic tests) should not have been permitted to serve on the panel.

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Clinical Questions and Evidence Review

Pg 6-8, lines 133-179

PICO

Page 7-8, Lines 170-179

Outcomes important to patients

GRADE requires specification of all critically important and important outcomes "whether or not evidence from research studies is or is not available". (Guyatt 2010) For clinical treatment guidelines, the outcomes must be selected before the assessment of evidence and should reflect the perspective of "those who are affected"— and should "generally be that of the patient". (Guyatt 2010) When evidence of an outcome important to patients does not exist, GRADE states that while "guideline developers may be tempted to use the surrogates as outcomes measures. This is not the approach GRADE recommends. Rather they should specify the important outcomes and associated surrogates they must use as surrogates." (Guyatt 2010) When patient important outcomes are not used, the outcomes should be downgraded to reflect "indirectness" of using a surrogate outcome. These outcomes are then further broken down into those that are critically important to patients and those that are important but not critically important to patients. (Guyatt 2010)

There is a fundamental lack of transparency regarding the ranking in importance of outcomes used by the panel. For example, there is no listing of the outcome importance ranking, as required under GRADE, for any of the PICO questions evaluated. However, it is clear that the panel did not adhere to the standards of GRADE in formulating its patient important outcomes as explained more fully below.

The determination of outcomes critically important or important to Lyme disease patients under GRADE has been delineated in two independent GRADE assessments regarding Lyme disease as well as in patient surveys. The NICE GRADE assessment and the ILADS GRADE assessment independently assessed outcomes important to patients. These have been confirmed by patient advocacy groups as well. Generally, all three sources agree on the ranking of patient important outcomes. (NICE 2018, Cameron 2014, Johnson 2018, LymeDisease.org 2011) For example, the NICE GRADE assessment for most questions identified the following outcomes as critically important to patients: 1. Quality of life (any validated measure)

2. Cure (resolution of symptoms)

3. Reduction of clinical symptoms

4. Avoidance of symptom relapse

Adverse events were considered a less important patient outcome (Important, but not critically important). (NICE 2018 Management of Non-Specific Symptoms). This distinction is important because it means that the potential benefits of an intervention will generally outweigh the potential adverse events. Patients value the opportunity to restore their health and are willing to risk certain adverse events to do so.

For diagnostic tests, NICE identified only one critically important patient outcome, sensitivity. (NICE 2018) The remaining factors (e.g. specificity, positive predictive value, negative predictive value, and receiver operating characteristic) were deemed to be important, but not critically important. This conforms with patient important outcomes recognized in the community as well as survey data from LymeDisease.org of over 5,000 patients. (LymeDisease.org 2011) Patients place the highest value on obtaining early diagnosis and treatment that provides them with the opportunity to restore their health. They want to avoid diagnostic delays that could permit their disease to progress and become less responsive to treatment.

We refer the authors of the proposed guidelines to the evidence tables used in the NICE analysis, which start with the critically important outcomes for patients. (NICE 2018) While NICE guidelines may be inappropriate for some aspects of

GRADE analysis in the US (e.g. cultural differences, socialized medicine, etc.), their general approach in terms of questions asked, determination of patient-important outcomes, their assessment of the evidence quality for United States studies, and analysis of trade-offs between treatment benefits and harms (adverse events) conforms to GRADE and is informative.

We also note that the ILADS guidelines panel, which included meaningful patient representation from a major Lyme disease organization, clearly laid out the patient outcomes and values considered important. (Cameron 2014) Significantly, these outcomes are generally the same as those identified by NICE GRADE assessment, which was published subsequently. In contrast, the IDSA proposed guidelines did not include any community representatives on its panel and did not use patient-important outcomes in its assessment.

The outcomes selected in the draft guidelines for all clinical questions except prolonged symptoms of Lyme disease are the outcomes used by the original researchers that are not patient important outcomes, such as prevention or resolution of EM rash, objective measures of disease, etc. While these measures may simplify research, they are not the patient important outcomes required by GRADE. For example, resolution of an EM rash in and of itself would not be considered a patient important outcome if the patient was otherwise symptomatic or had an impaired quality of life. Another example is the pronounced emphasis on "objective signs of disease", which is a researcher-centric outcome. As noted above, patient important outcomes emphasize quality of life and resolution of symptoms, rather than objective signs of disease.

GRADE further provides that "[o]utcomes selected by the guideline panel should be included in an evidence profile whether or not information about them is available, that is an empty row in an evidence profile can be informative in that it identifies research gaps." (GRADE Handbook) For example, the EM rash studies do not generally consider patient important outcomes such as quality of life or resolution of other symptoms. This represents a research gap that the guidelines should then identify.

The method specified in lines 170-179 for ranking of outcomes is inappropriate under GRADE. Beginning at line 170, the process is described as follows: "Ranking of the outcomes by importance for decision-making was determined by consensus for each PIC0 question. In situations where a PICO question was comparing the use of an antibiotic regimen to no antibiotics (either as a treatment or prophylaxis), if the beneficial effects of the antibiotic regimen were uncertain, undesirable outcomes would usually be ranked higher in importance than if benefits were certain (i.e., ranked as critical for decision-making rather than important). Moreover, in situations where a PICO question compared the use of a specific antibiotic regimen to another antibiotic regimen (either regarding specific molecules, classes of antibiotics, route of administration or duration of therapy] and the beneficial effects of the two regimens were similar, then the undesirable outcomes could be ranked as critical for decision-making, but several other considerations might have also been taken into account such as stewardship issues, costs, etc."

The method specified does not result in the "patient-important outcomes" required under GRADE. Further, the re-ranking of outcome important to prioritize "undesirable outcomes" to a level of "critical for decision-making" undermines the concept of "patient-important outcomes". Patient-important outcomes are required to be determined in advance of the evidence assessment and are not subject to adjustment once the assessment has been done.

Finally, "patient-important outcomes" are not to be determined by a consensus of the panel, but rather are based on evidence of the outcomes that the patients affected regard as important. There is an abundance of evidence on outcomes patients regard as important in two other GRADE assessments which are confirmed by patient organization surveys. The panel was advised that patient important outcomes were reflected in the ILADS guidelines as well as in the results of the patient survey in response to its request for comments on the development plan for these guidelines.

Recommendation: The proposed IDSA guidelines should identify the following as critically important patient outcomes: quality of life, cure (resolution of symptoms), reduction of clinical symptoms and avoidance of symptom relapse. Note

that adverse events should not be considered critically important. Both the NICE and ILADS analysis rank adverse events lower in patient importance than potential treatment benefits (such as improving quality of life etc.). This aligns with the patient survey results as well. This means that these potential benefits will carry more weight in the trade-offs analysis compared to adverse events. For diagnostic outcomes, sensitivity is the only critically important outcome, other diagnostic test statistical measures rank below this in importance. The guidelines panel needs to reanalyze its evidence using patient-important outcomes as identified above. This will require that the quality of evidence for assessments that are based on surrogates be reduced for indirectness under GRADE. The process described in lines 170-179 is not permissible under GRADE. Accordingly, that section of the guidelines should be deleted and the guidelines panel should use the patient important outcomes previously identified by ILADS and NICE and confirmed by a patient survey on this topic to conduct its evidence assessment. It should then revise its analysis and recommendations to reflect patient important outcomes. Any gaps between identified patient important outcomes and surrogate outcomes used in research trials evaluated should be identified as a research gap.

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Inappropriate use of European studies throughout

European treatment studies on other Borrelia species, such as *B. garinii* and *B. afzelii*, are known to have different disease manifestations from *B. burgdorferi* species of the US and may respond differently to treatment approaches used. Hence, these treatment trials are not applicable to the North America population. There is no evidence that results from European studies on European strains can be used as surrogates for US GRADE analysis. Hence, these studies should be excluded.

Geographic based diagnostic limitations are no longer appropriate given big data findings

The use of CDC geographic surveillance criteria related to endemicity is inappropriate for clinical diagnosis because they exclude a large portion of the clinical population of patients who have Lyme disease. The disease has spread geographically and is now in half of all US counties. (Asher 2016) In addition, two big data studies, one by Quest labs (one of five major Lyme disease diagnostic labs) and one by FAIR Health insurance database (which includes over 23 billion healthcare claims), indicate that CDC surveillance cases do not accurately reflect the geographic distribution of the disease. (Quest 2018, Gelburd 2018)

A recent study from Quest lab reports Lyme disease positive serology in every state in the nation. Quest reported a large number of positive lab tests in 28 states, 20 of which the CDC classifies as low incidence states. based on surveillance case reports: “Based on more than six million de-identified laboratory test results conducted over the past seven years, the Quest Diagnostics study also found that outside of the northeastern U.S. which is historically associated with Lyme disease, California and Florida saw the largest absolute increases in positive test results. California found 483 infected patients in 2017, a 194.5 percent increase over 2015 levels. Florida found 501 infected patients in 2017, a 77 percent increase over 2015 levels.” (Quest 2018)

The Wall Street Journal (WSJ) recently reported on a study by the FAIR Health using their claims database that found that some states considered by the CDC to be low incidence reported far higher rates of insurance claims than suggested by surveillance data. Noting, for example, that "North Carolina reported 32 Lyme cases to the CDC in 2016 but in the same year made 88,539 health-care claims for a Lyme diagnosis. California reported 90 cases to the CDC but had 46,820 claims. Texas reported 31 cases to the CDC but had 31,129 claims. All three are considered low-incidence states." (McGinty 2018) A chart accompanying the article shows California and North Carolina as being among the states with the largest number of insurance claims. These states do not even make the top ten states identified by the CDC.

In addition, a research study of a rural subdivision in northern California found that 24% of the residents had positive Lyme tests, and 37% had definite or probable Lyme disease. (Lane 1992) Tick surveys of the area revealed that the nymphal tick infection rate averaged 13% (and as high as 41%), comparable to or higher than hyperendemic areas in the northeastern U.S. (Talleklint-Eisen 1999) This is significant because although the guidelines introduction (page 2, lines 60-61) identifies "three expanding regions: the northeastern states from Virginia to eastern Canada; the upper Midwest, particularly Wisconsin and Minnesota; and in northern California," other portions of the report mention only the northeast. Most states do not have the good fortune or funding to have a talented epidemiologist like Dr. Robert Lane to conduct tick studies in the region, not to mention the role of birds and climate change in the rapid spread of ticks to new areas. (Sonenshine 2018)

The fact that these independent data points are so incongruent tells us that it is time to abandon the "diagnosis by geography" aspects of the proposed guidelines (e.g. EM rash, STARI, prophylaxis). It should be noted that no other country imposes a geographical restriction on Lyme disease. For example, the NICE guidelines do not include geographic diagnosis restrictions. The inappropriate use of inaccurate geographic endemicity data based on CDC surveillance for diagnosis will leave many patients with Lyme disease undiagnosed and untreated. The greatest opportunity in Lyme disease is to achieve earlier diagnosis and treatment for those who contract the disease to prevent the development of persistent Lyme disease.

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IDSA proposed guidelines GRADE assessments conflict with those of NICE and ILADS

Summaries of evidence under GRADE should be very similar as it provides a uniform scheme for evidence assessment. (Andrews 2013) Hence, the fact that the evidence assessments under the proposed guidelines are discordant with those of both NICE and ILADS GRADE assessment indicates that the IDSA assessment has missed the mark. (NICE 2018, Cameron 2014) In particular, the IDSA evidence assessments incorrectly rank evidence as being of higher quality than the other assessments of evidence. Note that the NICE and ILADS guidelines assessments align. A portion of this problem is that the IDSA proposed guidelines fail to downgrade evidence to reflect indirectness resulting from surrogate outcomes for patient important outcomes and for the European treatment studies on different bacteria.

References:

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Important Patient Subgroups and Omitted Clinical Questions

The questions posed fail to consider significant subgroups of patients with Lyme disease.

Early Non-EM Rash Lyme Disease

Significantly, the proposed guidelines fail to address how to diagnose or treat early Lyme disease when the patient does not present with an EM rash. The CDC estimates that approximately 30% of early Lyme patients do not have a rash. (Schwartz 2017) It is clear that diagnostic criteria for those with early Lyme disease who do not have an EM rash needs to be included so that these patients can be adequately diagnosed and treated.

NICE dealt with this issue by including a specific question regarding both early and late non-rash manifestations of Lyme disease. (NICE 2018) The proposed guidelines should include a question on this topic.

