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EXPERT REVIEWS

Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease

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Evidence-based guidelines for the management of patients with Lyme disease were developed by the International Lyme and Associated Diseases Society (ILADS). The guidelines address three clinical questions – the usefulness of antibiotic prophylaxis for known tick bites, the effectiveness of erythema migrans treatment and the role of antibiotic retreatment in patients with persistent manifestations of Lyme disease. Healthcare providers who evaluate and manage patients with Lyme disease are the intended users of the new ILADS guidelines, which replace those issued in 2004 (Exp Rev Anti-infect Ther 2004;2:S1–13). These clinical practice guidelines are intended to assist clinicians by presenting evidence-based treatment recommendations, which follow the Grading of Recommendations Assessment, Development and Evaluation system. ILADS guidelines are not intended to be the sole source of guidance in managing Lyme disease and they should not be viewed as a substitute for clinical judgment nor used to establish treatment protocols.

KEYWORDS: antibiotic prophylaxis • antibiotics • erythema migrans • GRADE • Lyme disease • persistent disease • treatment

Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values [1]. The International Lyme and Associated Diseases Society (ILADS) has adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as its basis for evidence assessment and the development of recommendations to ensure a transparent and trustworthy guideline process [2–5].

These guidelines address three fundamental treatment questions: the usefulness of antibiotic prophylaxis for known tick bites, the effectiveness of erythema migrans (EM) treatment and the role of antibiotic retreatment in patients with persistent manifestations of Lyme disease. ILADS anticipates performing GRADE assessments on additional topics related to the diagnosis and treatment of tick-borne diseases in the future.

The GRADE scheme classifies the quality of the evidence as high, moderate, low or very low. The quality of evidence from randomized controlled trials (RCTs) is initially rated as high, but may be downgraded based on five limitations: study bias, publication bias, indirectness (generalizability), imprecision and inconsistency. Evidence quality from observational studies is generally low, but may be upgraded based on a large effect or

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dose–response gradient [6]. Rather than labeling recommendations as strong or weak, these guidelines use the terms 'recommendation' or 'strong recommendation' for or against a medical intervention. The GRADE scheme itself is a continually evolving system. These guidelines attempt to incorporate the current state of GRADE.

Although Lyme disease is not rare, the treatment of Lyme disease has not attracted pharmaceutical interest and the evidence base for treating Lyme disease is best described as sparse, conflicting and emerging. For example, Hayes and Mead of the CDC performed a systematic review of the evidence regarding the treatment of late neurologic Lyme disease and their GRADE-based evaluation rated the quality of the evidence as very low [7]. The ILADS guidelines working group reached a similar conclusion after assessing the research evidence pertaining to its three clinical questions, rating the evidence quality as very low. The low quality of evidence seen in Lyme disease is consistent with the evidence base for the field as a whole. Indeed, the majority of recommendations in infectious disease medicine generally are based on low-quality evidence [8].

When high-quality evidence is not available, guideline panels are faced with making recommendations based on low- or very low-quality evidence. Although evidence alone is never sufficient to determine guideline recommendations [2], when evidence is weak, the values of those on the panel, including differing specialty perspectives, may carry more weight [8]. One of the goals of the GRADE scheme is to make the value judgments underlying recommendations transparent.

When the evidence base is of low or very low quality, guideline panels should be circumspect about making strong recommendations to avoid encouraging uniform practices that are not in the patient's best interest and to ensure that research regarding benefits and risks is not suppressed [8]. Guidelines panels should also make the role of their values and those of patients in recommendations explicit and should promote informing and empowering patients to engage in shared decision-making [8].

This panel has placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary [9].

In addition, this panel believes the goals of medical care in Lyme disease are to prevent the illness whenever possible and to cure the illness when it occurs. When this is not possible, the panel believes the emphasis for treatment should be on reducing patient morbidity. Therefore, the panel placed a high value on reducing patient risks for developing the chronic form of the disease and on reducing the serious morbidity associated with these disease forms. Thus, the panel's values align with the Institute of Medicine (IOM) goal of reducing the impact of chronic illness at the individual and national levels by, among other things, treating the treatable [10]. To this end, the panel valued primary prevention (by effectively treating a tick bite), secondary prevention (by treating an EM rash sufficiently so as to restore health and prevent disease progression) and tertiary prevention (by treating patients whose illness may be responsive to additional therapy, thereby reducing the morbidity associated with the chronic forms of the disease).

ILADS is mindful of the role of patient preferences and values in GRADE as well as the IOM's call for patient-centered care that is responsive to the needs, values and expressed preferences of individual patients [11]. Patient-centered care focuses on achieving treatment outcomes that patients value [11], including the restoration of health, prevention of health deterioration and the provision of treatments that have the potential to improve quality of life (QoL). To facilitate the development of treatment plans addressing the unique circumstances and values of individual patients, patient-centered care encourages shared medical decision-making.

Shared decision-making takes into account the best scientific evidence available, clinical expertise and the role of patient's values and preferences in deciding among available treatment options [12,13]. Despite the terminology, decision-making is not truly shared between clinician and patient; the responsibility for choosing between options remains with the clinician.

To effectively engage in shared decision-making, patients need to understand the implications of their choices. Physicians should not assume that patients share their values in making risk/benefit determinations. Studies have demonstrated that patients and physicians may have very different assessments of preferences and risk tolerance [8]. In addition, there is considerable variation among individual patients in their tolerance for risk and in what they regard as a valuable benefit. Patients may also tolerate more risk when they have severe presentations of disease or when there are no other treatment options available [14].

In the GRADE system, recommendations take into account not only the quality of the evidence, but also the balance between benefits and harms and patient values and preferences [5]. In instances where a GRADE evaluation concludes that the evidence quality is low or very low or that there are trade-offs between risks and benefits that depend on the values of the individual, the GRADE system recommends that recommendations should identify a range of therapeutic options and acknowledge that different choices may be appropriate for different patients.

In assessing the balance between the risks and benefits of antibiotic treatments for Lyme disease, the panel weighed the burden of disease, the magnitude and relative importance of patient-centered outcomes as well as treatment-associated risks and the risks attendant on not treating. The panel acknowledged that the health-related and economic consequences of chronic disease are enormous for individuals, families, communities, healthcare systems and the nation, impacting the wellbeing of individuals, family functioning and economic productivity [15–18]. Therefore, the panel recommends that patients be informed of the risks and benefits of treating and not treating, including the risks of continuing to suffer significant morbidity or permitting a serious systemic infection to progress.

The panel assessed risks and benefits of treatment on a generalized basis. In addition, the panel recognizes that there is a need for clinicians, in the context of shared medical decision-

making, to engage in a risk–benefit assessment that reflects the individual values of the particular patient.

Guidelines for the diagnosis and treatment of Lyme disease are conflicting (Supplementary Appendix I [Supplementary material can be found online at www.informahealthcare.com/suppl/10.1586/14787210.2014.940900]) The IOM recently highlighted the conflicting Lyme guidelines of ILADS and the Infectious Diseases Society of America (IDSA) and noted that the National Guidelines Clearinghouse has identified at least 25 different conditions in which conflicting guidelines exist [19]. According to the IOM, conflicting guidelines most often arise when evidence is weak, organizations use different assessment schemes or when guideline developers place different values on the benefits and harms of interventions [20].

The adoption of GRADE by ILADS is, in part, an effort to use the same assessment scheme as the IDSA, although it should be noted that the IDSA's Lyme disease guidelines listed on the National Guidelines Clearinghouse were originally published in 2006 and do not reflect the organization's adoption of GRADE for guideline revisions after 2008. Additionally, the use of GRADE is one element of ILADS' compliance with the eight standards identified by the IOM as being integral to creating trustworthy treatment guidelines (Supplementary Appendix II).

The guidelines were developed in phases. A working group identified three questions to address, conducted a literature search and subsequent assessment of the evidence quality and evaluated the role of patient preferences and values for each question. A preliminary draft of the guidelines was sent to the full guidelines panel and, subsequently, outside reviewers for review and comment, with the document being further refined. The panel and working group members were required to disclose potential financial conflicts of interest. The full panel, which consisted of the board of directors of ILADS, determined that fee for service payments are inherent in the provision of healthcare and did not disqualify experienced clinicians from serving on the guideline panel nor did serving on the boards of nonprofit organizations related to Lyme disease. Financial relationships exceeding US$10,000 per year that were not intrinsic to medical practice were viewed as potential conflicts; no panel or working group members held such financial conflicts of interest.