Recommendation: Include as new questions the following:

“What is the best method for diagnosing people who have non-specific symptoms that may be related to Lyme disease?”

“What is the most clinically effective treatment for people who have non-specific symptoms that may be related to Lyme disease?”

Late Lyme Disease with Non-Specific Symptoms

The proposed guidelines fail to address how to diagnose or treat late manifestations (signs or symptoms) of Lyme disease when the patient is not diagnosed and treated timely. The optimal diagnostic method and treatments with antibiotics or combination of antibiotics as well as duration of treatment are unknown. To our knowledge, no treatment studies have been conducted in this population.

Recommendation: Include as a new question the following:

“What is the most clinically effective treatment for people who have non-specific symptoms that may be related to Lyme disease who are diagnosed late in the disease?”

Lyme Encephalopathy

The proposed guidelines fail to address how to diagnose or treat Lyme encephalopathy which may include those with non-specific symptoms including disturbed cognitive function, (for example, memory loss), dizziness, fatigue headache, neck pain or stiffness, paraesthesia, and photophobia.

Recommendation: Include as a new question the following:

"What is the most clinically effective treatment for people who have Lyme encephalopathy?" **References:**

NICE guideline [NG95], Lyme disease (Published date: April 2018). https://www.nice.org.uk/guidance/ng95

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Development of Clinical Recommendations

Pg 8-9, lines 181-203

Most medical decisions involve trade-offs between the potential benefits of treatment and its associated harms. (Andrews GRADE 14: 2013) In GRADE, these trade-offs are between patient-important outcomes and undesirable outcomes. Consideration of trade-offs involves a number of factors a) the quality of evidence, b) the balance between desirable and undesirable effects, and c) patient values and preferences. (Guyatt 2008) If the quality of the evidence is low, strong recommendations should not be made. (Guyatt 2008) When advantages and disadvantages are closely balanced, a weak recommendation becomes appropriate. In addition, GRADE provides that "In situations where there is a large variability in values and preferences, it is less likely that a single recommendation would apply uniformly across all patients. If this is so, a weak recommendation is likely warranted." (Grade Handbook) The goal of each of these factors in GRADE is to allow room for clinical judgment and individualized care when it is appropriate.

The proposed guidelines fail to follow these GRADE principles. For example, the proposed guidelines make a strong recommendation regarding treatment of patients with prolonged symptoms of Lyme disease stating "for patients who have persistent or recurring non-specific symptoms such as fatigue, pain, or cognitive impairment following treatment for appropriately diagnosed Lyme disease, but who lack objective evidence of reinfection or treatment failure, we recommend against additional antibiotic therapy (Strong recommendation, moderate-quality evidence)." (Pages 61-62, lines 1425-1428) The accompanying comment provides: "Evidence of persistent infection or treatment failure would include objective signs of disease activity, such as arthritis, meningitis, or neuropathy). (Page 62, lines 1429-1430). The rationale cited for this conclusion is that "[t]his recommendation places a high value on avoiding harm due to unnecessary antibiotic exposure or to unnecessary IV access devices. The risks of these interventions were not matched by convincing evidence that antibiotics improved patients' symptom experiences or quality of life any better than placebo." (Page 63, lines 1469-72)

This approach and rationale does not comply with the requirements of GRADE. First, the evidence quality for retreatment has been evaluated as low by both NICE and ILADS GRADE assessment. While value assessments are expected to differ between GRADE assessments typically the evidence evaluation does not. Here the panel makes clear that it has not in fact followed GRADE but instead has adopted its own rules so that (pages 7-8, lines 170-179) "if the beneficial effects of the antibiotic regimen were uncertain, the undesirable outcome would usually be ranked higher in importance than if benefits were certain". This artificially inflates the evidence level assessment of studies with adverse effects above potential treatment benefits and is not permissible under GRADE.

It also supplants patient important outcomes (such as quality of life and symptom reduction) and with researcher important outcomes "objective signs. Similarly, it replaces patient values with panel values. The panel's obligation under

GRADE to evaluate the patient important outcomes, interventions, values, preferences and utilities requires that the panel integrate into the process of developing a recommendation, "how those affected by its recommendations assess the possible consequences". (GRADE Handbook) The IDSA CPG Handbook explains this clearly: "How much do those affected by the option value each of the outcomes in relation to the other outcomes (i.e., what is the relative importance of the outcomes)? Is there evidence to support those value judgments, or is there evidence of variability in those values that is large enough to lead to different decisions?" (IDSA Handbook)

GRADE provides that evidence is assessed based on patient-important outcomes, which, in this case, rank potential treatment benefits above adverse events. The panel is not permitted to elevate its own values over those of patients. Re-ranking of outcome important to prioritize "undesirable outcomes" to a level of "critical for decision-making" undermines the concept of "patient-important outcomes" and the evaluation of trade-offs that patients and clinicians would value in medical decision making. It is tantamount to substituting expert opinion for the GRADE process. However, as noted in GRADE, expert opinion is not a category of quality of evidence and panels are not entitled to substitute their values for those of patients. (GRADE Handbook)

Further, the justification for the recommendation against retreatment of persistent Lyme disease is that "[t]he risks of these interventions were not matched by convincing evidence that antibiotics improved patients' symptom experiences or quality of life any better than placebo." However, it is not the panel's role to be "convinced" about whether the potential benefits of treatment outweigh the risks when the quality of the evidence is low or the balance between desirable and undesirable effects is close. This again substitutes expert values for those of patients. That trade-off decision belongs to the patients and clinicians in the context of individualized care and must be based on their values. Similarly, it is not a matter of "consensus" as variation in patient values requires weak recommendations to allow clinical judgment and the consideration of individual patient values.

The IDSA CPG Handbook reinforces the fact that the outcomes and values used are those of the patient when it asks: "[h]ow is the balance of the magnitude of effects of benefits and harms when weighing the importance of these desirable and undesirable outcomes (based on typical patients' values and preferences)?". (IDSA Handbook) Because the balance between potential benefits and the risks of adverse events are balanced, this recommendation should have been a weak recommendation.

The utilities or the values held by patients for different trade-offs might be reflected in peer reviewed literature identifying such values (as the NICE and ILADS GRADE assessment do, for example) or through consultation with representative patients for those affected by the recommendation. Although this panel may have included patients on its panel, these patients do not represent the interests of patients in Lyme community. Hence, they are tokens and cannot represent "those affected" by the proposed guidelines or serve as their proxies. (IOM 2011)

Evidence of patients' values and interests are included in a number of publications about Lyme disease (Johnson 2011, 2014, 2018) as well as in both the NICE and ILADS GRADE assessments. (NICE 2018, Cameron 2014) Over 5,500 patients responded to a 2011 survey by LymeDisease.org about factors that would influence treatment choices, patients identified a number of highly individualized factors: the possibility of preventing disease progression, their level of functional impairment, the severity of their illness, the availability of alternative treatments, whether treatments have been beneficial in the past, their ability to tolerate treatment side effects, and the cost of the treatment. (LymeDisease.org 2011) These answers indicate that patients' values and preferences vary considerably when deciding whether the benefits of pursuing treatment outweigh its potential harms based on their individual circumstances and preferences. Weak recommendations are appropriate when there is substantial variation in patient preferences and values. (Guyatt 2008)

The strength of the recommendation should reflect the strength of the evidence as well as the relative weight of the treatment trade-offs and variation among patients in values and preferences. The weak recommendation compelled by

GRADE here reflects the need for clinical judgment on the part of the physician and the consideration of patient preferences and values in medical decision making. The trade-offs determinations are made in the context of the factors that patients and their clinician deem relevant in the decision-making process, including current quality of life, severity of symptoms, and functional impairment. (GRADE Handbook) Finally, it should reflect the need for individualized treatment in the face of heterogeneity of patient presentation (quality of illness, severity of symptoms, functional impairment), treatment response, and patient values. As the NAM brief on trustworthy guidelines notes: "Rather than dictating a one-size-fits-all approach to patient care, clinical practice guidelines offer an evaluation of the quality of the relevant scientific literature and an assessment of the likely benefits and harms of a particular treatment." (IOM Brief 2011)

Recommendation: The proposed IDSA guidelines evidence assessment, evaluation, and recommendations should conform with the identified critically important patient outcomes: quality of life, cure (resolution of symptoms), reduction of clinical symptoms and avoidance of symptom relapse. Adverse events should not be considered critically important. Both the NICE and ILADS analysis rank adverse events lower in patient importance than potential treatment benefits (such as improving quality of life etc.). This aligns with the patient survey results as well. This means that these potential benefits will carry more weight in the trade-offs analysis compared to adverse events in determining recommendations. The guidelines panel needs to correctly identify the quality of the evidence in the assessment on retreatment of prolonged symptoms of Lyme disease as low using patient-important outcomes, expressly recognize that the trade-offs between risks and benefits is uncertain and close, acknowledge the variation in patient values and preferences, and provide for a weak recommendation here to permit individualized care. The process described in lines 170-179 is not permissible under GRADE. Accordingly, that section of the guidelines should be deleted.

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Revision Process

Pg 9, lines 204-215

In accordance with the NAM requirements, this panel should "consider all external reviewer comments and keep a written record of the rationale for modifying or not modifying a CPG in response to reviewers' comments." (IOM Standard 7 2011) **References:**

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General principles

Diagnostic Testing for Lyme Disease

Page 10, lines 225 – 243:

Any discussion of diagnostic testing should reflect patient-centered values regarding test characteristics. Per the NICE GRADE assessment on diagnostic testing, sensitivity is the only critical outcome; specificity, positive and negative predictive values and receiver operating characteristic (ROC) curve or area under curve are important. (NICE 2018) This outcome ranking reflects the goal of reducing false negative results, which often lead to diagnostic, and subsequently, therapeutic delays. Critical patient values for Lyme disease treatment include: 1) Return to pre-Lyme health status (cure), 2) Reduction of symptoms, 3) Quality of life (any validated measure), and 4) Prevention of symptom relapse. (NICE 2108; Cameron 2014) Therapeutic delays result in poorer outcomes; (Aucott 2009; Cameron 2007; Fallon 2008; Shadick 1994) therefore, avoiding false negative results is the critical testing outcome for patients.

The assertion that serologic testing is highly sensitive in non-cutaneous manifestations is only partially correct. As demonstrated in the two papers cited by the panel, (Molins 2016; Steere 2008) the two-tier diagnostic algorithm works well for many acute disseminated disease manifestations and Lyme arthritis. However, none of the samples used by Molins came from patients with late neurologic disease and the Steere sample panel had only two. Although two-tier testing appears to be sensitive for Lyme arthritis, it is incorrect to generalize those findings to late neurologic Lyme disease. Therefore, these papers cannot inform as to the sensitivity of serology in late neurologic Lyme disease.

When considering the reported sensitivity of available tests, it is important to acknowledge that the process for generating sensitivity data for serologic tests is flawed. Tests evaluated under the FDA-clearance process measure their sensitivity against known sample panels. Samples qualified as "late disease" come from cases meeting the CDC surveillance case definition, which includes two-tier positivity. (Molins 2016; Steere 2008) This produces a pre-selection bias favoring a finding of high sensitivity on these bench samples. Whether this translates to clinically validated sensitivity is unknown. All of the clinically available serologic tests have been cleared through the FDA 510(k) process; (FDA website) there are no FDA-approved serologic tests for Lyme disease. The distinction is important. In contrast to FDA-approved tests, cleared tests are not required to demonstrate clinical validity. (FDA 510(k) process)

The NICE guidelines panel noted the following regarding reported sensitivity from case-control studies: "There is a strong potential of the results being an overestimate of the true sensitivity and specificity values due to the way case-control studies are conducted. Populations in case-control studies tend to differ from 'true populations' found in clinical practice as cases tend to be more severely ill than the average patient population in clinical practice in order to fit inclusion criteria of studies." (NICE 2018)

IgG seropositivity requires specimens to produce positive results on a step 1 EIA and a subsequent step 2 Western blot, using the CDC Western blot interpretive criteria. (CDC 1995) IgG interpretation criteria are based on the work of Dressler. (Dressler 1993) Although the 5 of 10 bands criteria is highly specific, it is insensitive for neurologic disease. (Dressler 1993) Dressler conducted a prospective study using the 5 of 10 band criteria in his well-characterized patients who had either active neuroborreliosis or active arthritis. Although 96% (24/25) of the arthritis patients were Western

blot positive, sensitivity was considerably lower, 72% (21/29) for the neuroborreliosis group. Given the performance of the Western blot criteria in Dressler's patient group, claims of very high sensitivity for neuroborreliosis based on bench samples are unlikely to be clinically substantiated. Examples of seronegativity in late Lyme disease are not rare. (Coyle 1995; Lawrence1995; Logigian 1999; Ang 2011)

In sequential diagnostic testing schemes, step 1 tests are selected on the basis of sensitivity and step 2 tests on the basis of specificity. Therefore, the overall sensitivity of the combined tests is lower than the sensitivity of either test and it is governed by the sensitivity of the second step test as true positives from the first test will be rejected if the second test is insensitive. Specificity, on the other hand, is heightened by sequential testing. Step 2 cannot generate new false positives and is likely to reject the false positives from step 1.