Scope of problem

The burden of Lyme disease for individuals and society remains high. Despite the availability of numerous preventative measures [21,22], the incidence of acute Lyme disease is significant. The CDC currently estimates that the annual number of new cases of Lyme disease in the USA exceeds 300,000 [23]; how these individual patients fare is an important consideration and ILADS is primarily interested in preventing and reducing the morbidity associated with chronic disease. Although some prospective studies found long-term outcomes were good, many had significant limitations [24–26]. There is substantial evidence of varying quality demonstrating that the severity [16–18,27–29], duration [16,18,27,29,30] and cost [15,31] of persistent manifestations of Lyme disease can be profound. While the etiology of these manifestations is uncertain, their impact is clear. Two retrospective cohorts [27,30], two case series [32,33], a meta-analysis [34], two prospective European studies and four NIH-sponsored clinical trials [16–18] describe significant long-term consequences of Lyme disease. Findings include:

- Thirty-four percent of a population-based, retrospective cohort were ill an average of 6.2 years after antibiotic treatment [27];
- Sixty-two percent of a retrospective evaluation of 215 Lyme disease patients from Westchester County, NY, remained ill an average of 3.2 years after antibiotic treatment [30];
- A meta-analysis of 504 patients treated for Lyme disease found this group had more fatigue, musculoskeletal pain and neurocognitive difficulties than 530 controls [34]. Additionally, it demonstrated that persistent Lyme disease symptoms were a distinct set of symptoms, which differed from those of fibromyalgia, chronic fatigue syndrome and depression [34];
- Among 23 European pediatric patients with objective findings of Lyme neuroborreliosis sequelae, daily activities or school performance were negatively impacted in 10 (43%) [28];
- A European study of adults treated for neuroborreliosis found that at 30 months post-treatment, 16% were cognitively impaired [29];
- On entrance, patients enrolling in the four NIH-sponsored clinical trials on antibiotic retreatment had experienced poor long-term outcomes from their prior therapy. Participants in the two trials by Klempner *et al*. had persistent symptoms, which were sufficiently severe as to interfere with daily functioning [18];
- Using a combined total of 22 standardized measures of QoL, fatigue, pain and cognition [16–18], the investigators of the four NIH-sponsored retreatment trials documented that the patients' QoL was consistently worse than that of control populations [16–18] and equivalent to that of patients with congestive heart failure [18]; pain levels were similar to those of post-surgical patients and fatigue was on par with that seen in multiple sclerosis [16,18]. Table 1 compares the QoL scores of the NIH Lyme disease participants at the time of their study enrollment to those of patients with other chronic diseases, including diabetes, heart disease, depression, osteoarthritis, rheumatoid arthritis, lupus, fibromyalgia and epilepsy [35–40].

Executive summary of treatment recommendations

With the goal of fostering evidence-based, patient-centered care for patients with Lyme disease, the panel performed a deliberate GRADE assessment of the pertinent trial evidence regarding three fundamental treatment questions and reviewed the risks and benefits of antibiotic therapies used in the treatment of Lyme disease. The panel also considered the ramifications of withholding antibiotic treatments or using non-curative regimens and acknowledged that either may result in a significant disease burden. Following the completion of these activities, the panel drew several conclusions regarding the treatment of Lyme disease.

Table 1. Long-term consequences (or impairments) of Lyme disease.

	Clinical trials	Lyme disease cases mean (SD)	Healthy controls mean (SD)	Impairments in other illnesses – (mean)	Ref.
QoL PCS – range 1–100 (the lower the score, the worse the QoL)†					
PCS	Klempner *et al.*, seropositive	33.1 (9.9)	50 (10)	Diabetes (42), heart disease (39), depression (45), osteoarthritis (39) and rheumatoid arthritis (42)	[18,202]
PCS	Klempner *et al.*, seropositive	35.8 (8.8)	50 (10)		[18]
PCS	Cameron recurrent	39.6 (9.7)	50 (10)		[87]
PCS	Fallon *et al.*	37.1 (8.6)	55.9 (3.6)		[16,38]
QoL MCS – range 1–100 (the lower the score, the worse the QoL)‡					
MCS	Klempner *et al.*, seropositive	43.4 (11.6)	50 (10)	Diabetes (48), heart disease (49), depression (37), osteoarthritis (49) and rheumatoid arthritis (48)	[18]
MCS	Klempner *et al.*, seropositive	46.7 (9.7)	50 (10)		[18]
MCS	Cameron recurrent	35.9 (14.6)	50 (10)		[87]
MCS	Fallon *et al.*	39.2 (11.6)	56.2 (2.9)‡		[16,38]
Fatigue – FSS – range 0–7, severe fatigue (>4.0)§					
FSS	Krupp *et al.*, post-treatment	5.7 (1.4)	2.1 (0.5)	ALS (4.35), multiple sclerosis (5.1)	[16,17]
FSS	Fallon *et al.*	5.2 (1.5)	2.1 (0.5)		[16,203,204]
FIQ – range 0–100 [205] (the higher the score, the greater the impairment)¶					
FIQ	Klempner *et al.*, seropositive	58.4 (19.7)	14 and 21.9	Fibromyalgia (58–78)	[18,35,36,39,206]
FIQ	Klempner *et al.*, seropositive	47.9 (15.2)	14 and 21.9		[18,206]
Pain – MPQ range 0–78 [207] and VAS range 0–10 (the higher the scores, the greater the pain) [208]#					
MPQ	Fallon *et al.*	11.6 (1.5)	1.1 (2.5)	Widespread pain after breast cancer surgery (7.0)	[16,40]
VAS	Fallon *et al.*	5.2 (3.1)	0.1 (0.2)	Fibromyalgia (6.48)	[16,35]
Neurocognitive dysfunction index††					
Index	Fallon *et al.*	–0.49 (0.63)	0.55 (0.40)		[16]

†The PCS on the SF-36 measure of QoL is a measure of physical health, role physical, bodily pain and general health [209].
‡The MCS on the SF-36 measure of QoL is a measure of mental health, emotional role functioning, social functioning and vitality [209].
§The FSS assesses the impact of fatigue on everyday functioning [210].
¶The FIQ is a measure of 'functional disability, ability to have a job, pain intensity, sleep function, stiffness, anxiety, depression and the overall sense of wellbeing' adopted by Burckhardt *et al.* for fibromyalgia [211] and subsequently used in Lyme disease [16,212].
#The MPQ estimates the sensory and affective elements of pain, both qualitatively and quantitatively [213].
††An index based on motor, psychomotor, attention, total memory, Buschke, Benton, working memory, fluency, IQ by Barona, IQ by NAART-R, immediate memory and delayed memory; higher values indicate better cognitive functioning. Additional outcomes described in the NIH-sponsored retreatment trials include cognitive, role functioning and pain on MOS abnormalities [18], psychopathology [16] and a OspA measure of spinal fluid [17].
ALS: Amyotrophic lateral sclerosis; FIQ: Fibromyalgia impact questionnaire; FSS: Fatigue severity scale; MCS: Mental component score; MPQ: McGill Pain Questionnaire; MOS: Medical outcome scale; PCS: Physical component score; SD: Standard deviation; VAS: Visual analog scale; QoL: Quality of life.

Based on these conclusions, the panel formulated treatment recommendations reflecting ILADS values and patient preferences. Recommendations for the individual clinical questions are summarized here. A detailed discussion of each question, including the complete GRADE analysis, the risk–benefit evaluation, ILADS statement of values and the subsequent individual treatment recommendations, in full, follows this summary.

Q1. Does a single 200 mg dose of doxycycline following a tick bite provide effective prophylaxis for Lyme disease?

Organizational values

The panel placed a high value on preventing disease, thereby avoiding both the unnecessary progression from a potentially preventable infection to one that is chronic and associated with significant morbidity and costs. The panel placed a high value on not causing the abrogation of the immune response. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary.

Recommendation 1a

Clinicians should not use a single 200 mg dose of doxycycline for Lyme disease prophylaxis (Recommendation, very low-quality evidence).

Role of patient preferences

Low: The relative trade-offs between risks and benefits are clear enough that most patients will place a high value on avoiding a seronegative state and its attendant delays in diagnosis and treatment.

Recommendation 1b

Clinicians should promptly offer antibiotic prophylaxis for known *Ixodes* tick bites in which there is evidence of tick feeding, regardless of the degree of tick engorgement or the infection rate in the local tick population. The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: Most patients will place a high value on preventing chronic illness. However, some patients will value avoiding unnecessary antibiotics and prefer to not treat a tick bite prophylactically. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 1c

During the initial visit, clinicians should educate patients regarding the prevention of future tick bites, the potential manifestations of both early and late Lyme disease and the manifestations of the other tick-borne diseases that may have been contracted as a result of the recent bite. Patients receiving antibiotic prophylaxis should also be given information describing the symptoms and signs of a *Clostridium difficile* infection and the preventative effect of probiotics. Patients should be encouraged to immediately report the occurrence of any and all tick-borne disease manifestations and manifestations suggestive of a *C. difficile* infection (Recommendation, very low-quality evidence).

Role of patient preferences

Low: The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

Q2. Should the treatment of an EM rash be restricted to 20 or fewer days of oral azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin?

Organizational values

The panel placed a high value on avoiding both the unnecessary progression from a potentially curable infection to one that is chronic and the morbidity and costs associated with chronic disease. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary.