With regard for Lyme disease testing, and contrary to the nature of the two-tier testing scheme noted above, patients and their treating clinicians prioritize sensitivity over specificity. (NICE 2018) For the individual, the risks posed by falsely negative results from insensitive tests is greater than the risks of false positives from nonspecific tests. While it is true that false positive results may lead to unnecessary exposure to antibiotics, such exposure would be relatively brief (several weeks). Given the general safety parameters of the antibiotics commonly used in Lyme disease, (Cameron 2014; NICE 2018) the exposure risk would be small. Clinicians may underestimate the pre-test likelihood of disease as many frequently fail to recognize many of the clinical features and epidemiologic risks of Lyme disease that patients present with. (Aucott 2009) In such instances, positive results may be erroneously labeled as "false".

In contrast, false negative results are likely to lead to substantial diagnostic delays. Having once "ruled out" a disease, many clinicians find it difficult to reconsider it. (Groopman 2007) The list of differential diagnoses for Lyme disease is substantial and could take many weeks or more to work through while the infection goes untreated. For this reason, interpretation of test results must be done within the context of the individual patient's clinical history and exam and patients and clinicians should be informed of "the limitations of tests, in particular of false negative results and the importance of clinical judgment." (NICE 2018)

While seronegativity in actively infected patients can be due to testing before antibody production has sufficiently developed and/or poor test performance, there are other potential causes. Seronegativity can be due to the formation of immune complexes, leading to a lack of available antibodies to interact with the test antigens. (Schutzer 1990). Patients who receive ineffective antibiotic therapy early in disease but remain ill may be seronegative if the course of antibiotics sufficiently reduced the antigenic load such that the humoral response never matured; (Dattwyler 1988) Examples of post-treatment seronegative Lyme disease are not rare. (Lawrence 1995; Logigian 1999; Luft 1996) Seronegativity in patients with longstanding untreated Lyme disease may be the result of a waning immune response. This has been demonstrated in untreated monkeys. (Embers 2012; Embers 2017) Although positive on C6 ELISA testing early in disease, this initial response lessened over time. While necropsy clearly demonstrated the continued presence of *B. burgdorferi* in the tissues on the untreated animals, their C6 ELISA results had reverted to normal. (Embers 2012; Embers 2017)

NICE guidelines recommend repeat antibody testing where the clinical suspicion for Lyme disease is high and Western blot testing in patients with 12 or more weeks of unexplained symptoms.

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Pages 10-11, lines 244-263
Clinicians are allowed to use clinical judgment in reaching a diagnosis of re-infection in a seropositive patient with a past history of Lyme disease and new Lyme-compatible symptoms but the use of clinical judgment is not extended to seronegative patients with Lyme-compatible clinical and epidemiologic features. This inconsistency is concerning as it may lead to diagnostic and therapeutic delays.

Although the antibody response is "expected" to expand in early disease, there are no supporting references. Therefore, the lack of expansion should not be used to rule out the diagnosis.

The existence and significance of ongoing or recurrent IgM response in patients without evidence of reinfection is missing from the discussion. The immune response to *Borrelia burgdorferi* is dynamic and evolves over time (Aguero-Rosenfeld 1996; Craft 1986) Although the CDC algorithm for laboratory testing does not consider positive IgM results beyond the first 30 days of illness, IgM seropositivity in the setting of persistent manifestations/prolonged symptoms following antibiotic treatment is not unusual and may represent chronic activity. (Fallon 2008; Fallon 2014) One NIH-sponsored retreatment trial only enrolled subjects who satisfied the CDC surveillance case definition at the time of their original diagnosis and who were IgG Western blot positive at enrollment. (Fallon 2008) In this cohort, 49% were also IgM Western blot positive. Specimens from patients with persistent manifestations following antibiotic treatment were used in comparative study of serologic results from four laboratories. (Fallon 2014) The lab that had 100% specificity on IgM testing found that 16% of the patients were IgM positive. The underlying mechanism for the persistent IgM response is unknown but could be indicative of ongoing *B. burgdorferi* infection. Findings from a murine model of Lyme disease support this concept. (Hastey 2012) In this model, the bacteria actively entered lymph nodes and disrupted the formation of germinal centers such that long-acting plasma cells were not formed, antibody class switching did not occur and IgM production persisted.

Research gap: the significance of persistent or recurrent IgM antibodies in patients who have been ill for > 4 weeks or who have persistent manifestations of Lyme disease despite prior antibiotic therapy for their stage of illness

Page 12, lines 270-285
Per the NICE GRADE assessment on diagnostic testing, sensitivity is the only critical outcome; specificity, positive and negative predictive values and receiver operating characteristic (ROC) curve or area under curve are important. (NICE 2018) This outcome ranking reflects the goal of reducing false negative results, which often lead to diagnostic, and subsequently, therapeutic delays.

Lab developed tests in CLIA labs are required to have validation studies on file. Labs providing service to New York residents must have adequate validation studies approved by New York Department of Health. In contrast, labs offering FDA-cleared tests have to provide little validation despite the fact that these tests were not clinically validated before coming to market.

There is sufficient evidence to assert that some patients with Lyme disease would not be identified were it not for the use of non-standard Western blot interpretation criteria. Several investigators have recommended using modified Western blot interpretation criteria to improve sensitivity, (Engstrom 1995; Hilton 1996; Sivak 1996; Tilton 1997) such approaches are discouraged (page 12, line 282). Yet elsewhere in the draft (pages 26, lines 617-620), it is suggested that one could consider using the non-CDC testing algorithm of sequential EIAs. The lack of internal consistency regarding adherence to CDC protocol is concerning.

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Treatment of Lyme Disease

Page 14, lines 315-324

This section reads as a recommendation and, in fact, it is generally a rewording of Recommendation 5, page 1105 of the 2006 IDSA Lyme guidelines:

"5. Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are not recommended for treatment of patients with any manifestation of Lyme disease: first generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G, combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), long-term antibiotic therapy, anti-Bartonella therapies, hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, specific nutritional supplements, and others (see table 4) (EIII)."(Wormser 2006)

As such, the agents that the panel recommends against using should be subject to a GRADE evidence assessment rather than relying on unsupported panel opinion masquerading as statements of fact. The lack of transparency here is appalling and undermines the credibility of the entire guidelines document.

Additionally, the unlabeled recommendation ignores substantial work in these areas, including bench, animal and innovative clinical research that has been published after the last set of IDSA Lyme guidelines. (Citera 2017; Feng 2014; Feng 2015; Feng 2016; Feng 2019; Liegner 2019; Sapi 2012; Sapi 2016; Sharma 2015) Rather than dismiss out of hand, the panel should recommend research into the roles of morphologic variants, biofilms, and persister cells in treatment failure. Similarly, the panel should support the exploration of innovative therapies that can prevent and/or treat therapeutic failures.

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Tick Bites Prevention and Prophylaxis of Lyme Disease

Who should receive antibiotic prophylaxis to prevent Lyme disease following presentation with a tick bite?

Page 21, lines 492-495

This strong recommendation to offer antibiotic prophylaxis only to adults and children within 72 hours of a high-risk blacklegged tick bite is said to be made on high quality evidence yet the ILADS GRADE assessment of the evidence rated the quality of the evidence to be very low. (Cameron 2014) Given the disparity between the ILADS evidence rating and that of the proposed guidelines, the proposed guidelines either need to appropriately downgrade the evidence rating or explain why its GRADE-based assessment of the evidence is considerably higher.

A careful assessment of the underlying evidence demonstrates that the "high quality" strength rating is inflated. Many of the studies included in the summary of evidence table (pages 23-31 of the supplement) were not conducted in the target population – North American patients who were bitten by an *Ixodes scapularis* or *I. pacificus* tick. Of the 14 listed studies, 5 were European, 1 was done in an animal model, 2 were tick infection surveys (1 of these was a systematic review), 1 was a cost effectiveness study, and 2 were cross-sectional human and animal studies conducted in North America to calculate feeding times. It is incorrect to assume that European studies, which investigated a different tick vector and Borrelial species than what are found in North America, (Rudenko 2011) are generalizable to North American patients. Thus, only 6 studies specifically addressed the target population and none examined *I. pacificus* bites in humans. The evidence should be downgraded for indirectness.

The design of the largest of the North American human studies (Nadelman 2001) only evaluated the effectiveness of oral doxycycline prophylaxis to reduce the incidence of an erythema migrans (EM) lesion at the bite site, not the prevention of Lyme disease. (Cameron 2014) Erythema migrans is not an appropriate surrogate for Lyme disease. (Cameron 2104) Additionally, it is not the outcome that is most important to patients. Critical patient-centered outcomes, include 1) prevention of Lyme disease, 2) prevention of persistent manifestations of Lyme disease, 3) quality of life (any validated measure). (Cameron 2014) Adverse events are important but not critical patient-centered outcomes.
Given the numerous and substantial limitations noted above, the quality rating should have been down-graded at least two levels for indirectness.

Furthermore, the portion of the recommendation that deals with the timing of the initiation of antibody prophylaxis does not align with the findings by Piesman et al. (Piesman 2012) It is unclear why this study was not included in the search evidence. In that mouse model, initiating antibiotics more than 48 hours post-tick removal was ineffective for preventing Lyme disease. (Piesman 2012) Thus, the portion of the recommendation that allows for prophylaxis within 72 hours should be revised to "within 48 hours".

Finally, the high-risk criterion imposes a restriction that may be difficult for clinicians to overcome. Establishing with "high certainty" that a specific bite is high-risk will pose a significant challenge to clinicians in many areas of the country, particularly areas where Lyme disease is an emerging rather than well-established disease. Data regarding the prevalence of *B. burgdorferi* infected ticks is often unavailable or no longer current. (Johnson TL 2018; Talleklint 1999) National and/or state-wide maps used to inform clinicians about endemicity are often based on insufficient data and paint with too broad a brush, failing to illustrate that infection rates can vary significantly between locales. (Johnson TL 2018; Talleklint 1999) The reliance on CDC geographic surveillance data for estimating risk will not prove useful as surveillance data under-represents a large portion of the clinical population of patients who have Lyme disease. Two reports which drew on very large datasets indicate that CDC surveillance cases do not accurately reflect the geographic distribution of the disease. (Quest 2018; McGinty 2018) Quest lab reported positive Lyme disease serology in every state

in the nation. Of the 28 states with a large number of positive lab tests, 20 are classified by the CDC as low incidence states. (Quest 2018) Faced with uncertain epidemiologic and vector data, many clinicians will be unable to define a bite as high-risk with high-certainty. If clinicians follow this recommendation as written, the impact is clear – patients who would benefit from antibiotic prophylaxis will be denied this intervention, putting them at risk for Lyme disease.

In reaching a strong recommendation the guideline panel is violating basic GRADE guidance governing how the strength of a recommendation is chosen. Specifically, a weak recommendation is called for when: the gradient between benefits and harms is narrow or unclear, the evidence quality is low, and patient values and preferences vary significantly or are uncertain. (Andrews 2013b) All three of these are operating with regard to antibiotic prophylaxis, making the strong recommendation to offer prophylaxis for only highly certain, high-risk tick bites untenable.

Additionally, the strong recommendation is not in keeping with the IDSA Handbook for Clinical Practice Guidelines Development available on the IDSA website. From page 51:

> *"When deciding the direction and the SoR, an important step is to assess our confidence in the assumed patients' values and preferences. Two factors need to be considered: 1) Variability among patients' values and preferences: In situations where there is a large variability in values and preferences, it is less likely that a single recommendation would apply uniformly across all patients. If this is so, a weak recommendation is likely warranted. 2) Certainty concerning values and preferences: The greater the uncertainty around the patients' values and preferences, the more likely a weak recommendation is preferred.*

References:

Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013 Jul;66(7):726-35. doi: 10.1016/j.jclinepi.2013.02.003

Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900.

IDSA Handbook on Clinical Practice Guideline Development. Available at: https://www.idsociety.org/globalassets/idsa/topics-of-interest/lyme/idsa-handbook-on-cpg-development-10.15.pdf. Last accessed August 6, 2019.McGinty, J., Lyme Disease: An Even Bigger Threat Than You Think: A look at why cases of the tick-borne illness are undercounted. Wall Street Journal (June 22, 2018). https://www.wsj.com/articles/lyme-disease-an-even-bigger-threat-than-you-think-1529672401,

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Rudenko N, Golovchenko M, Grubhoffer L, Oliver, Jr. JH. Updates on Borrelia burgdorferi sensu lato complex with respect to public health. Ticks Tick Borne Dis. 2011 Sep; 2(3): 123–128.

Quest http://newsroom.questdiagnostics.com/2018-07-30-New-Quest-Diagnostics-Data-Shows-Lyme-Disease-Prevalence-Increasing-and-is-Now-Present-in-New-U-S-States.

Page 21, lines 495-499

Two of the three criteria for establishing that a bite is "high risk" – prevalence of tick infection rate of 20% or higher and attachment time equal to or greater than 36 hours, appear to be arbitrary and do not reflect what is known about calculating the risk from a specific bite.

If prophylaxis decisions are based on a risk-benefit assessment, these hard cut-offs will lead to high-risk bites going unprophylaxed. The calculated risk posed by a specific bite equals the prevalence of *B. burgdorferi* in the local tick population multiplied by the risk of disease transmission, (which is based on the tick attachment time). Thus, when one

variable is well above the required threshold it may offset the other being below its threshold. For example, if a bite is sustained in an area where the prevalence of infected ticks is 10% and the tick is attached for 72 hours (correlating to an 80% risk of transmission), the overall risk is 8%. This is greater than the risk posed by a bite in a 20% prevalence area with a 48-hour attachment time (20% transmission risk) and overall risk of 4%. Therefore, the recommendation and supporting language should encourage clinicians to calculate a bite-specific risk rather than rely on arbitrary criteria.

Pages 21-22, lines 503-510

Comment: State-wide data regarding the prevalence of *B. burgdorferi* infected ticks is often unavailable or no longer current and infection rates can vary significantly between locales in a given state. (Johnson TL 2018; Talleklint 1999) Thus, within a high-incidence state there can be tick populations with low infection rates. (Johnson TL 2018) Perhaps more importantly, clinicians should be aware that areas within a low-incidence state can be highly endemic for Lyme disease. (Johnson TL 2018; Talleklint 1999)

References:

Johnson TL, Graham CB, Maes SE, Hojgaard A, Fleshman A, Boegler KA, et al. Prevalence and distribution of seven human pathogens in host-seeking Ixodes scapularis (Acari: Ixodidae) nymphs in Minnesota, USA. Ticks Tick Borne Dis. 2018 Sep;9(6):1499-1507. doi: 10.1016/j.ttbdis.2018.07.009

Talleklint-Eisen L, Lane RS. Variation in the Density of Questing Ixodes pacificus (Acari: Ixodidae) Nymphs Infected with Borrelia burgdorferi at Different Spatial Scales in California. J Parasitol 1999;85(5):824-31.

Page 22, lines 525-526

It is suggested that antibiotic prophylaxis of *Ixodes* tick bites that do not meet the high-risk criteria may not be beneficial and could result in adverse events. While that is correct, it is equally true that prophylaxis in some of those situations may be beneficial and not lead to adverse events. Situations in which the risk-benefit assessment is uncertain call for shared decision-making, (Elwyn 2012) which is driven by the patient's goals and values. Critical patient-centered outcomes are the prevention of all early and late manifestations of Lyme disease. (Cameron 2014) Adverse events are important patient-centered outcomes. (Cameron 2014) Given the uncertainty of the evidence, the failure of the recommendation to allow for therapeutic options in such situations is not in keeping with GRADE-based approach for developing treatment recommendations. (Andrews 2013)

References:

Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013 Jul;66(7):726-35. doi: 10.1016/j.jclinepi.2013.02.003 (b)

Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900.

Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared decision making: a model for clinical practice. J Gen Intern Med. 2012 Oct;27(10):1361-7.

Johnson TL, Graham CB, Maes SE, Hojgaard A, Fleshman A, Boegler KA, et al. Prevalence and distribution of seven human pathogens in host-seeking Ixodes scapularis (Acari: Ixodidae) nymphs in Minnesota, USA. Ticks Tick Borne Dis. 2018 Sep;9(6):1499-1507. doi: 10.1016/j.ttbdis.2018.07.009

Talleklint-Eisen L, Lane RS. Variation in the Density of Questing Ixodes pacificus (Acari: Ixodidae) Nymphs Infected with Borrelia burgdorferi at Different Spatial Scales in California. J Parasitol 1999;85(5):824-31.

What is the preferred antibiotic regimen for the chemoprophylaxis of Lyme disease following a high-risk bite?

Page 24, Lines 560-562

The strong recommendation for a single dose of doxycycline within 72 hours of tick removal is said to be based on moderate-quality evidence but this strength rating is inflated. The ILADS GRADE assessment of the evidence rated the quality of the evidence to be very low. (Cameron 2014) Given the disparity between the ILADS evidence rating and that of the proposed guidelines, the proposed guidelines either need to appropriately downgrade the evidence rating or explain why its GRADE-based assessment of the evidence is considerably higher.

Critical patient-centered outcomes for prophylaxis of tick bites include: 1) prevention of early and late manifestations of Lyme disease, 2) prevention of persistent manifestations of Lyme disease, 3) quality of life (any validated measure), and 4) not abrogating the immune response to *B. burgdorferi*. (Cameron 2014) Adverse events, other than not abrogating the immune response, are important but not critical patient-centered outcomes. (Cameron 2914)

The evidence is indirect on multiple points. First, the question does not directly address patient-centered outcomes. There is an important distinction between asking about actual effectiveness versus comparing the relative effectiveness of different regimens. As asked, the question assumes that at least one of the studied regimens is effective and safe but there is evidence to suggest that this may not be the case. (Zeidner 2004; Zeidner 2008) Mouse studies conducted by CDC researchers testing the utility of antibiotic prophylaxis demonstrated via necropsy that single dose doxycycline was only 43% effective. (Zeidner 2004) In the case of ticks being concurrently infected with *B. burgdorferi* and *A. phagocytophilum*, single dose doxycycline was only 20% effective for preventing Lyme disease and 30% for preventing anaplasmosis. (Zeidner 2008)

Most importantly, the available evidence only indirectly addresses the prevention of Lyme disease because it relies on surrogate outcomes. As noted on page 3, lines 62-66, *"Lyme disease is a clinically complex infection, and there can be a wide range of clinical latency after the infecting tick bite. Presentations include an early localized skin lesion at the site of the tick bite, and disseminated disease resulting in neuropathy, meningitis, cardiac conduction abnormalities, and arthritis. Clinical disease can manifest as early as days and as late as many months following an infectious tick bite."* However, for the purposes of this question, the associated evidence assessment tables (pages 32-36 of the supplement) restricted the clinical definition to "*Erythema Migrans and/or Flu-like symptoms of Febrile illness accompanied by seroconversion*". The revised definition is an inappropriate surrogate for all of Lyme disease. The sole trial that investigated the recommended regimen had an observation period of only six weeks. (Nadelman 2001) This is too short to detect many of the other clinical presentations noted above.

As noted in the evidence table, the findings in the Nadelman trial had serious imprecision.

For all of the above reasons, the evidence supporting single dose doxycycline should have been down-graded by at least two levels.

The recommendation for single dose doxycycline apparently failed to consider an important safety concern regarding failed therapy because this potential harm was not discussed. It should have been noted that the patient in the treatment arm of the single dose study who developed an EM lesion failed to satisfy two-tier testing on follow-up. (Nadelman 2001) Inducing a seronegative status could lead to diagnostic delays when patients who are treated in this manner present with non-EM manifestations of Lyme disease. (Maloney 2011) As noted earlier, not abrogating the immune response is a critical patient value. (Cameron 2014)

In reaching a strong recommendation for antibiotic prophylaxis with single dose doxycycline, the guideline panel is violating basic GRADE guidance governing how the strength of a recommendation is chosen. Specifically, a weak recommendation is called for when: the gradient between benefits and harms is narrow or unclear, the evidence quality

is low, and patient values and preferences vary significantly or are uncertain. (Andrews 2013b) All three of these are operating with regard to antibiotic prophylaxis, making the strong recommendation for single dose doxycycline untenable. More importantly, the relative ineffectiveness of single dose doxycycline and its potential to abrogate the immune response requires a weak recommendation against single dose doxycycline.

References:

Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014; 12(9):1103-35. doi: 10.1586/14787210.2014.940900.

Maloney EL. The management of Ixodes scapularis bites in the upper Midwest. WMJ. 2011 Apr;110(2):78-81; quiz 85.

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

Zeidner N, Brandt KS, Dadey E, Dolan MC, Happ C, Piesman J. Sustained release formulation of doxycycline hyclate for prophylaxis of tick bite infection in a murine model of Lyme borreliosis. Antimicrob Agents Chemother 2004;48:2697-2699.

Zeidner N, Massung R, Dolan M, et al. A sustained-release formulation of doxycycline hyclate (Atridox) prevents simultaneous infection of Anaplasma phagocytophilum and Borrelia burgdorferi transmitted by tick bite. J Med Microbio. 2008;57:463-468.

Page 24, lines 570-571

The draft language is a bit misleading. While there were 1082 total subjects, only 539 were treated with placebo. Although it is correct that only 3% of the placebo-treated subjects developed Lyme disease, without learning of additional details about these relatively old studies, clinicians may underestimate the current risk of contracting Lyme disease. Of the four cited trials, two did not test ticks for infection. (Agre 1993; Nadelman 2001) In the smallest of the two studies that did test ticks, only 21/56 ticks (38%) were suitable for testing; (Costello 1989) the infection rate was 29%. In the larger study 344/387 (89%) ticks were tested and the infection rate was much lower – 15%. (Shapiro 1992) The low infection rate in this larger trial strongly influences the placebo risk. Given that *Ixodes* populations in many areas of the country have infection rates well above 20%, it is likely that the risk of untreated tick bites in these areas surpasses the cut-off for empiric treatment established by Magid and colleagues. (Magid 1992)

References:

Agre F, Schwartz R. The value of early treatment of deer tick bites for the prevention of Lyme disease. Am J Dis Child. 1993;147:945-947.

Costello C, Steere A, Pinkerton R, Feder H Jr. A prospective study of tick bites in an endemic area for Lyme disease. J Infect Dis. 1989;159:136-139.

Magid D, Schwartz B, Craft J, Schwartz JS. Prevention of Lyme disease after tick bites. A cost-effectiveness analysis. N Engl J Med. 1992 Aug 20;327(8):534-41.

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

Shapiro E, Gerber M, Holabird N, et al. A controlled trial of antimicrobial prophylaxis for Lyme disease after deer-tick bites. N Engl J Med. 1992;327:1769-1773.

Early localized Lyme disease (erythema migrans)

Page 25, line 585

Early localized Lyme disease is not synonymous with erythema migrans (EM) as some patients with early localized disease present with flu-like symptoms without an accompanying EM. It is important that clinicians be made aware that

there is great uncertainty as to whether diagnostic and treatment studies of EM patients are generalizable to early Lyme disease patients who lack an EM. According to the CDC surveillance case data, 30% of reported cases lacked an EM rash. (Schwartz 2017)

In contrast to the NICE guidelines, (NICE 2018) the current draft offers no guidance on this clinically important topic. The guidelines should remind clinicians that a flu-like illness will be the only manifestation of early disease in a significant proportion of patients and that a clinical diagnosis of Lyme disease is warranted in situations where there has been a known blacklegged tick bite or potential tick exposure. (Steere 2003) Furthermore, the guidelines should inform clinicians about the lack of trial evidence for non-EM clinical presentations of early Lyme disease. Although the certainty regarding the effectiveness of antibiotic treatment with front-line oral agents for EM presentations is very low, (Cameron 2014; NICE 2018) the potential benefits for non-EM early disease (cure, prevention of disease progression and relapse, quality of life) are likely to outweigh the risks of adverse events. (Steere 2003a; Steere 2003b) Thus, a recommendation for treatment should be made.

References:

Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900.