Recommendation 2a

Treatment regimens of 20 or fewer days of phenoxymethylpenicillin, amoxicillin, cefuroxime or doxycycline and 10 or fewer days of azithromycin are not recommended for patients with EM rashes because failure rates in the clinical trials were unacceptably high. Failure to fully eradicate the infection may result in the development of a chronic form of Lyme disease, exposing patients to its attendant morbidity and costs, which can be quite significant. (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: Although many patients will value avoiding the risk of treatment failure over a potentially modest increase in the risk of significant adverse events that may be associated with longer treatment durations, others may prefer to avoid the additional risks of longer treatment. Clinicians should inform patients that: the combined failure rate for the individual agents investigated in the previously discussed EM trials were judged by this panel to be unacceptably high when antibiotic treatment was restricted to 20 or fewer days (provide the appropriate value for each); the evidence supporting the use of longer treatment durations is limited and of low quality [41–43] and increases in antibiotic duration may increase the risk of antibiotic-associated adverse events, although the risks associated with oral antibiotics are low and some of this risk can be mitigated by the concomitant use of probiotics [44,45]. Treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2b

Clinicians should prescribe amoxicillin, cefuroxime or doxycycline as first-line agents for the treatment of EM. Azithromycin is also an acceptable agent, particularly in Europe, where trials demonstrated it either outperformed or was as effective as the other first-line agents [46–49]. Initial antibiotic therapy should employ 4–6 weeks of amoxicillin 1500–2000 mg daily in divided doses, cefuroxime 500 mg twice daily or doxycycline 100 mg twice daily or a minimum of 21 days of azithromycin 250–500 mg daily. Pediatric dosing for the individual agents is as follows: amoxicillin 50 mg/kg/day in three divided doses, with a maximal daily dose of 1500 mg; cefuroxime 20–30 mg/kg/day in two divided doses, with a maximal daily dose of 1000 mg and azithromycin 10 mg/kg on day 1 then 5–10 mg/kg daily, with a maximal daily dose of 500 mg. For children 8 years and older, doxycycline is an additional option. Doxycycline is dosed at 4 mg/kg/day in two divided doses, with a maximal daily dose of 200 mg. Higher daily doses of the individual agents may be appropriate in adolescents.

Selection of the antibiotic agent and dose for an individual patient should take several factors into account. In the absence of contraindications, doxycycline is preferred when concomitant Anaplasma or Ehrlichia infections are possibilities. Other considerations include the duration [27,32,50] and severity [50–53] of symptoms, medication tolerability, patient age, pregnancy status, co-morbidities, recent or current corticosteroid use [54,55] cost, the need for lifestyle adjustments to accommodate certain antibiotics and patient preferences. Variations in patient-specific

details and the limitations of the evidence imply that clinicians may, in a variety of circumstances, need to select therapeutic regimens utilizing higher doses, longer durations or combinations of first-line agents (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: See recommendation 2a.

Recommendation 2c

Clinicians should provide ongoing assessments to detect evidence of disease persistence, progression or relapse or the presence of other tick-borne diseases. Lacking a test of cure, ongoing assessments are crucial for determining if treatment has been clinically effective. The first assessment should immediately follow the completion of therapy and subsequent evaluations should occur on an as-needed basis (Recommendation, very low-quality evidence).

Role of patient preferences

Low: The benefits of monitoring the response to treatment clearly outweigh any attendant risks associated with monitoring.

Recommendation 2d

Clinicians should continue antibiotic therapy for patients who have not fully recovered by the completion of active therapy. Ongoing symptoms at the completion of active therapy were associated with an increased risk of long-term failure in some trials and therefore clinicians should not assume that time alone will resolve symptoms. There is a wide range of options and choices must be individualized, based on the strength of the patient's initial response.

Strong-to-moderate responses favor extending the duration of therapy of the initial agent; modest responses may prompt an increase in the dose of the original antibiotic or a switch to a different first-line agent or tetracycline. Minimal or absent responses suggest a need for a combination of first-line agents, which includes at least one that is able to effectively reach intracellular compartments; injectable penicillin G benzathine (Bicillin LA) or intravenous (iv.) ceftriaxone are other options. Disease progression or recurrence suggests that the iv. antibiotics or injectable penicillin G benzathine, as discussed previously, may be required. For patients requiring antibiotic therapy beyond the initial treatment period, subsequent decisions regarding the modification or discontinuation of treatment should be based on the therapeutic response and treatment goals. Additionally, minimal or absent responses and disease progression require a re-evaluation of the original diagnosis (see remarks following Recommendation 2f). (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: While most patients will place a high value on the potential of regaining their pre-morbid health status and preventing chronic illness by continuing treatment, a substantial portion may also value avoiding unnecessary antibiotics. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2e

Clinicians should retreat patients who were successfully treated initially but subsequently relapse or have evidence of disease progression. Therapeutic options include repeating the initial agent, changing to another oral agent or instituting injectable penicillin G benzathine or iv. ceftriaxone therapy. Choices must be individualized and based on several factors, including: the initial response to treatment; the time to relapse or progression; the current disease severity and the level of QoL impairments.

Prior to instituting additional antibiotic therapy, the original diagnosis should be reassessed and clinicians should evaluate patients for other potential causes that would result in the apparent relapse or progression of symptoms and/or findings (see remarks following Recommendation 2f). The presence of other tick-borne diseases, in particular, should be investigated if that had not already been done.

Following a long period of disease latency, minimal manifestations causing little deterioration in the patient's QoL favor continued observation or repeating therapy with the initial agent; mild manifestations or QoL impairments may prompt a switch to a different first-line agent, tetracycline or the use of a combination of first-line agents. Disease relapse or progression with mild manifestations or QoL impairments occurring within a few months of treatment suggests a need for longer regimens using either tetracycline, a combination of oral first-line agents, injectable penicillin G benzathine or iv. ceftriaxone. Regardless of the duration of disease latency, when disease manifestations or QoL impairments are significant or rapidly progressive, injectable penicillin G benzathine or iv. ceftriaxone may be required. Subsequent decisions regarding the modification or discontinuation of a patient's treatment should be based on individual therapeutic response and preferences (Recommendation, very low-quality evidence).

Role of patient preferences

High: While most patients will place a high value on the potential of regaining their pre-morbid health status and improving their QoL and preventing chronic disease through continued antibiotic treatment, a substantial portion will also value avoiding potentially unnecessary antibiotics. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2f

Clinicians should educate patients regarding the potential manifestations of Lyme disease, carefully explaining that disease latency can be prolonged. Education should also include information on preventing future bites, the manifestations of the other tick-borne diseases that they may have contracted as well

as the symptoms and signs of a *C. difficile* infection and the preventative effect of probiotics. Patients should be encouraged to immediately report the occurrence of any recurrent or newly developing manifestation of Lyme disease as well as those suggestive of other tick-borne diseases or a *C. difficile* infection. Clinicians should emphasize that the need to report manifestations of tick-borne diseases never expires (Recommendation, very low-quality evidence).

Role of patient preferences

Low: The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

Q3. Should patients with persistent manifestations of Lyme disease be retreated with antibiotics?

Organizational values

The panel placed a high value on reducing the morbidity associated with chronic Lyme disease and improving the patient's QoL as well as on the need for individualized risk/benefit assessment and informed shared decision-making. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong compelling evidence to the contrary.

Recommendation 3a

Clinicians should discuss antibiotic retreatment with all patients who have persistent manifestations of Lyme disease. These discussions should provide patient-specific risk–benefit assessments for each treatment option and include information regarding *C. difficile* infection and the preventative effect of probiotics (although none of the subjects in the retreatment trials developed *C. difficile* infection). (Strong recommendation, very low-quality evidence. *Note*: In GRADE, a strong recommendation may be made in the face of very low-quality evidence when the risk–benefit analysis favors a particular intervention such that most patients would make the same choice).

Role of patient preferences

Low: The benefits of educating patients about the potential benefits of retreatment and the risks associated with various treatment options, including not treating, clearly outweigh any attendant risks associated with education.

Recommendation 3b

While continued observation alone is an option for patients with few manifestations, minimal QoL impairments and no evidence of disease progression, in the panel's judgment, antibiotic retreatment will prove to be appropriate for the majority of patients who remain ill. Prior to instituting antibiotic retreatment, the original Lyme disease diagnosis should be reassessed and clinicians should evaluate the patient for other potential causes of persistent disease manifestations. The presence of other tick-borne illnesses should be investigated if that had not already been done. Additionally, clinicians and their patients should jointly define what constitutes an adequate therapeutic trial for this particular set of circumstances.

When antibiotic retreatment is undertaken, clinicians should initiate treatment with 4–6 weeks of the selected antibiotic; this time span is well within the treatment duration parameters of the retreatment trials. Variations in patient-specific details and the limitations of the evidence imply that the proposed duration is a starting point and clinicians may, in a variety of circumstances, need to select therapeutic regimens of longer duration.

Treatment options are extensive and choices must be individualized. Each of these options would benefit from further study followed by a GRADE assessment of the evidence and consideration of associated risks and benefits, but until this information is available, clinicians may act on the currently available evidence.

In choosing between regimens, clinicians should consider the patient's responsiveness to previous treatment for Lyme disease, whether the illness is progressing and the rate of this progression; whether untreated co-infections are present; whether the patient has impaired immune system functioning or has received immunosuppressant corticosteroids and whether other co-morbidities or conditions would impact antibiotic selection or efficacy. Clinicians should also weigh the extent to which the illness interferes with the patient's QoL, including their ability to fully participate in work, school, social and family-related activities and the strength of their initial response against the risks associated with the various therapeutic options. Antibiotic selection should also consider medication tolerability, cost, the need for lifestyle adjustments to accommodate the medication and patient preferences.

For patients with mild impairments who had a strong-to-moderate response to the initial antibiotic, repeat use of that agent is favored. Patients with moderate impairments or only a modest response to the initial antibiotic may benefit from switching to a different agent or combination of agents. For patients with significant impairments and/or a minimal or absent therapeutic response, a combination of oral antibiotics, injectable penicillin G benzathine or iv. ceftriaxone (with the latter two used alone or in combination with other agents) is preferred. For patients who experienced disease progression despite earlier therapy, treatment with injectable penicillin G benzathine or iv. ceftriaxone, alone or in combination with other antibiotics, is advisable. Additionally, minimal or absent responses and disease progression require a re-evaluation of the original diagnosis (Recommendation, very low-quality evidence).

Role of patient preferences

High: The heterogeneous nature of the patient population seen in clinical practice, particularly with regard to variations in disease severity, QoL impairments and aversion to treatment-related risk is likely to affect the risk–benefit assessment. Although many patients will value the opportunity to improve their individual QoL through antibiotic treatment over the risk

of adverse events, others may prefer to avoid the risks associated with treatment. Hence, treatment options, including their associated risks and benefits, should be discussed with the patient in the context of shared medical decision-making.

Recommendation 3c

Clinicians should re-assess patients immediately following the completion of the initial course of retreatment to evaluate the effectiveness of retreatment and the need for therapeutic adjustments. Reassessment may need to be done much earlier and with greater scrutiny in patients with severe disease or when the therapeutic intervention carries substantial risk.

For patients who improve yet continue to have persistent manifestations and continuing QoL impairments following 4–6 weeks of antibiotic retreatment, decisions regarding the continuation, modification or discontinuation of treatment should be based on several factors. In addition to those listed in Recommendation 3b, the decision to continue treatment may depend on the length of time between the initial and subsequent retreatment, the strength of the patient's response to retreatment, the severity of the patient's current impairments, whether diagnostic tests, symptoms or treatment response suggest ongoing infection and whether the patient relapses when treatment is withdrawn.

In cases where the patient does not improve after 4–6 weeks of antibiotic retreatment, clinicians should reassess the clinical diagnosis as well as the anticipated benefit. They should also confirm that other potential causes of persistent manifestations have been adequately investigated prior to continuing antibiotic retreatment. Decisions regarding the continuation, modification or discontinuation of treatment should consider the factors noted above as well as the definition of an adequate therapeutic trial.

Whenever retreatment is continued, the timing of subsequent follow-up visits should be based on the level of the therapeutic response, the severity of ongoing disease, the duration of current therapy and the need to monitor for adverse events. (Recommendation, very low-quality evidence).

Role of patient preferences

High: See Recommendation 3b.

The complete discussion of the individual clinical questions

Q1. Does a single 200 mg dose of doxycycline following a tick bite provide effective prophylaxis for Lyme disease?

Evidence

The panel conducted a Medline search on 5 March 2013 for RCTs and meta-analyses, which investigated using a single dose of doxycycline for antibiotic prophylaxis of *Ixodes scapularis* bites. The search used this strategy: *Ixodes scapularis* bites OR erythema migrans/prevention OR erythema chronicum migrans/prevention OR Lyme disease/prevention and these filters: comparative study, clinical trial, meta-analysis, humans. The search identified 99 papers. Four trials of antibiotic prophylaxis following an *I. scapularis* bite that were conducted in the USA and two meta-analyses involving some or all of those trials were identified and reviewed [56–61]. Three trials were excluded because they investigated the efficacy of various 10-day antibiotic regimens rather than the efficacy of a single 200 mg dose of doxycycline [56–58]. Given that the two meta-analyses drew substantially from these trials, both were excluded. The fourth trial evaluated the effectiveness of a single 200 mg dose of doxycycline following a tick bite for the prevention of an EM rash at the bite site [59].

Bias

The single-dose doxycycline trial was designed using prevention of an EM rash at the bite site as a surrogate for the prevention of Lyme disease [62]. This surrogate has not been validated. Although 15 years of CDC surveillance data documented that 31% of reported surveillance cases lacked an EM rash [63], the single-dose doxycycline trial was not designed to detect cases of Lyme disease in which the rash was absent. Instead, the trial design regarded all subjects lacking an EM as disease negative, thus biasing the trial in favor of finding treatment effective.

It should be noted that the single-dose doxycycline trial identified three subjects with clinical and laboratory evidence (seroconversion) of early Lyme disease who lacked an EM at the bite site, thus demonstrating that the prevention of an EM rash at the bite site is not an appropriate surrogate for prevention of Lyme disease [62].

Later manifestations of Lyme disease may take months or years to develop [64–68]. The trial's 6-week observation period was therefore insufficient to detect treatment failure and thus biased the trial toward finding treatment to be effective [62].

Investigators neglected to state that failed treatment resulted in seronegative disease as exhibited by one subject in the study [62]. This unfavorable outcome was not included in the risk–benefit assessment, biasing the study in favor of treatment.

Precision

The single-dose doxycycline trial was incapable of measuring the effectiveness of a single 200 mg dose of doxycycline for Lyme disease prevention because outcome measurements were limited to documenting the occurrence of an EM rash at the bite site as opposed to all disease manifestations [62]. However, the trial did demonstrate that treatment with doxycycline resulted in fewer EM rashes than placebo, 1 of 235 (0.4%) and 8 of 247 (3.2%), respectively ($p < 0.04$) [59]. Yet the data here are sparse, coming from a single study with few events, and, thus, imprecise.

The corresponding relative treatment effectiveness was reported to be 87%, with a 95% CI of 25–98% [59]. The wide CI indicates that the finding was imprecise. This value, however, appears to be incorrect. Although the authors reported using the Fisher exact test to calculate the odds ratio, by our calculations, the correct CI is 0.003–0.968, corresponding to a 95% CI on the scaled risk difference from 3.2 to 99.7%. This wider 95% CI suggests the study findings are consistent with a

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

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

EM: Erythema migrans.

much smaller minimum treatment effect, with the lower limit of the CI reflecting the possibility of only a 3.2% reduction in the risk of EM in the antibiotic arm compared with placebo. Thus, the trial was not well powered to precisely measure the treatment effect despite being adequately powered to detect statistical significance.

Although the dropout rate was low (11%), the assumption that none of the participants who dropped out developed an EM is unsupported and biased the estimated incidence in each arm downward. Furthermore, had a single EM in the antibiotic arm been missed due to patient dropout, then the statistical significance of the primary outcome would have been lost ($p = 0.11$). It is unsettling when changing one participant's outcome can dramatically affect a study's conclusion.

Consistency

No other clinical trials have evaluated the effectiveness of a single 200 mg dose of doxycycline for the prevention of an EM rash at the bite site; therefore, the consistency of this finding in humans cannot be judged.

However, the effectiveness of doxycycline prophylaxis has been studied in a murine model [69,70] and the findings were inconsistent with that of the single-dose doxycycline trial [62]. In contrast to the human trial, which used a surrogate marker, the murine study used tissue cultures and post-treatment necropsy findings to provide direct evidence of treatment effectiveness. In the murine model, single-dose oral doxycycline was 43% effective for preventing Lyme disease [69]. A second murine study using ticks dually infected with *Borrelia burgdorferi* and *Anaplasma phagocytophilum* demonstrated that single-dose oral doxycycline was 20 and 30% effective for preventing *B. burgdorferi* and *A. phagocytophilum* infections, respectively [70].

While it has been suggested that the lower efficacy of doxycycline in the murine studies was related to differences between mice and humans with regard to the duration of time that doxycycline levels exceeded the minimal inhibitory concentration for *B. burgdorferi* following a single oral dose of doxycycline (T > minimal inhibitory concentration) [71], subsequent pharmacodynamic modeling found that other pharmacodynamic parameters correlated better with efficacy [72]. However, these findings were based on flawed assumptions. Thus, the reason for the apparently lower efficacy of single-dose oral doxycycline in mice is unclear. It is worth noting that the 95% CI in the study by Nadelman *et al.* was quite large, 3.2–99.7% (see precision discussion above), suggesting that true treatment effectiveness was approximately 50% [69], a value comparable to that of the murine study [69].

Directness (generalizability)

The directness of the trial is limited to patients bitten by *I. scapularis* ticks treated with a single-dose doxycycline. The effectiveness of single-dose regimens using other antibiotics and the effectiveness of single-dose doxycycline in other *Ixodes* species have not been evaluated. Further, animal models suggest single-dose oral doxycycline prophylaxis is less effective when multiple pathogens are simultaneously transmitted to a host [70]; therefore, the findings are not applicable to patients exposed to *B. burgdorferi* and *A. phagocytophilum* and the applicability to patients exposed to *B. burgdorferi* and other co-infecting pathogens cannot be assumed.

Evidence quality, in aggregate

Overall, the quality of the evidence supporting the use of a single 200 mg dose doxycycline following a tick bite is very low (Table 2), implying that the true effectiveness of a single 200 mg dose of doxycycline is likely to be substantially different from the trial's reported effectiveness rate [6].

Benefits

The single 200 mg dose doxycycline trial design employed an unvalidated and inappropriate surrogate and the duration of the observation period was inadequate. The reported 87% efficacy of single-dose doxycycline therapy was with regard to the observed reduction in the incidence of an EM rash at the bite site in the doxycycline subjects compared with the placebo subjects (Table 3) [59], but the reliability of this finding is diminished by its imprecision and its clinical significance is questionable (see quality of evidence discussion above). Therefore, the trial's significant design deficiencies prohibit conclusions regarding the efficacy and, thus, the benefits of single-dose doxycycline therapy for the prevention of Lyme disease.

Table 3. Summary of findings regarding the effectiveness of single-dose doxycycline for prevention of erythema migrans rashes.

	Incidence placebo	Incidence single-dose doxy	Treatment efficacy	N (trials)	Evidence quality
EM prevention	8/247	1/235	87%; 95% CI: 3.2–99.7%	482 (1)	Very low

Safety of single-dose doxycycline.
N = 235; Adverse events: 1 patient who failed therapy was persistently seronegative; no other serious adverse events.
EM: Erythema migrans.