National Institute for Health and Care Excellence. Lyme disease: diagnosis and management [D] Evidence review for the management of erythema migrans NICE guideline 95 Evidence review April 2018. https://www.nice.org.uk/guidance/ng95/evidence. Accessed on July 21,2019.

Schwartz AM, Hinckley AF, Mead PS, Hook SA, Kugeler KJ. Surveillance for Lyme Disease - United States, 2008-2015. MMWR Surveill Summ. 2017, 66(22),1 –12, doi: 10.15585/mmwr.ss6622a1.

Steere AC (a), Dhar A, Hernandez J, Fischer PA, Sikand VK, Schoen RT, Nowakowski J, McHugh G, Persing DH. Systemic symptoms without erythema migrans as the presenting picture of early Lyme disease.Am J Med. 2003 Jan;114(1):58-62.

Steere AC (b), Sikand VK. The presenting manifestations of Lyme disease and the outcomes of treatment. N Engl J Med. 2003 Jun 12;348(24):2472-4.

What is the preferred diagnostic testing strategy for erythema migrans?

Page 25, lines 595-598

As noted by NICE, sensitivity is the only critical patient-centered diagnostic outcome; specificity, positive and negative predictive values and receiver operating characteristic (ROC) curve or area under curve are important diagnostic outcomes. (NICE 2018a) As two-tier testing is insensitive in early disease, the panel is correct to recommend that clinicians make clinical judgments with respect to the diagnosis of erythema migrans rather than relying on laboratory testing.

The clinical diagnosis of erythema migrans should rest on potential exposure to infected ticks. However, it is overly restrictive to require, as the added comment does, that the diagnosis can only be made in known endemic areas. Tick ranges are expanding rapidly and public health department statistics on actual endemicity naturally lag behind real-world experience. (Eisen 2016) It is crucial to recognize that low endemicity at a state-wide level, due to large areas of low endemicity, can mask focal areas of high endemicity. Infection rates across various locales in California bear this out. (Eisen 2017) Limiting the clinical diagnosis of EM in this way will lead to missed and delayed diagnoses. While serologic testing of EM patients in low endemic areas could pick up some of the missing, the sensitivity of two-tier testing is too low to make this a plausible safeguard against the underdiagnosis of EM. (NICE 2018b)

Both NICE and ILADS include these critical patient-centered outcomes: 1) Return to pre-Lyme health status (cure), 2)

Reduction of symptoms, 3) Quality of life (any validated measure), and 4) Prevention of symptom relapse. (Cameron 2014; NICE 2108b) As NICE makes clear, adverse events may be important to patients but they are not critically important. (NICE 2018b) Hence, adverse events are relatively less important than the potential benefits of treatment. The potential exposure to a short course of antibiotics that ultimately proves to be unnecessary is a trade-off that many patients are willing to make.

In making a strong recommendation regarding the clinical diagnosis of erythema migrans that imposes restrictive epidemiologic data that is often unknown or unavailable to clinicians, the guideline panel is violating basic GRADE guidance governing how the strength of a recommendation is chosen. Specifically, a weak recommendation is called for when: the gradient between benefits and harms is narrow or unclear, the evidence quality is low, and patient values and preferences vary significantly or are uncertain. (Andrews 2013) All three of these are operating with regard to restricting the clinical diagnosis of erythema migrans to highly endemic areas, making the strong recommendation untenable. Thus, the strength of the recommendation should be reduced to "weak" and/or the epidemiologic aspect of the recommendation removed.

References:

Eisen RJ, Eisen L Beard CB. County-Scale Distribution of Ixodes scapularis and Ixodes pacificus (Acari: Ixodidae) in the Continental United States. J Med Entomol. 2016 Mar;53(2):349-86.

Eisen RJ, Clark RJ, Monaghan AJ, Eisen L, Delorey MJ, Beard CB. Host-Seeking Phenology of Ixodes pacificus (Acari: Ixodidae) Nymphs in Northwestern California in Relation to Calendar Week, Woodland Type, and Weather Conditions.J Med Entomol. 2017 Jan;54(1):125-131. doi: 10.1093/jme/tjw155.

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National Institute for Health and Care Excellence, (a). Lyme disease: diagnosis and management [C] Evidence reviews for diagnostic tests. NICE guideline 95 Diagnostic evidence review April 2018 https://www.nice.org.uk/guidance/ng95/evidence. Accessed on Aug 5,2019.

National Institute for Health and Care Excellence, (b). Lyme disease: diagnosis and management [D] Evidence review for the management of erythema migrans NICE guideline 95 Evidence review April 2018. https://www.nice.org.uk/guidance/ng95/evidence. Accessed on July 21,2019.

Page 26-27, lines 617-622

Patient-centered diagnostic outcomes prioritize test sensitivity over specificity as this will lead to fewer people being denied antibiotics when they are most effective. (NICE 2018a) This passage acknowledges the insensitivity of conventional two-tier testing in early Lyme disease and identifies a modified testing approach with increased sensitivity. However, the passage goes on to suggests that the degree of improved sensitivity achieved via a modified two-tier methodology (sequential EIAs) is driven by which particular tests were used. If the likelihood of positive results is indeed manufacturer-dependent, it underscores the inaccuracies and poor reproducibility of available serologic assays.

Given the limitations of two-tier testing and the modified serologic testing approach in early, untreated disease and convalescence, the guidelines should remind clinicians and patients that despite negative test results they need to be mindful of the ongoing possibility of Lyme disease. If the suspicion for Lyme disease remains, testing should be repeated in 4-6 weeks. (NICE 2018b)

References:

National Institute for Health and Care Excellence, (a). Lyme disease: diagnosis and management [D] Evidence review for the management of erythema migrans NICE guideline 95 Evidence review April 2018. https://www.nice.org.uk/guidance/ng95/evidence. Accessed on July 21,2019

National Institute for Health and Care Excellence, (b). Lyme disease: diagnosis and management [C] Evidence reviews for diagnostic tests. NICE guideline 95 Diagnostic evidence review April 2018 https://www.nice.org.uk/guidance/ng95/evidence. Accessed on Aug 5,2019.

What are the preferred antibiotic regimens for the treatment of erythema migrans?

Page 28, line 663

The strength of the evidence supporting this recommendation is inflated. The NICE and ILADS guidelines rated the evidence quality as low or very low. (NICE 2018; Cameron 2014) Given the disparity between the NICE and ILADS evidence rating and that of the proposed guidelines, the proposed guidelines either need to appropriately downgrade the evidence rating for these trials or explain why its assessment of the evidence is considerably higher than other sources.

Critical patient-centered outcomes include: 1) Return to pre-Lyme health status, 2) Prevention of persistent manifestations of Lyme disease, 3) Quality of life (any validated measure), 4) Prevention of EM relapse, 5) Resolution of EM and 6) reduction of EM symptoms. (NICE 2018; Cameron 2014) Adverse events are important patient-centered outcomes. (NICE 2018; Cameron 2014) The trials cited in the evidence assessment tables generally did not evaluate the critical outcomes head-on. Instead they used surrogate outcomes, such as "Patients experiencing objective findings of Lyme disease (at 6 months and beyond)". (Arnez 1999; Arnez 2002; Barsic 2000; Dattwyler 1990; Eliassen 2018; Eppes 2002; Luft 1996; Luger 1995; Massarotti 1992; Nadelman 1992; Strle 1992; Strle 1993; Strle 1996; Weber 1993) As such, all of the evidence should be downgraded for indirectness. Of note, a more recent US trial by Aucott used quality of life, not a surrogate, as the outcome of interest. (Aucott 2013)

Although "Patients experiencing objective findings of Lyme disease (at 6 months and beyond)" is an inadequate surrogate for quality of life, it is useful to look at evidence strength ratings within the eight assessment tables for this outcome. While the cefuroxime/amoxicillin and the azithromycin vs. amoxicillin tables, rated the evidence strength as moderate on this outcome, the evidence in the remaining six was rated as low quality. It should be noted that subjects in the amoxicillin arm of the trial by Massarotti et al also received probenecid;(Massarotti 1992) thus, the evidence in the azithromycin vs. amoxicillin table should have been downgraded two levels for serious indirectness on this point.

Nine of the fifteen studies cited in the evidence tables were conducted in Europe. (Arnez 1999; Arnez 2002; Barsic 2000; Eliassen 2018; Strle 1992; Strle 1993; Strle 1996; Weber 1993) Given that European EM lesions are much more likely to be caused by *B. afzelii* than *B. burgdorferi* (Makhani 2011) and there is no evidence that the findings from the European trials are generalizable to North American patients, those studies should be ignored outright or downgraded for indirectness.

In addition to the Massarotti trial, the Dattwyler trial also included probenecid in the amoxicillin regimen. (Dattwyler 1990; Massarotti 1992) Therefore, both studies have two sources of indirectness and should be downgraded at least two levels.

Bias was noted by both the NICE and ILADS evidence assessments. (Cameron 2014; NICE 2018) One US trial was biased by high non-completion rates;(Luger 1995) its strength should be further downgraded. Additional sources of bias across the trials included length of observation period (shorter observation periods are less likely to detect relapse), overly broad definitions of success, use of non-ITT statistical methodology.

Taking these deficiencies as a whole, the cited body of literature is of low or very low quality. In making a strong recommendation regarding the preferred antibiotic regimen for the treatment of EM, the guideline panel is violating basic GRADE guidance governing how the strength of a recommendation is chosen. Specifically, a weak recommendation is called for when: the gradient between benefits and harms is narrow or unclear, the evidence quality is low, and

patient values and preferences vary significantly or are uncertain. (Andrews 2013) All three of these are operating with regard to the treatment of EM, making the strong recommendation untenable. While it is true that the GRADE system allows for a strong recommendation in the face of low quality evidence, this should only be done when the risk-benefit favors a particular action such that most patients would agree with that choice. (Andrews 2013a) Patient values with regard to antibiotic interventions are heterogeneous. (NICE 2018; Cameron 2014) Therefore, the strong recommendation for certain antibiotics is not in keeping with the GRADE model on the development of guideline recommendations. (Andrews 2013a) Thus, the strength of the recommendation should be reduced to "weak".

References:

Arnez M, Radsel-Medvescek A, Pleterski-Rigler D, Ruzic-Sabljic E, Strle F. Comparison of cefuroxime axetil and phenoxymethyl penicillin for the treatment of children with solitary erythema migrans. Wiener Klinische Wochenschrift. 1999; 111(22-23):916-922.

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Pages 28-29, lines 667-670

The cited papers (Steere 1980; Steere 1983; Steere 1987) do not support the statement that "currently used antibiotic regimens … will effectively prevent the development of disseminated manifestations of Lyme disease". In the 1987 study, patients already had arthritis at the time of the intervention. In the 1983 paper, ~ 25% had ongoing manifestations for 1-2 years posttreatment. Additionally, the regimens used in that study (tetracycline/erythromycin/ phenoxymethyl penicillin 250 mg four times daily) are not currently used. In the 1980 study, 8 subjects received antibiotics yet, despite the initiation of penicillin therapy within 2 weeks of the onset of an EM, 2(25%) patients developed carditis. Preventing the development of persistent manifestations of Lyme disease is a critical patient-centered outcome. (NICE 2018; Cameron 2014) Given that the failure rate in the last two studies was 25% (Steere 1980; Steere 1983), the cited papers do not demonstrate that currently used antibiotic regimens are therapeutically sufficient.

The statement also fails to note trial and case reports of patients who developed disseminated disease despite having received antibiotic therapy for EM. For example, subjects in trials by Logigian et al developed central and/or peripheral nervous system manifestations of Lyme disease despite prior antibiotic therapy. (Logigian 1990; Logigian 1999) "Prior to enrollment in our study, 15 (83%) of the 18 patients had been treated previously with antibiotics, usually oral regimens for early disease or Lyme arthritis."(Logigian 1999)

References:

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How long should a patient with EM be treated?

Page 30, line 700 -703

The recommended durations and evidence strength assessment are not supported by the evidence. The strength of the evidence supporting this recommendation is inflated. The NICE and ILADS guidelines rated the evidence quality as low or very low. (NICE 2018; Cameron 2014) Given the disparity between the NICE and ILADS evidence rating and the proposed guidelines, the proposed guidelines either need to appropriately downgrade the evidence rating for these trials or explain why its assessment of the evidence is so much higher than other sources.