Harms

Treatment failure may result in seronegative Lyme disease. Although the single-dose doxycycline trial was not designed to determine whether this regimen could result in seronegative Lyme disease, the subject in the doxycycline arm who failed treatment remained negative on follow-up serologic testing, suggesting that this occurred [62,73]. Clinical trials, case reports and studies in non-human primates have also documented instances of seronegative disease [33,74–76]. While the mechanisms allowing for seronegative disease have yet to be fully investigated, antibiotic treatment has been shown to abrogate the immune response in *Coccidioides* spp. [77], primary syphilis [78], rheumatic fever [79] as well as Lyme disease [80,81]. It is postulated that antibiotic therapy reduces the antigenemia needed for the immune system to establish an immunologic response [77]. Inducing a seronegative disease state may lead to diagnostic and treatment delays, which are associated with poorer outcomes, and the development of a chronic form of the illness [16,27,32,82,83].

Risk–benefit assessment

The potential harms of the single-dose oral doxycycline prophylactic regimen and the magnitude of those harms significantly outweigh its benefits. In assessing the risk–benefit profile, the panel considered the unknown efficacy of single dose prophylaxis in preventing the development of Lyme disease and the magnitude of the potential harm created by inducing a seronegative state, including its concomitant diagnostic and treatment delays and the resultant increased risk of developing a chronic form of the disease, which is more difficult to treat successfully. The panel also considered findings from a murine model, which demonstrated that the effectiveness of single-dose doxycycline is further reduced in dual infections involving *B. burgdorferi* and *A. phagocytophilum*, an important consideration in many regions of the USA. Additionally, the panel noted that the effects of this regimen on the clinical presentation, detection and prevention of other common *Ixodes*-borne co-infections are unknown.

Values

The panel placed a high value on preventing disease, thereby avoiding both the unnecessary progression from a potentially preventable infection to one that is chronic and associated with significant morbidity and costs. The panel placed a high value on not causing the abrogation of the immune response. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary.

Recommendation 1a

Clinicians should not use a single 200 mg dose of doxycycline for Lyme disease prophylaxis. (Recommendation, very low-quality evidence)

Role of patient preferences

Low: The relative trade-offs between risks and benefits are clear enough that most patients will place a high value on avoiding a seronegative state and its attendant delays in diagnosis and treatment.

Recommendation 1b

Clinicians should promptly offer antibiotic prophylaxis for known *Ixodes* tick bites, in which there is evidence of tick feeding, regardless of the degree of tick engorgement or the infection rate in the local tick population. The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis (see remarks below). (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: Most patients will place a high value on preventing chronic illness. However, some patients will value avoiding unnecessary antibiotics and prefer to not treat a tick bite prophylactically. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 1c

During the initial visit, clinicians should educate patients regarding the prevention of future tick bites, the potential manifestations of both early and late Lyme disease and the manifestations of the other tick-borne diseases that may have been contracted as a result of the recent bite. Patients receiving antibiotic prophylaxis should also be given information describing the symptoms and signs of a *C. difficile* infection and the preventative effect of probiotics. Patients should be encouraged to immediately report the occurrence of any and all tick-borne disease manifestations and manifestations suggestive of a *C. difficile* infection (Recommendation, very low-quality evidence).

Role of patient preferences

Low: The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

Remarks

Lyme disease often results from unrecognized tick bites [32,84], which do not provide an opportunity for administering antibiotic prophylaxis. When antibiotic prophylaxis is employed for known bites, it is imperative that treatment begin without delay. A recent murine study demonstrated that prophylaxis was most effective when given immediately after a bite and that effectiveness diminished with treatment delays [85]. Although no studies to date have specifically investigated the efficacy of antibiotic prophylaxis for bites from other *Ixodes* species, it is reasonable to provide prophylaxis for such bites pending future research.

The evidence supporting use of 20 days of antibiotics is limited to the previously mentioned murine trials [69,70]. In the first trial, investigators demonstrated that a long-acting form of doxycycline, with measurable levels for 19 days, was 100% effective for preventing Lyme disease [69]. In the dual-exposure model, the long-acting form of doxycycline was 100% effective for preventing *B. burgdorferi* and *A. phagocytophilum* infections [70]. No long-acting, injectable doxycycline preparation is available for use in humans [62], which is why the panel recommends using 100–200 mg of doxycycline twice daily for a minimum of 20 days. One advantage to this regimen is that it would also address situations where patients are exposed to both *B. burgdorferi* and *A. phagocytophilum*.

Analysis of the single-dose doxycycline trial highlights the problems inherent in formulating treatment recommendations on the basis of a single study and demonstrates that a randomized, placebo-controlled study design, in and of itself is not a guarantee that the study will produce high-quality evidence. The panel recognizes that recommendations based solely on animal models are also problematic. Therefore, the panel encourages the NIH to fund appropriately designed trials in order to investigate the optimum duration of treatment for a known *Ixodes* bite.

Given that doxycycline dosages of 100 mg twice daily may not provide adequate levels in all tissues or in all patients [86], some clinicians may prefer to prescribe higher daily doses [52,86–89]. Regardless of the selected dose, clinicians should advise patients to take probiotics daily while on antibiotic therapy. Probiotics reduce the risk of *C. difficile* colitis and antibiotic-associated diarrhea [44,45].

'Watchful waiting' does not satisfy a strict definition of prophylaxis. Rather than acting to prevent disease, this option seeks the early identification and treatment of Lyme disease infections resulting from a known bite. The hallmark of early disease is the EM rash; and as previously noted, almost a third of reported surveillance cases of Lyme disease lack this finding [16,18,63]. Given the possible absence of an EM rash in a patient with a known bite, this option not only withholds primary preventative therapy, it potentially loses an opportunity to provide secondary prevention as well, should the early, non-EM manifestations of the infection be missed. However, patients wishing to avoid antibiotics may prefer this option, in which case clinicians should emphasize that patients must immediately report the occurrence of Lyme-related symptoms so that appropriate antibiotic therapy can be instituted.

In cases where doxycycline is contraindicated, clinicians may consider using other antibiotics known to be effective in Lyme disease, such as amoxicillin, cefuroxime or azithromycin, although there is no evidence to guide decisions with regard to the dose and duration of use for these agents. The excluded trials of antibiotic prophylaxis investigated the therapeutic efficacy of 10 days of amoxicillin, three-times daily [58]; penicillin, four-times daily [56,57] and tetracycline, four-times daily [57]. None of the trials was able to demonstrate efficacy, primarily due to the low incidence of disease in the placebo groups [56,57].

Some guidelines recommend that clinicians learn to estimate attachment times for recovered ticks based on their scutal index, but expertise is required to do this and it is unrealistic to assume that all clinicians can or will acquire such skills. In the single-dose doxycycline study, 9.9% of the bites from nymphal ticks that exhibited any degree of engorgement resulted in the development of an EM at the bite site [59]. Therefore, the panel determined that it was prudent to routinely offer prophylaxis under such circumstances and that withholding therapy from patients who failed to meet an arbitrary minimum tick attachment time was inappropriate. Similarly, the panel recognizes that clinicians frequently lack information regarding current infection rates for a given tick population (often because the research to establish local infectivity rates has not been done) and that tick infection rates in the same locale vary significantly on an annual basis [90]. Therefore, the panel concluded that meeting a specific tick infection rate should not be a prerequisite for antibiotic prophylaxis.

Q2. Should the treatment of an EM rash be restricted to 20 or fewer days of the first-line oral agents (azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin)?

Evidence

The panel conducted a Medline search on 5 March 2013 for prospective randomized clinical trials investigating the effectiveness of 5–20 days of oral azithromycin, cefuroxime, doxycycline, phenoxymethylpenicillin or amoxicillin for the treatment of EM. The search used the following strategy: (erythema migrans OR erythema chronicum migrans OR lyme OR lyme borreliosis) AND (amoxicillin/therapeutic use OR azithromycin/therapeutic use OR penicillin/therapeutic use OR cefuroxime/therapeutic use OR doxycycline/therapeutic use) AND (Clinical trial OR comparative study OR meta-analysis). The search identified 76 papers; 51 reported trial outcomes.

A preliminary assessment found that 27 papers described studies that either investigated antibiotic treatment of non-EM presentations (23); were primarily interested in disseminated disease (3) or did not involve any of the antibiotics of interest

Table 4. Quality of the evidence, in aggregate, that supports restricting the antibiotic treatment of erythema migrans to 20 or fewer days.

No. of studies	Limitations	Precision	Consistency	Indirectness	Evidence quality
9 [46–49,53,74,88,91,92]	No single trial design investigated all agents Trials differed by agents, duration of therapy, length of observation Insufficient observation in most Overly broad definitions of success Lack of a standard outcome definition Use of non-ITT longitudinal data methods	Limited number of trials Small sample sizes Only 3 of 9 reported CI	No trial investigated all 4 classes of antibiotics. As originally reported: - Efficacies of individual agents were inconsistent - Relative efficacies among trials investigating the same agents were inconsistent When uniform design elements applied and outcomes assessed by treatment duration: - Inconsistent intra-agent success rates - Inconsistent relative outcomes in inter-agent comparisons	Not applicable to non-EM early Lyme; EM with CNS dissemination, co-infected or immunocompromised patients European trials may not be applicable to the US patients	Very low

†Several comparative studies described differing durations of therapy.
EM: Erythema migrans; ITT: Intention to treat.

(1). These were not considered further. An additional 15 trials were excluded because additional review demonstrated that they were either retrospective studies (2); incompletely randomized (1); used a symptom list during post-treatment assessments that did not include commonly reported symptoms of the disease (7) or had a non-completion rate of 20% or higher (5). Thus, nine trials met the requirements for this GRADE analysis and were evaluated in detail (Tables 4 & 5) [46–49,53,74,88,91,92].

Rating the quality of the evidence

Bias

None of the trials compared all four antibiotic classes (azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin). The nine trials had significant differences in design elements including: antibiotic agents investigated, duration of therapy, outcome definitions, length of observation period and longitudinal data methods; these differences potentially biased findings in favor of one or more agents and make it difficult to draw broad conclusions regarding the effectiveness of the various agents.

Observation periods ranged from 3 to 24 months. The optimum duration of post-treatment observation for EM has not been determined, in part, because while disease relapse is known to occur, the duration of the latent period is variable and can be prolonged [32,33,93]. For example, one trial reviewed here reported a relapse at 20 months [46] and Logigian *et al.* found that in their subjects (all of whom had neurologic manifestations of Lyme disease), the median time from EM to chronic CNS symptoms was 26 months, with a range of 1–168 months. Thus, trials with longer observation periods are more likely to capture disease relapse and subsequently report lower success rates. Therefore, variations in the length of the observation period may bias efficacy findings in favor of agents that were investigated in trials utilizing short observation periods.

Recognizing this, investigators in two of the EM trials cited the need for longer observation periods in their discussions [47,74]; one suggested that to accurately compare agents, observation periods would need to extend 2 years post-treatment [47]. Of the nine trials reviewed by the panel, only one [46] met this suggested standard and, given that relapse may occur even later, 2 years may not be sufficient.

The lack of standardized outcome definitions also introduces bias. The trials used broad definitions of treatment success that differed by trial [46–49,53,74,88,91,92]. All required the complete resolution of EM and an absence of new findings but, to varying degrees, each trial allowed subjects with improved yet persistent symptoms and subjects who had developed new symptoms consistent with Lyme disease during the observation period to be included within the success group. Thus, treatment success was not synonymous with the full restoration of the pre-Lyme disease health status and prevention of late manifestations of Lyme disease and, therefore, all of the trials were biased toward finding treatment to be effective.

The choice of longitudinal data methods may bias findings by either overstating or understating success rates [94] and the nine trials employed different methods for handling subjects who did not complete the study as designed [46–49,53,74,88,91,92]. Seven trials used complete-case methodology [46–48,53,74,88,91], one reported results in both complete-case and last observation

Table 5. Summary of findings regarding the effectiveness of treating an erythema migrans rash with 20 or fewer days of antibiotics based on a re-analysis of the original trial data to reflect patient-centered outcomes.

Duration of treatment, in days	Outcome	Number of trials, success rate by agent†			
		Azith	*Cefur*	*Doxy*	*PMP/Amox*
≤10 days	Return to baseline without relapse	6 trials [46–49,53,74] 230/298 (77.8%)	No trials	1 trial [53] 14/22 (63.6%)	2 trials [48,53] 11/52 (78.8%)
11–19	Return to baseline without relapse	No trials	1 trial [92] 110/140 (78.6%)	3 trials [46,47,49] 77/115 (67.0%)	1 trial [46] 12/23 (52.2%)
20	Return to baseline without relapse	No trials	2 trials [88,91] 48/78 (61.5%)	No trials	2 trials [74,91] 114/135 (84.4%)
5–20	Adverse events	Serious adverse events, defined as allergic reactions, *Clostridium difficile* infections, any adverse event resulting in withdrawal from study or change in therapeutic agent, and any adverse event labeled by the investigators as 'serious' occurred in 21 of 1068 subjects (2.0%) [46–49,53,74,88,91,92]. None of the adverse events was specifically categorized as allergic reactions. The majority of serious adverse events involved the skin (13), including non-specific skin rash (6) [74], drug eruptions (6) [53] and serious photosensitivity reaction (1) [46]. Gastrointestinal adverse events were also common, including poor medication palatability in pediatric subjects (2) [91], nausea and vomiting (1) [48] and diarrhea (5) [49,74,88]. A single subject was treated for *C. difficile* infection shortly after completing treatment [91]. No deaths were reported.			

†CIs for the individual trials are available in Supplementary Appendix III.
Azith: Azithromycin; Cefur: Cefuroxime; Doxy: Doxycycline; PMP/Amox: Phenoxymethylpenicillin/amoxicillin.

carried forward [92] and one trial employed an intention-to-treat (ITT) approach [49].

Complete-case methodology is likely to overstate treatment success because subjects who leave the trial prematurely due to treatment ineffectiveness or intolerance are excluded from outcome calculations [94,95]. Thus, the trials that used this approach were biased towards finding higher treatment success rates. Last observation carried forward completes the data set for missing subjects by imputing the value from the most recent visit to all subsequently missed observation points, implying outcomes are static [94,95]. Because relapses occur in Lyme disease, this methodology may overstate treatment success; thus, the trials that used last observation carried forward were likely biased towards finding higher treatment success rates.

ITT models evaluate subjects by their assigned treatment, regardless of compliance [94,95]. These models also impute data for the missing and the chosen values reflect assumptions regarding the likelihood that certain potential outcomes actually occurred [95]. Potential assumptions range from worst-case to best-case scenarios. In general, ITT methodology is thought to better represent clinical realities, where patients may inadvertently or purposefully supplement treatment with other interventions that affect outcomes or elect to abandon ineffective treatment altogether [94,96]. The EM trial that employed ITT methodology assumed that missing subjects fulfilled the worst case scenario, that is, had failed [49], biasing the trial toward finding treatment less successful. However, adopting a conservative approach to efficacy determinations avoids the potential harms associated with overstating treatment success and understating treatment failures.

Precision

The number of trials that investigated a given antibiotic was limited and sample sizes in the individual trials were small. Trial numbers per agent ranged from 3 to 5 and median sample sizes per agent ranged from 28 to 63. Small sample sizes are susceptible to random chance and small study bias [97–99].

Only three of the nine trials reported CIs for treatment efficacy [74,88,92]; a fourth reported CIs for the risk of a drug eruption [53].

Consistency

Outcomes, as originally reported by the nine trials, were inconsistent. Two trials simultaneously evaluated the effectiveness of azithromycin, doxycycline and phenoxymethylpenicillin/amoxicillin plus probenecid [46,53]. Strle *et al.* reported that 28% of subjects, overall, had post-treatment signs/symptoms. By agent, 15% of azithromycin, 26% of doxycycline and 43% phenoxymethylpenicillin subjects had post-treatment manifestations [46]. In contrast, Massarotti *et al.* reported that azithromycin, doxycycline and amoxicillin plus probenecid were equally efficacious [53].

Seven trials compared two of the three agents, although the pairings differed [48,49,74,88,91,92,100]. Weber *et al.* found that

azithromycin and phenoxymethylpenicillin were comparable, while Luft *et al*. found amoxicillin to be more efficacious for preventing late disease than azithromycin [48,74]. Azithromycin was more efficacious than doxycycline in the 1993 trial by Strle *et al*., but Barsic *et al*. found the two agents equivalent [47,49].

In a separate analysis, success rates for the individual agents were determined after uniform patient-centered outcome definitions and longitudinal data methods were applied to the original data (see Benefits section below and Table 5). These results were also inconsistent. Success, in relation to treatment duration, demonstrated inter- and intra-agent inconsistencies. For example, when the treatment duration was 11–19 days, cefuroxime (78.6%) outperformed phenoxymethylpenicillin/amoxicillin (52.2%) but for 20 days of treatment, success for phenoxymethylpenicillin/amoxicillin (84.4%) was greater than that of cefuroxime (61.5%). Success rates for individual agents were also inconsistent; both cefuroxime and phenoxymethylpenicillin/amoxicillin had higher success rates with shorter, rather than longer, treatment durations.

Directedness (generalizability)

Findings are applicable to patients with EM rashes, without evidence of CNS dissemination. It cannot be assumed that findings are applicable to patients with Lyme disease inclusive of CNS dissemination, other tick-borne diseases or immunocompromised states [101]. Nor can it be assumed that findings are applicable to non-EM early Lyme disease [102]. Given the clinical variations between the genospecies [103,104], results from European trials, where *Borrelia afzelii* is the dominant cause of EM rashes [102], may not be applicable to the US patients.

Evidence quality, in aggregate

The quality of the evidence addressing the effectiveness of 5–20 days of antibiotics for the treatment of EM is very low, implying that the true effectiveness of a 5–20 day course of antibiotics for the treatment of an EM rash is likely to be substantially different from the trials' reported effectiveness rate.

Benefits

The limitations of the evidence from the original trials reduce the reliability of their findings. Given that no trial directly compared all classes of agents (azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin) and direct comparisons between individual trials are hampered by differences in outcome definitions, length of the observation periods and longitudinal data methodologies, the ability to draw valid conclusions regarding the relative effectiveness of commonly prescribed antibiotic regimens is impaired.

To provide comparative information on patient-centered outcomes by agent – information of clinical import to clinicians and patients – the original trial data were reanalyzed. To minimize biases due to variations in trial design, standardized, patient-centered definitions of treatment success and failure and uniform statistical methodology, utilizing the conservative approach of Barsic *et al*. [49], were applied to the original trial data. To avoid overstating the effectiveness of the investigated antibiotics, the panel specifically chose to assume that those who failed to complete the trial were treatment failures.