Only 4 papers are evaluated in the 5 evidence tables. (Dattwyler 1997, Eliassen 2018; Stupica 2012; Wormser 2003) Of these, 3 trials were conducted in Europe. (Eliassen 2018; Stupica 2012) The single trial that investigated 14d of amoxicillin was conducted in Europe. (Stupica 2012) Of the two cited studies that evaluated 10 days of doxycycline vs. a

longer duration of doxycycline, (Stupica 2012, Wormser 2003) only one was conducted in North America. (Wormser 2003)

None of the trials cited in the evidence evaluation tables for this question examined the use of cefuroxime or azithromycin.

There appear to be missing tables for US trials comparing 5 days of azithromycin to 10 days of doxycycline, (Massarotti 1992) 5 days of azithromycin to 10 days of amoxicillin plus probenecid, (Massarotti 1992) and 7 days of azithromycin vs 20 days of amoxicillin. (Luft 1996) The information regarding the 5 days of azithromycin vs 10 days of doxycycline is especially relevant. In that trial, 27 subjects were initially randomized to the doxycycline arm but 5 were subsequently excluded for failure to meet the entrance criteria. (Massarotti 1992) Of the 22 remaining subjects, 7 were immediately retreated with oral antibiotics and another was later retreated with ceftriaxone. (Massarotti 1992) Clinically, 10 days of doxycycline failed in 8/22 (36%) of subjects. Not including this trial in the evidence assessment biases and overstates the overall efficacy findings for 10 days of doxycycline.

Evidence assessments for the two US-conducted trials that examined the duration of antibiotic therapy (Dattwyler 1997; Wormser 2003) did not consider quality of life or return to pre-Lyme health status, outcomes of critical importance to patients. (NICE 2018; Cameron 2014) The evidence assessment for the Dattwyler study did consider this outcome – Patients experiencing objective findings of Lyme disease (at 6 months and beyond), but the evidence assessment for the Wormser et al trial did not. That assessment only evaluated the evidence strength for resolution of the EM rash at 20 days (note: symptom resolution was not an element of this outcome) and various adverse events.
(Wormser 2003)
Although the table lists “EM resolution at 20 days” as a critical outcome, it is not a critical patient-centered outcome. In addition to the two patient-centered outcomes noted above, critical patient-centered outcomes include prevention of persistent manifestations of Lyme disease, prevention of EM relapse, resolution of EM and reduction of EM symptoms. (NICE 2018; Cameron 2014) Given that this trial had a 30-month observation period, it is very disconcerting for the assessment’s only disease-related outcome to be EM resolution at 20 days. The supplemental tables draft should be revised to include the interval and final (30 month) outcome data.

The strength assessment for the Dattwyler et al outcome in the draft is “low”, due to indirectness and imprecision. It should be down-graded further because of bias. The strength assessment for the Wormser et al 20-day outcome was “high” but this rating is not based on patient-centered outcomes, as the table did not include any. The Wormser et al trial should be downgraded 2 levels for severe indirectness. The trial should also be downgraded for bias due to exceptionally high attrition rates and use of non-ITT statistical methodology.

Of note, the detailed NICE evidence assessment table regarding the Wormser trial (NICE 2018, pages 23-24) highlighted several problems not noted in the draft supplement materials. Across its multiple assessment parameters, NICE rated the evidence strength of the trial to be low/very low. The evidence for individual outcomes was downgraded due to bias, imprecision and, in some cases, indirectness (use of indirect outcomes).

For all of the reasons listed above, the proposed guidelines need to appropriately downgrade the evidence rating to very low.

Patients with erythema migrans lesions are a heterogeneous group. They differ with regard to the types and severity of their associated symptoms, duration of illness, infecting *Borrelia* species, presence of coinfections, and their serologic

status. (Arnez 1999; Arnez 2002; Barsic 2000; Dattwyler 1990; Eliassen 2018; Eppes 2002; Luft 1996; Luger 1995; Massarotti 1992; Nadelman 1992; Strle 1992; Strle 1993; Strle 1996; Weber 1993)
In reaching a strong recommendation on duration of antibiotic treatment, the guideline panel is violating basic GRADE guidance governing how the strength of a recommendation is chosen. Specifically, a weak recommendation is called for when: the gradient between benefits and harms is narrow or unclear, the evidence quality is low, and patient values and preferences vary significantly or are uncertain. (Andrews 2013, b) All three of these are operating with regard to the duration of antibiotic treatment for patients with erythema migrans, making the strong recommendation for duration of erythema migrans treatment untenable.

Additionally, the strong recommendation is not in keeping with the IDSA Handbook for Clinical Practice Guidelines Development available on the IDSA website. From page 51:

> *"When deciding the direction and the SoR, an important step is to assess our confidence in the assumed patients' values and preferences. Two factors need to be considered: 1) Variability among patients' values and preferences: In situations where there is a large variability in values and preferences, it is less likely that a single recommendation would apply uniformly across all patients. If this is so, a weak recommendation is likely warranted. 2) Certainty concerning values and preferences: The greater the uncertainty around the patients' values and preferences, the more likely a weak recommendation is preferred.*

The panel's priorities are wrongly focused on potential risks without fully considering the impact failed therapy may have on quality of life, which is a critical outcome to patients. While the assessment methodology adopted for the development of these guidelines and described in lines 170 -179, allows ranking adverse events as critical outcomes, doing so, as noted above, does not align with GRADE or the IDSA Handbook for Clinical Practice Guidelines Development available on the IDSA website. (Andrews 2013b; IDSA Handbook) The choice to rank adverse events as critically important inappropriately inflates the quality assessment and improperly gives greater weight to adverse events than the beneficial effects of treatment. Thus, the strength of the recommendation does not align with the actual quality of the evidence or patient values.

While it is true that the GRADE system allows for a strong recommendation in the face of low quality evidence, this should only be done when the risk-benefit favors a particular action such that most patients would agree with that choice. (Andrews 2013a) The burden of disease among patients with erythema migrans patients is quite heterogeneous, as are patient values with regard to antibiotic intervention. Therefore, it is unlikely that most patients would agree with shortening the course of antibiotic therapy. (Cameron 2014; NICE 2008) Thus, the strong recommendation for the duration of erythema migrans treatment is not in keeping with the GRADE model on the development of guideline recommendations. (Andrews 2013a)

The distinction between a strong recommendation and a weak recommendation is not mere semantics. Strong recommendations strictly limit therapeutic choices while weak recommendations allow for additional treatment options and individualized care. Speaking more broadly, weak recommendations require the exercise of clinical judgment while strong recommendations prohibit its use. Guideline recommendations, both strong and weak, are judgments formed at the group level but averaged outcomes from clinical trials may or may not pertain to the particular circumstances of a given patient. (Maloney 2009; Kravitz 2008) Asserting a strong recommendation essentially allows the panel to supplant clinician-generated decisions for patients the panel has never seen or assessed. Patient-specific risk-benefit analyses are the essence of clinical judgment, judgments which rightly fall to individual treating physicians.

Therapeutic decisions require that clinicians weigh an extensive list of patient-specific variables. (Maloney 2009) Yet all of the erythema migrans trials were too small to assess subgroup analysis identifying treatment responders and nonresponders. (Arnez 1999; Arnez 2002; Barsic 2000; Dattwyler 1990; Eliassen 2018; Eppes 2002; Luft 1996; Luger 1995; Massarotti 1992; Nadelman 1992; Strle 1992; Strle 1993; Strle 1996; Weber 1993) The decision regarding the duration of antibiotic therapy should consider the type and severity of the ongoing symptoms, including functional or quality of life impairments; whether the disease appears to be progressing; immune status; the presence of concurrent infections and co-morbidities; and medication tolerability. (Cameron 2014; Maloney 2009) The decision to forego additional antibiotics should consider whether alternative therapies exist; the associated risks and benefits of alternative therapies; and the risks associated with failing to treat an ongoing infection. (Cameron 2014; Maloney 2009)

Two other groups, ILADS and NICE, have considered the question of the duration of antibiotic treatment in patients with erythema migrans and their recommendations are distinctly different than the one offered in this draft. (NICE 2108; Cameron 2014) ILADS recommends that the duration of antibiotic treatment should be 4-6 weeks and NICE recommends 3 weeks.

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Pages 30, line 706
Reference 114 (Tibbles) did not evaluate treatment duration.

Page 30-31, lines 708-711
It is misleading to state that "(a) prospective, randomized, double-blind, placebo controlled clinical trial of patients with EM showed equivalent efficacy of 10 days compared with 20 days of doxycycline therapy" without enumerating all of the identified problems with that trial. (NICE 2018; Cameron 2014) Problems such as the following: bias due to a high noncompletion rate (~ 50%) and the use of non-ITT statistical methodology. The efficacy finding being referred to only

relates to resolution of EM at 20 days, which is not a patient-centered outcome and certainly doesn't reflect the fact that Lyme disease, as described on page 3, line 62 is a "complex clinical infection".

The second comparison study of the duration of doxycycline therapy is a European trial that was not randomized. (Stupica 2012) Given that European EMs are typically due to *B. afzelii* and North American EMs are almost exclusively due to *B. burgdorferi,* (Makhani 2011) it is incorrect to assume that the trial's findings are generalizable to North American patients.

References:

Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900.

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Neurologic Lyme Disease

Page 32, lines 747-756

Lyme encephalopathy, a well-characterized presentation of *B. burgdorferi* infection, (Dattwyler 1988; Fallon 2008; Logigian 1990; Logigian 1997; Logigian 1999) can produce profound and disabling quality of life impairments yet it is essentially ignored in this document. There is no serious discussion as to cause, review of the existing treatment data, or identification of evidence gaps. Given that many patients report cognitive concerns, these are significant shortcomings.

Descriptions of Lyme encephalopathy first appeared in the 1980's. (Dattwyler 1987; Dattwyler 1988) Later, Logigian defined it this way: "*Lyme encephalopathy (LE) is a neuropsychiatric disorder beginning months to years after the onset of infection with Borrelia burgdorferi. Objective evidence of memory impairment for verbal and, less commonly, visual information is usually present on formal neuropsychological testing even though standard bedside memory tests may be unrevealing. Other associated symptoms and signs may include mild depression, irritability, fatigue, and excessive daytime sleepiness. CSF examination may show a positive polymerase chain reaction (PCR) for B burgdorferi DNA, local production of antibody to B burgdorferi, or the less specific finding of elevated protein or CSF may be normal. CSF pleocytosis is rarely found."*(Logigian 1997)

Although the pathophysiologic mechanisms underlying Lyme encephalopathy have yet to be delineated, this clinical entity is under-investigated. Potential explanations include subacute CNS infection, CNS inflammation due to locally produced inflammatory mediators, influx of inflammatory mediators originating outside the brain, molecular mimicry, and cerebral hypoperfusion. (Fallon 2008, Fallon 2010; Logigian 1997; Logigian 1999),

Regardless of the underlying mechanisms, several generally small investigations conducted in the US documented improvement with antibiotic treatment directed at *B. burgdorferi*. (Bloom 1998; Dattwyler 1988; Dattwyler 2005; Fallon 2008; Logigian 1990; Logigian 1997; Logigian 1999) It is important to note that several studies found that Lyme encephalopathy responded to repeat antibiotic treatment for Lyme disease. (Bloom 1998; Dattwyler 1988; Logigian 1990; Logigian 1997; Logigian 1999). In some cases, retreatment was undertaken without objective findings of ongoing infection. In the 1999 Logigian study, one patient reported the return of encephalopathic symptoms which were accompanied by a decline in his neurocognitive test scores. He was retreated, and improved, despite acknowledgment from the investigator that his relapse was not proven to be the result of treatment failure. (Logigian 1999)

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Dattwyler RJ, Halperin JJ, Pass H, Luft BJ. Ceftriaxone as effective therapy for refractory Lyme disease. J Infect Dis 1987;155:1322–5.Dattwyler RJ, Halperin JJ, Volkman DJ, Luft BJ. Treatment of late Lyme borreliosis—randomized comparison of ceftriaxone and penicillin. Lancet 1988; 1:1191–4.

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Logigian EL, Kaplan RF, Steere AC. Successful treatment of Lyme encephalopathy with intravenous ceftriaxone. J Infect Dis 1999;180:377–83.

XI: For which neurologic presentations should patients be tested for Lyme disease?

Page 36, lines 839-841

The strong recommendation against testing for patients with ALS, relapsing-remitting multiple sclerosis, Parkinson's disease, or dementia is based on weak evidence and is inappropriate for these patient groups. The panel is concerned that some false positive results will be generated and that such results would delay approriate evaluations and treatment and expose patients to unnecessary antibiotics and their attendant risks. However, the panel is not weighing the potential harms of testing against the potential benefits. The diagnoses under consideration are degenerative in nature and lack curative therapies. A true positive result will be life-changing, a false result would likely have short-lived consequences.

In reaching a strong recommendation against testing, the guideline panel is violating basic GRADE guidance governing how the strength of a recommendation is chosen. Specifically, a weak recommendation is called for when: the gradient between benefits and harms is narrow or unclear, the evidence quality is low, and patient values and preferences vary significantly or are uncertain. (Andrews 2013) All three of these are operating with regard to patients with acute neurologic manifestations without parenchymal involvement, making the strong recommendation against retreatment untenable.

Additionally, the strong recommendation is not in keeping with the IDSA Handbook for Clinical Practice Guidelines Development available on the IDSA website. From page 51:

> *"When deciding the direction and the SoR, an important step is to assess our confidence in the assumed patients' values and preferences. Two factors need to be considered: 1) Variability among patients' values and preferences: In situations where there is a large variability in values and preferences, it is less likely that a single recommendation would apply uniformly across all patients. If this is so, a weak recommendation is likely warranted. 2) Certainty concerning values and preferences: The greater the uncertainty around the patients' values and preferences, the more likely a weak recommendation is preferred.*

References:

Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013 Jul;66(7):726-35. doi: 10.1016/j.jclinepi.2013.02.003.

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XIV. What are the preferred antibiotic regimens for the treatment of acute neurologic manifestations of Lyme disease without parenchymal involvement of the brain or spinal cord?

Page 39-40, lines 915-924

The panel's assessment regarding the strength of the evidence for this question, which the panel assesses as moderate, is inflated. Both the NICE and Cochrane GRADE assessments found the evidence to be very low. (Cochrane 2016; NICE 2018) Given the disparity between the NICE and Cochrane evidence rating and that of the proposed guidelines, the

panel either needs to appropriately downgrade the evidence rating for these trials or explain why its GRADE-based assessment of the evidence is considerably higher than other sources.

NICE include these critical patient-centered outcomes: 1) Return to pre-Lyme health status (cure), 2) Reduction of symptoms, 3) Quality of life (any validated measure), and 4) Prevention of symptom relapse. (NICE 2108) As NICE makes clear, adverse events may be important to patients but they are not critically important. (NICE 2018) Hence, adverse events are relatively less important than the potential benefits of treatment. In contrast, the draft's outcomes do not include cure or prevention of disease relapse.

With regard to the question being examined in this GRADE assessment, all of the 6 analyzed trials were conducted in Europe. European neuroborreliosis is generally due to *B. garinii*, not *B. burgdorferi* (the agent of Lyme in the US). There is no evidence demonstrating that findings regarding the treatment of *B. garinii* are generalizable to North American patients; therefore, all trials should be downgraded for indirectness. Although the information could be valuable, there is no table comparing 2 weeks of IV ceftriaxone followed by 100 days of oral amoxicillin to 2 weeks of IV ceftriaxone followed by 100 days of oral amoxicillin. (Oksi 1998; Oksi 2007). The panel ranked adverse outcomes as critically important, which is a significant error. Given the very low quality of the evidence with regard to treatment effects, the panel's "strong recommendation" primarily rests on an inflated ranking for adverse events.

Patients with acute neurologic manifestations are a heterogeneous group. They differ with regard to the types and severity of their manifestations, time to diagnosis, presence of coinfections, age and comorbidities. It is important to recognize that there was significant variation in the types of patients who were enrolled in the different studies.

In reaching a strong recommendation on the treatment of acute neurologic manifestations without parenchymal involvement, the guideline panel is violating basic GRADE guidance governing how the strength of a recommendation is chosen. Specifically, a weak recommendation is called for when: the gradient between benefits and harms is narrow or unclear, the evidence quality is low, and patient values and preferences vary significantly or are uncertain. (Andrews 2013, b) All three of these are operating with regard to patients with acute neurologic manifestations without parenchymal involvement, making the strong recommendation against retreatment untenable.

Additionally, the strong recommendation is not in keeping with the IDSA Handbook for Clinical Practice Guidelines Development available on the IDSA website. From page 51:

> *"When deciding the direction and the SoR, an important step is to assess our confidence in the assumed patients' values and preferences. Two factors need to be considered: 1) Variability among patients' values and preferences: In situations where there is a large variability in values and preferences, it is less likely that a single recommendation would apply uniformly across all patients. If this is so, a weak recommendation is likely warranted. 2) Certainty concerning values and preferences: The greater the uncertainty around the patients' values and preferences, the more likely a weak recommendation is preferred.*

The panel's priorities are wrongly focused on potential risks without fully considering the impact even modest improvement may have on quality of life, which is a critical outcome to patients. While the assessment methodology adopted for the development of these guidelines and described in lines 170 -179, allows ranking adverse events as critical outcomes, doing so, as noted above, does not align with GRADE or the IDSA Handbook for Clinical Practice Guidelines Development available on the IDSA website. (Andrews 2013b; IDSA Handbook) The choice to rank adverse events as critically important inappropriately inflates the quality assessment and improperly gives greater weight to adverse events than the beneficial effects of treatment. Thus, the strength of the recommendation does not align with the actual quality of the evidence or patient values.

While it is true that the GRADE system allows for a strong recommendation in the face of low quality evidence, this should only be done when the risk-benefit favors a particular action such that most patients would agree with that choice. (Andrews 2013a) The burden of disease among patients with acute neurologic manifestations without parenchymal involvement is quite heterogeneous, as are patient values with regard to antibiotic intervention. (Cameron 2014) Thus, the strong recommendation against antibiotic retreatment is not in keeping with the GRADE model on the development of guideline recommendations. (Andrews 2013a)

The distinction between a strong recommendation and a weak recommendation is not mere semantics. Strong recommendations strictly limit therapeutic choices while weak recommendations allow for additional treatment options and individualized care. Speaking more broadly, weak recommendations require the exercise of clinical judgment while strong recommendations prohibit its use. Guideline recommendations, both strong and weak, are judgments formed at the group level but averaged outcomes from clinical trials may or may not pertain to the particular circumstances of a given patient. (Maloney 2009; Kravitz 2008) Asserting a strong recommendation essentially allows the panel to supplant clinician-generated decisions for patients the panel has never seen or assessed. Patient-specific risk-benefit analyses are the essence of clinical judgment, judgments which rightly fall to individual treating physicians.

Clinical judgment is critical to the management of patients with acute neurologic manifestations without parenchymal involvement. Therapeutic decisions require that clinicians weigh an extensive list of patient-specific variables. (Maloney 2009) Yet all of the included trials were too small to assess subgroup analysis identifying treatment responders.

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Prolonged symptoms following treatment of Lyme disease

Page 61, lines 1410-1421:

The prevalence of persistent symptoms following prevailing antibiotic regimens for Lyme disease is unknown and the severity of these symptoms is highly variable. This uncertainty leads to divergent opinions regarding the underlying mechanisms of persistent manifestations and how to best manage them. (Cameron 2104; Maloney 2016) However, the suggestion that these symptoms may represent anchoring bias on the part of patients and not Lyme-related symptomatology is contradicted by many of the studies cited in this section. The language regarding anchoring bias should be eliminated.

While case-control studies can be informative, such studies are often biased;(Dersch 2016) therefore they should not be used to challenge the linkage between ongoing symptoms and the Lyme disease infection that gave rise to them. For example, the doxycycline arm of the Stupica trial had an 18% attrition rate which significantly biases the outcomes. (Stupica 2018) Control subjects were recruited from the subjects' families and investigators "did not actively search for borrelial infection in the control group". The authors specifically noted that their results do not rule out that symptoms in the patient group were triggered by the infection. (Stupica 2018) And, although the study by Bechtold et al is cited in support of the anchoring theory, that research actually identified a subset of patients – those who subsequently met the criteria for PTLDS, who differed "significantly from controls on all symptom measures". (Bechtold 2017)

Dersh et al performed a systematic review of studies of the prevalence and found a 28% prevalence rate for persistent symptoms following treatment for neuroborreliosis. (Dersch 2016) That same study demonstrated that the prevalence rate correlates with disease stage at time of treatment. Therefore, findings from ideally treated EM patients are not generalizable to patients diagnosed later in disease.

Additionally, the study by Nowakowski et al, which followed patients treated for erythema migrans, should not be used to support statements regarding long-term outcomes because, as the authors reported on page 2, column 1, 25% were followed for less than one year. (Nowakowski 2003) This unacceptably high attrition rate has a significant likelihood of biasing outcomes as attrition bias minimizes the risk of treatment failure. (Nunan 2018; Schulz 2002)

The assertion that symptoms improve over time is not supported by the studies cited, which all suffered from attrition bias. Attrition artificially diminishes the number of patients reporting symptoms. In the study by Wills et al (312), (Wills 2016) unacceptably high noncompletion rates introduced bias. (Nunan 2018; Schulz 2002) For example, Supplemental Table 2, which documents symptoms at the 2-year follow-up point, was missing responses from 22/97 (23%) and Supplemental Table 4, which looks at SF-36 QOL scores, was missing 46/94 (47%). The two longitudinal studies by Wormser et al are hampered by selection and/or attrition bias as less than half of the enrolled subjects completed the designated symptoms tool for their particular study. (Wormser 2015a; Wormser 2015b) The fatigue paper by Wormser et al is also limited by investigator bias in determining the etiology of a subject's fatigue. (Wormser 2015a) It is important to recognize that the persistent symptoms may be severe; a study of over 3,000 patients demonstrated that the symptoms experienced were severe, a factor these other studies did not take in account. (Johnson 2014)

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XXVII. Should patients with persistent symptoms following standard treatment of Lyme disease receive additional antibiotics?

Pages 61-63, lines 1424-1472

The panel's assessment regarding the strength of the evidence for this question, which the panel assesses as moderate, is inflated. Both the NICE and ILADS GRADE assessments of the evidence generally rate the quality of the evidence to be low or very low. (NICE 2108; Cameron 2014) Given the disparity between the NICE and ILADS evidence rating and that of the proposed guidelines, the proposed guidelines either need to appropriately downgrade the evidence rating for these trials or explain why its GRADE-based assessment of the evidence is considerably higher than other sources.

Both NICE and ILADS include these critical patient-centered outcomes: 1) Return to pre-Lyme health status (cure), 2) Reduction of symptoms, 3) Quality of life (any validated measure), and 4) Prevention of symptom relapse. (NICE 2108; Cameron 2014) As NICE makes clear, adverse events may be important to patients but they are not critically important. (NICE 2018) Hence, adverse events are relatively less important than the potential benefits of treatment.

In contrast, the IDSA outcomes do not include cure or prevention of disease relapse. The IDSA ranked adverse outcomes as critically important, which is a significant error. Given the very low quality of the evidence with regard to treatment effects (detailed below), the panel's "strong recommendation" against retreatment primarily rests on an inflated ranking for adverse events.

Patients with persistent manifestations are a heterogeneous group. They differ with regard to the types and severity of their manifestations, time to diagnosis, presence of coinfections, the nature of their prior antibiotic treatment and their serologic status. (Cameron 2014; Maloney 2009) The degree of patient diversity, makes it exceedingly difficult to design

studies that would be able to demonstrate meaningful treatment effects across this broad cohort. It is important to recognize that there was significant variation in the types of patients who were enrolled in the different studies. (Krupp 2003; Fallon 2008; Klempner 2001)

With regard to the question being examined in this GRADE assessment, it is unclear why neither Krupp nor Fallon were downgraded for significant indirectness as their findings only apply to seropositive patients who had severe fatigue (Krupp) or cognitive impairment (Fallon). (Krupp 2003; Fallon 2008) NICE and ILADS assessed the evidence strength of the Klempner trials to be low or very low. (NICE 2108; Cameron 2014) The Klempner trials did not establish a symptom severity level as an inclusion criterion. (Klempner 2001) This omission allowed for the potential inclusion of patients with very mild impairments. Under these conditions it would make it difficult to find a small but meaningful treatment effect given the small sample size. (Delong 2012) Thus, the Klempner trials should have been downgraded for bias. Additionally, the methodology did not control for baseline differences between subjects on their SF-36 scores,(Fallon 2012) which should have further lowered the evidence quality of this study.