Success was defined as the complete resolution of EM and all associated symptoms and findings, without evidence of disease relapse or the development of new manifestations consistent with Lyme disease during the observation period. The panel viewed this outcome definition as the outcome that would matter most to patients and thought it was consistent with the expectation that the appropriate treatment of an EM rash should restore the patient to their pre-morbid baseline.

Failure included any outcome short of that. Subjects described by the investigators as failures and those who were retreated (regardless of the post-retreatment outcome) were considered failures for the purpose of this outcome analysis. Subjects who had ongoing symptoms at the final end point, including those described as 'partial responders', were also considered failures. In some instances, this resulted in subjects being re-categorized as failures. Subjects who were 'unevaluable', wrongly enrolled, non-compliant, withdrawn prematurely due to adverse reactions to their assigned antibiotic or lost to follow-up were also considered failures for the purpose of this analysis.

Success rates across the nine trials differed significantly. The lowest, 52.2% (CI: 30.6, 73.3), was in the phenoxymethylpenicillin arm of the 1992 trial by Strle *et al*. and the highest, 93.3% (CI: 68.1, 99.8), was in the high-dose cefuroxime arm in the trial by Eppes and Childs (see Supplementary Appendix III). The two arms with the highest success rates had exceptionally small sample sizes; one arm had 13 subjects, the other had 15 [91]. The two arms with the lowest success rates also had small samples sizes, 23 subjects in one and 26 in the other [46,53].

Success rates were subsequently regrouped by agent and treatment duration and weighted average success rates for the various regimens were then calculated. The outcome results from arms which had non-completion rates equal to or exceeding 20% were excluded from the calculations. As shown in Table 5, success rates for a given treatment duration vary by antibiotic class. Twenty days of phenoxymethyl-penicillin/amoxicillin had the highest overall success rate of all of the regimens, 84.4%, while 11–19 days of these same agents had the lowest success rate, 61.5%.

Harms

Serious adverse events, defined as allergic reactions, *C. difficile* infections, any adverse event resulting in withdrawal from study or change in therapeutic agent and any adverse event labeled by the investigators as 'serious' occurred in 20 of 1068 subjects (1.9%) (Table 5). None of the adverse events was specifically categorized as allergic reactions. The majority of serious adverse events involved the skin (11), including non-specific skin rash (6) [74], drug eruptions (4) [53] and serious

photosensitivity reaction (1) [46]. Gastrointestinal adverse events were also common, including poor medication palatability in pediatric subjects (2) [91], nausea and vomiting (1) [48] and diarrhea (5) [49,74,88]. A single subject was treated for *C. difficile* infection shortly after completing treatment [91]. No deaths were reported.

Although the panel did not consider a Jarisch–Herxheimer reaction an adverse event, four EM trials reported a Jarisch–Herxheimer reaction in 60 of 351 subjects (17.1%) (range 12.1–18.7%) [47,53,88,91].

Risk–benefit assessment

The harms associated with restricting treatment of an EM rash to 20 or fewer days of oral azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin outweigh the benefits. In assessing the risk–benefit profile, the panel determined that the failure rates for antibiotic treatment of 20 or fewer days were unacceptably high and that for those who failed treatment, the magnitude of the potential harm created by delaying definitive treatment, which includes the increased risk of developing a chronic and more difficult to treat form of the disease, was too great.

Although it is generally assumed that antibiotic regimens of shorter duration will be associated with a lower rate of significant adverse events, adverse event rates for oral antibiotics are generally quite low regardless of the duration of use [105–107]. The panel concluded that while antibiotic treatment regimens of 20 or fewer days may result in slightly fewer significant adverse events compared with regimens of longer duration, that benefit does not offset the potential harms associated with the unacceptably high failure rates resulting from this treatment approach. Furthermore, as previously noted, the concomitant use of probiotics should reduce the risk of *C. difficile* colitis and antibiotic-associated diarrhea [44,45].

Values

The panel placed a high value on avoiding both: the unnecessary progression from a potentially curable infection to one that is chronic and the morbidity and costs associated with chronic disease. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary.

Recommendation 2a

Treatment regimens of 20 or fewer days of phenoxymethylpenicillin, amoxicillin, cefuroxime or doxycycline and 10 or fewer days of azithromycin are not recommended for patients with EM rashes because failure rates in the clinical trials were unacceptably high. Failure to fully eradicate the infection may result in the development of a chronic form of Lyme disease, exposing patients to its attendant morbidity and costs, which can be quite significant. (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: Although many patients will value avoiding the risk of treatment failure over a potentially modest increase in the risk of significant adverse events that may be associated with longer treatment durations, others may prefer to avoid the additional risks of longer treatment. Clinicians should inform patients that the combined failure rate for the individual agents investigated in the previously discussed EM trials were judged by this panel to be unacceptably high when antibiotic treatment was restricted to 20 or fewer days; the evidence supporting the use of longer treatment durations is limited and of low quality [41–43] and increases in antibiotic duration may increase the risk of antibiotic-associated adverse events, although the risks associated with oral antibiotics are low and some of this risk can be mitigated by the concomitant use of probiotics [44,45,108]. Treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2b

Clinicians should prescribe amoxicillin, cefuroxime or doxycycline as first-line agents for the treatment of EM. Azithromycin is also an acceptable agent, particularly in Europe, where trials demonstrated it either outperformed or was as effective as the other first-line agents [46–49]. Initial antibiotic therapy should employ 4–6 weeks of amoxicillin 1500–2000 mg daily in divided doses, cefuroxime 500 mg twice daily or doxycycline 100 mg twice daily or a minimum of 21 days of azithromycin 250–500 mg daily. Pediatric dosing for the individual agents is as follows: amoxicillin 50 mg/kg/day in three divided doses, with a maximal daily dose of 1500 mg; cefuroxime 20–30 mg/kg/day in two divided doses, with a maximal daily dose of 1000 mg and azithromycin 10 mg/kg on day 1 then 5–10 mg/kg daily, with a maximal daily dose of 500 mg. For children 8 years and older, doxycycline is an additional option. Doxycycline is dosed at 4 mg/kg/day in two divided doses, with a maximal daily dose of 200 mg. Higher daily doses of the individual agents may be appropriate in adolescents.

Selection of the antibiotic agent and dose for an individual patient should take several factors into account. In the absence of contraindications, doxycycline is preferred when concomitant Anaplasma or Ehrlichia infections are possibilities. Other considerations include the duration and severity of symptoms, medication tolerability, patient age, pregnancy status, co-morbidities, recent or current corticosteroid use [54,55], cost, the need for lifestyle adjustments to accommodate certain antibiotics and patient preferences. Variations in patient-specific details and the limitations of the evidence imply that clinicians may, in a variety of circumstances, need to select therapeutic regimens utilizing higher doses, longer durations or combinations of first-line agents. (Recommendation, very low-quality evidence)

Role of patient preferences

Moderate: See Recommendation 2a.

Recommendation 2c

Clinicians should provide ongoing assessments to detect evidence of disease persistence, progression or relapse or the presence of other tick-borne diseases. Lacking a test of cure, ongoing assessments are crucial for determining if treatment has been clinically effective (see remarks following Recommendation 2f). The first assessment should immediately follow the completion of therapy and subsequent evaluations should occur on an as-needed basis. (Recommendation, very low-quality evidence)

Role of patient preferences

Low: The benefits of monitoring the response to treatment clearly outweigh any attendant risks associated with monitoring.

Recommendation 2d

Clinicians should continue antibiotic therapy for patients who have not fully recovered by the completion of active therapy. Ongoing symptoms at the completion of active therapy were associated with an increased risk of long-term failure in some trials and therefore clinicians should not assume that time alone will resolve symptoms (see remarks following Recommendation 2f). There is a wide range of options and choices must be individualized, based on the strength of the patient's initial response. Dosage ranges for oral agents are as noted in Recommendation 2b.

Strong-to-moderate responses favor extending the duration of therapy of the initial agent at the same dosage. Modest responses may prompt an increase in the dosage of the initial antibiotic or a switch to a different first-line agent. Tetracycline, with a total daily dose of 1000–1500 mg in three or four divided doses, is an additional option [50,109]. Due to its favorable pharmacokinetics, tetracycline may be more effective than doxycycline when initial therapy is non-curative [109].

Minimal or absent responses suggest a need for a combination of first-line agents, which includes at least one antibiotic that is able to effectively reach intracellular compartments [109,110]. Injectable penicillin G benzathine (Bicillin LA), totaling 1.2–3.6 million units weekly, or iv. agents such as ceftriaxone are other options. Intramuscular (IM) benzathine penicillin avoids the risks associated with gaining iv. access and it was effective in seemingly recalcitrant Lyme arthritis [111]. Ceftriaxone, 2 g iv. per day is known to be effective [16,17,32,33,54,112] and iv. cefotaxime [113], another cephalosporin, has also been recommended. iv. penicillin is less effective and requires more frequent dosing [114]. Additional iv. cell wall agents from the carbapenem and monobactam classes were effective *in vitro*, but have not been studied clinically [115].