The evidence rating for the Krupp fatigue outcome is out of sync with the NICE evidence assessment, which rated the quality to be high. IDSA downgraded Krupp for serious bias but the rationale is weak. One stated reason was that Krupp did not prove that subjects had neuroborreliosis. Neither Fallon nor Klempner offered such proof yet those studies were not downgraded on that point. The proposed “potential attrition bias” is baseless. Krupp went through a detailed analysis around attrition and found that it didn’t affect outcomes,(Delong 2012;Krupp 2003) The concern regarding “potentially compromised blinding” has been debunked by others. (Delong 2012; Fallon 2012) The study by Krupp was assessed to be imprecise because the FSS-11 has not been specifically validated for Lyme disease. However, the use of any broadly validated measure is appropriate.

The evidence summary regarding antibiotic retreatment trials suffers from factual omissions and poorly supported assertions. The lack of a demonstrated treatment effect in the Klempner/Kaplan subjects could be due to design flaws such that the designated outcome, change in SF-36 score, is substantially greater than the MCID. (Delong 2012) The failure to establish inclusion criteria for baseline impairment and the failure to adjust for baseline heterogeneity may have also contributed to the inability to find a treatment effect. (Delong 2012; Fallon 2012)

The description of the Krupp trial omits important facts that may mislead clinicians caring for patients with persisting and significant fatigue. As critiques of these trials have made clear, the Krupp trial was well-designed on the fatigue endpoint and retreatment with 30 days of ceftriaxone resulted in sustained, moderate to large treatment effects. (Delong 2012; Fallon 2012; Krupp 2003) The other endpoints were poorly designed. (Delong 2012) The lack of efficacy on the poorly designed endpoints does not negate the positive finding on fatigue. (NICE 2018)

The discussion regarding the fatigue finding from the trial by Fallon is misleading. It is based on an apples-to-oranges comparison that doesn’t hold up to scrutiny. Severe fatigue was not an entrance criterion for the Fallon trial. (Fallon 2008) Although there was internal variation on this symptom, the group as a whole did not have severe fatigue. (Fallon 2008) Thus, it is not surprising that the study cohort did not improve on fatigue. However, a post-hoc analysis of the Fallon subjects who met the fatigue entrance criterion of the Krupp study found that they had a sustained improvement in fatigue comparable to that seen in the Krupp subjects. (Fallon 2008) Thus, Krupp’s findings on fatigue were corroborated by Fallon. (Delong 2012; Fallon 2008; Fallon 2012; Krupp 2003)

The study by Berende was conducted in Europe. (Berende 2016) Given the differences between European and North American genospecies, (Stupica 2018) the findings are not generalizable. In addition, the study was poorly designed – 11% of the subjects had no prior antibiotic treatment for Lyme disease, enrollment included subjects whose SF-36 scores

were more than 1 standard deviation higher than the mean of a healthy population and there was no true placebo arm because all subjects received two weeks of IV ceftriaxone. (Berende 2016)

Improvement in placebo subjects is a common finding in any trial, the goal of a placebo- controlled trial is to determine whether treatment results in more significant improvements. In both the Krupp and Fallon trials, treatment clearly outperformed placebo on the endpoints that were well-designed and critically important to patients. (Krupp 2003; Fallon 2008)

Adverse events are important but not critical outcomes to patients. (NICE 2108; Cameron 2014) The description of the serious adverse events lacks appropriate context. There was a combined total of twenty-two serious adverse events among the 501 subjects in the five retreatment trials discussed in the draft. (Berende 2016; Fallon 2008; Klempner 2001; Krupp 2003) This equates to a 4.4% risk of a serious adverse event. Given the significant level of impairments that some patients with prolonged symptoms/persistent manifestations of Lyme disease have, this degree of risk may not be considered excessive to many.

In reaching a strong recommendation against antibiotic retreatment, the guideline panel is violating basic GRADE guidance governing how the strength of a recommendation is chosen. Specifically, a weak recommendation is called for when: the gradient between benefits and harms is narrow or unclear, the evidence quality is low, and patient values and preferences vary significantly or are uncertain. (Andrews 2013, b) All three of these are operating with regard to antibiotic retreatment for patients with prolonged symptoms, making the strong recommendation against retreatment untenable.

Additionally, the strong recommendation is not in keeping with the IDSA Handbook for Clinical Practice Guidelines Development available on the IDSA website. From page 51:

> *"When deciding the direction and the SoR, an important step is to assess our confidence in the assumed patients' values and preferences. Two factors need to be considered: 1) Variability among patients' values and preferences: In situations where there is a large variability in values and preferences, it is less likely that a single recommendation would apply uniformly across all patients. If this is so, a weak recommendation is likely warranted. 2) Certainty concerning values and preferences: The greater the uncertainty around the patients' values and preferences, the more likely a weak recommendation is preferred.*

The panel's priorities are wrongly focused on potential risks without fully considering the impact even modest improvement may have on quality of life, which is a critical outcome to patients. While the assessment methodology adopted for the development of these guidelines and described in lines 170 -179, allows ranking adverse events as critical outcomes, doing so, as noted above, does not align with GRADE or the IDSA Handbook for Clinical Practice Guidelines Development available on the IDSA website. (Andrews 2013b; IDSA Handbook) The choice to rank adverse events as critically important inappropriately inflates the quality assessment and improperly gives greater weight to adverse events than the beneficial effects of treatment. Thus, the strength of the recommendation does not align with the actual quality of the evidence or patient values.

While it is true that the GRADE system allows for a strong recommendation in the face of low quality evidence, this should only be done when the risk-benefit favors a particular action such that most patients would agree with that choice. (Andrews 2013a) The burden of disease among patients with prolonged/persistent manifestations of Lyme disease is quite heterogeneous, as are patient values with regard to antibiotic intervention. Therefore, it is unlikely that most patients would agree with withholding additional antibiotic therapy. (Cameron 2014) Thus, the strong

recommendation against antibiotic retreatment is not in keeping with the GRADE model on the development of guideline recommendations. (Andrews 2013a)

The distinction between a strong recommendation and a weak recommendation is not mere semantics. Strong recommendations strictly limit therapeutic choices while weak recommendations allow for additional treatment options and individualized care. Speaking more broadly, weak recommendations require the exercise of clinical judgment while strong recommendations prohibit its use. Guideline recommendations, both strong and weak, are judgments formed at the group level but averaged outcomes from clinical trials may or may not pertain to the particular circumstances of a given patient. (Maloney 2009; Kravitz 2008) Asserting a strong recommendation essentially allows the panel to supplant clinician-generated decisions for patients the panel has never seen or assessed. Patient-specific risk-benefit analyses are the essence of clinical judgment, judgments which rightly fall to individual treating physicians.

Clinical judgment is especially critical to the management of patients with persistent manifestations of Lyme disease following antibiotic treatment. (Cameron 2014; Maloney 2009) Given that the manifestations of Lyme disease overlap with those of other illnesses and the absence of tests of cure, diagnostic decisions regarding the likelihood of ongoing infection vs. other conditions rest exclusively on clinical judgment. In some instances, clinicians and patients may elect to perform an empiric antibiotic retreatment trial as a means to gather additional diagnostic evidence. Therapeutic decisions require that clinicians weigh an extensive list of patient-specific variables. (Maloney 2009) Yet all of the US antibiotic retreatment trials were too small to assess subgroup analysis identifying treatment responders. (Fallon 2008; Klempner 2001; Krupp 2003) The decision to provide additional antibiotic therapy should consider the type and severity of the ongoing symptoms, including functional or quality of life impairments; whether the disease appears to be progressing; immune status; the presence of concurrent infections and co-morbidities; the response to previous treatment, including evidence of relapse when treatment was withdrawn; and medication tolerability. (Cameron 2014; Maloney 2009) The decision to forgo additional antibiotics should consider whether alternative therapies exist; the associated risks and benefits of alternative therapies; and the risks associated with failing to treat an ongoing infection. (Cameron 2014; Maloney 2009)

Two other groups, ILADS and NICE, (NICE 2108; Cameron 2014) have considered the question of antibiotic retreatment in patients with persistent manifestations of Lyme disease and their recommendations are distinctly different than the one offered in this draft. ILADS recommends that antibiotic retreatment as well as not retreating be discussed with all patients in the context of shared medical decision-making. It also offers additional recommendations regarding potential treatment regimens and ongoing monitoring during treatment. (Cameron 2014) The NICE guidelines recommend that a second course of antibiotic treatment be considered. (NICE 2108) When retreatment is undertaken, therapy should use an alternative, Lyme-effective antibiotic that is different from that used initially.

The original question regarding antibiotic retreatment appears to ignore the realities regarding the patient population it is attempting to address. Given the heterogeneity in the prolonged symptoms group, a more appropriate question would be: are there specific subgroups of patients with prolonged symptoms following standard treatment of Lyme disease that would benefit from additional antibiotics? Here the findings from Krupp and Fallon's subgroup analysis do apply. (NICE 2108; Cameron 2014) Both trials found that patients with severe fatigue who received additional ceftriaxone had a moderate to large improvement in fatigue that was sustained. (Krupp 2003; Fallon 2008) Identifying subgroups is a worthwhile research goal that could potentially lead to symptom-specific therapies and, potentially, avoid the risks of antibiotic under- and overtreatment.

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Pages 64-65, lines 1478-1498

Initially, the collective statements appear to make a case against chronic Lyme disease as an entity and the value of providing additional antibiotic treatment to those who were given that diagnosis. However, on closer inspection, the panel's logic is badly flawed. The authors correctly note that there is no widely accepted definition of chronic Lyme disease, that it describes a heterogenous patient population, and that it is sometimes wrongly applied to individual patients. Yet none of those facts actually invalidate the diagnosis. The lack of definitive diagnostic testing for chronic Lyme disease/persistent manifestations of Lyme disease leads to diagnostic uncertainty and misdiagnoses; some will be mistakenly labeled with chronic Lyme disease when they have a different condition and some cases of Lyme disease due to ongoing infection will be misdiagnosed as something else.

The panel apparently dismisses the concept/diagnosis of chronic Lyme disease because of a lack of "compelling" evidence of ongoing disease. Logically, one would expect that pretreatment symptoms associated with positive two-tier test results would qualify if they persisted post-treatment but the panel only accepts objective findings as evidence of ongoing infection. Serology will not be helpful post-treatment. (Maloney 2016) Prolonged elevations in antibody levels can be seen following effective treatment and antibiotic intervention early in disease can result in negative post-treatment titers. Given that direct evidence of infection is difficult to obtain in untreated cases of Lyme disease, it would be an undue burden to require it in patients who remain ill following treatment. This is not to say that direct evidence of infection is never obtained post-treatment. (Cassarino 2003; Chancellor 1993; Coyle 1995; Hudson 1998; Lawrence 1995) The panel extols the need to identify the best-fit diagnosis yet ignores the possibility that chronic Lyme disease is the best fit for some patients.

The panel wrongly asserts that the lack of a demonstrable treatment effect in the US antibiotic retreatment trials is evidence that chronic infection does not exist. This assertion is wrong on two points: 1) the US retreatment trials only investigated IV ceftriaxone alone or IV ceftriaxone followed by doxycycline;(Fallon 2008; Klempner 2001; Krupp 2003) hardly sufficient evidence to claim that no other regimen would work and 2) a positive treatment effect on fatigue was found by both Krupp and Fallon. (Fallon 2008; Krupp 2003) It is important to note that the Logigian trial on Lyme encephalopathy was essentially a retreatment study as 83% of the subjects had received antibiotics for an earlier stage of Lyme disease; 22% had received IV ceftriaxone. (Logigian 1999) These subjects had significant and sustained improvement in their encephalopathy following a 30-day course of IV ceftriaxone, improvement that the investigators attributed to successful treatment of an active *B. burgdorferi* infection.

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Page 65, line 1499

Research needs: Given that several potential mechanisms, with varying degrees of evidentiary support, have been proposed as the pathophysiologic basis for persistent manifestations of Lyme disease following antibiotic treatment,

developing diagnostic methodologies that can identify and distinguish between ongoing infection and other potential mechanisms would be clinically beneficial.

Identifying subgroups is a worthwhile research goal that could potentially lead to symptom-specific therapies and, potentially, avoiding the risks of antibiotic under- and overtreatment. Subgroup analysis could also identify high treatment responders for targeted therapy.

Given that all stage-specific antibiotic regimens have been known to fail and that many protocols are based on very limited, low quality evidence, it is important to identify the optimal treatment for early, localized disease, acute and late disseminated disease and persistent post-treatment manifestations.