Disease progression or recurrence suggests that the iv. agents or injectable penicillin G benzathine, as discussed above, may be required. For patients requiring antibiotic therapy beyond the initial treatment period, subsequent decisions regarding the modification or discontinuation of treatment should be based on the therapeutic response and treatment goals. Additionally, minimal or absent responses and disease progression require a re-evaluation of the original diagnosis (see remarks following Recommendation 2f). (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: While most patients will place a high value on the potential of regaining their pre-morbid health status and preventing chronic illness by continuing treatment, a substantial portion may also value avoiding unnecessary antibiotics. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2e

Clinicians should retreat patients who were successfully treated initially, but subsequently relapse or have evidence of disease progression. Support for retreatment is drawn from the EM trials themselves. In seven of the nine trials reviewed in this analysis [46,48,53,74,88,91,92], subjects who had evidence of treatment failure during the observation period were offered retreatment. Regimens used either oral [46,48,53,74,88,91,92] or iv. antibiotics [48,53,74,88,92], with the choice of agent and route apparently reflecting the investigators' clinical assessments and treatment preferences.

Therapeutic options include repeating the initial agent, changing to another oral agent or instituting injectable penicillin G benzathine or iv. ceftriaxone therapy. The previously listed dosage ranges for the individual agents would be appropriate. Choices must be individualized and based on several factors, including: the initial response to treatment; the time to relapse or progression; the current disease severity and the level of QoL impairments.

Prior to instituting additional antibiotic therapy, the original diagnosis should be reassessed and clinicians should evaluate patients for other potential causes that would result in the apparent relapse or progression of symptoms and/or findings (see remarks following Recommendation 2f).

The presence of other tick-borne diseases, in particular, should be investigated if that had not already been done. *I. scapularis* transmits several pathogens and the resulting infections may produce symptoms similar to those of Lyme disease. Thus, apparent relapse or disease progression following antibiotic therapy for Lyme disease may be indicative of a concurrent co-infection and not the failure to eradicate *B. burgdorferi*. The presence of other *Ixodes*-borne infections may increase the severity and duration of Lyme disease symptoms [116,117]. Treatment of dually infected patients has not been studied, therefore, the optimal antibiotic regimen for the Lyme disease component is unknown. The possibility of co-infections should not be casually dismissed. Two published surveys of Lyme disease patients found that many respondents were infected with more than one tick-borne pathogen [118,119]. A survey of 3090 patients diagnosed with Lyme disease found that laboratory confirmed cases of babesiosis and anaplasmosis were reported by 32.3 and 4.8% of respondents, respectively [119].

Following a long period of disease latency, minimal manifestations causing little deterioration in the patient's QoL favor continued observation or repeating therapy with the initial

agent; mild manifestations or QoL impairments may prompt a switch to a different first-line agent, tetracycline [50,109], or a combination of first-line agents (which includes at least one antibiotic that is able to effectively reach intracellular compartments) [109,110,120]. Intravenous or IM antibiotics such as injectable penicillin G benzathine or iv. ceftriaxone are other options.

Disease relapse or progression with mild manifestations or QoL impairments occurring within a few months of treatment suggests a need for longer regimens using either a combination of oral first-line agents, injectable penicillin G benzathine or iv. ceftriaxone. Regardless of the duration of disease latency, when disease manifestations or QoL impairments are significant or rapidly progressive, injectable penicillin G benzathine or iv. ceftriaxone may be required. Subsequent decisions regarding the modification or discontinuation of a patient's treatment should be based on the individual's therapeutic response and preferences (Recommendation, very low-quality evidence).

Role of patient preferences

High: While most patients will place a high value on the potential of regaining their pre-morbid health status and improving their QoL and preventing chronic disease through continued antibiotic treatment, a substantial portion will also value avoiding potentially unnecessary antibiotics. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2f

Clinicians should educate patients regarding the potential manifestations of Lyme disease, carefully explaining that disease latency can be prolonged. Education should also include information on preventing future bites, the manifestations of the other tick-borne diseases that they may have contracted as well as the symptoms and signs of a *C. difficile* infection and the preventative effect of probiotics. Patients should be encouraged to immediately report the occurrence of any recurrent or newly developing manifestation of Lyme disease as well as those suggestive of other tick-borne diseases or a *C. difficile* infection. Clinicians should emphasize that the need to report manifestations of tick-borne diseases never expires. (Recommendation, very low-quality evidence)

Role of patient preferences

Low: The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

Remarks

This patient-centered analysis of the evidence from nine clinical trials of EM treatment demonstrates that treatment regimens which used 20 or fewer days of antibiotics were often ineffective. The findings of this analysis are consistent with those from a recently published observational study of EM. In the study by Aucott *et al.*, the authors reported that 21 of 63 (33.3%) patients treated with three weeks of doxycycline met the study's definition of post-treatment Lyme disease syndrome in that they experienced disease manifestations during the 3–6 month post-treatment interval [121]. Furthermore, reports of neurocognitive problems were 9% higher at the 6-month end point than at baseline.

Identifying patients at higher risk for treatment failure and offering them more extensive treatment may improve outcomes. Outcomes might also be improved by assessing the immediate post-treatment response and taking appropriate action. Several studies suggested that certain clinical presentations are associated with a higher risk of treatment failure. Results from two trials suggested that patients who remained symptomatic at the completion of therapy [74] or 1 month post-treatment [88] were at higher risk for long-term failure. These findings form the basis for Recommendation 2c. Other high-risk presentations included: increased severity of initial symptoms [50], paresthesia [88], dysesthesias [53], irritability [52], arthralgia [52], multiple EM [88] and the presence of co-infections [117]. In such circumstances, clinicians should consider lengthening the initial phenoxymethylpenicillin, amoxicillin, cefuroxime or doxycycline therapy to a minimum of 6 weeks or extending azithromycin treatment to a minimum of 4 weeks.

Relapse and/or disease progression may occur at any time and this analysis notes that longer observation periods increase the likelihood of detecting disease relapse, which would decrease the long-term efficacy noted in these trials. This conflicts with the oft stated position that success rates improve with time [71]. In a trial frequently cited in support of this position, success rates did increase over time when calculated on a complete case basis (the trial's chosen methodology for handling longitudinal data) [122]. However, the ITT data supplied in Table 3 of that paper documented that the absolute numbers of successfully treated subjects declined significantly between the 12- and 30-month visits. In the 10-day doxycycline arm, complete success peaked at 12 months, with 44 of 61 (72.1%) returning to their pre-Lyme disease baseline while at 30 months, only 35 of 61 (57.4%) were categorized this way [122]. Readers should note that while Table 3 of the study is entitled 'Clinical Response Based on an Intention-To-Treat Analysis of Patients for Whom Information Was Available*', this was not an ITT analysis. Calculating response rates based on a portion of the group rather than on all who were randomized to a particular arm is contrary to ITT principles.

Additionally, given that prior *B. burgdorferi* infections do not provide durable immunoprotection [123], clinicians should consider the possibility that the patient was re-infected and seek information to confirm or dispel that this occurred [124]. In the absence of clear evidence of re-infection, clinicians and patients will need to consider the relative risks and benefits of assuming that relapsing symptoms such as EM lesions or flu-like symptoms in the summer are indicative of ongoing infection and not re-infection.

Disease manifestations may appear to relapse and/or progress for reasons unrelated to Lyme disease. In addition to the

possible presence of co-infections, many other illnesses and conditions have clinical features which may overlap with those of Lyme disease; some examples are: infections due to Epstein–Barr virus or syphilis; autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and vasculitis; metabolic and endocrine disorders such as diabetes, hypo- or hyperthyroidism and adrenal dysfunction; degenerative neurologic diseases such as Parkinson's disease and amyotrophic lateral sclerosis and neurologic conditions such as peripheral neuropathy and dysautonomia; musculoskeletal diseases including fibromyalgia and osteoarthritis, psychiatric disorders, especially depression and anxiety and other conditions such as chronic fatigue syndrome and sleep apnea. (*Note*: this list is not intended to be exhaustive and patient-specific circumstances will guide the physician in determining whether other potential etiologies of relapsing or progressive manifestations need to be investigated.)

Q3. Should patients with persistent manifestations of Lyme disease be retreated with antibiotics?

Evidence

The panel conducted a Medline search on 5 March 2013 for RCTs investigating the effectiveness of antibiotic retreatment in patients with persistent manifestations of Lyme disease following treatment considered by some to be standard and appropriate antibiotic therapy for their stage of illness. The search used this strategy: chronic Lyme disease OR Lyme encephalopathy OR persistent Lyme disease AND antibacterial Agents/ administration & dosage and this filter: clinical trial.

Five RCTs conducted in the USA were identified. Four met the inclusion criteria for this analysis [16–18]. A fifth trial had a non-completion rate in excess of 20% [87] and was excluded from this analysis on that basis. A Swedish trial was also excluded due to excessive incomplete data [125].

The four trials had unique designs. In one trial, Klempner *et al*. exclusively enrolled seropositive subjects and treatment consisted of 30 days of iv. ceftriaxone followed by 60 days of oral doxycycline or an identical placebo regimen [18]. A second trial by that same group used an identical design except enrolled subjects were exclusively seronegative [18]. Krupp *et al*. enrolled seropositive subjects with severe fatigue; participants received either 30 days of iv. ceftriaxone or an identical placebo [17]. Fallon *et al*. enrolled seropositive subjects with Lyme encephalopathy; treatment consisted of either 10 weeks of iv. ceftriaxone or an identical placebo [16].

Bias

The designs of three of the four trials introduced the potential for type II errors [126,127], which biased the trials against antibiotic retreatment. Type II errors occur when there is a failure to reject a false null hypothesis. With regard to treatment trials, type II errors would wrongly label effective treatment as ineffective.

Type II errors may arise when the designated treatment effect for a trial is too large. The primary end point in the trials by Klempner *et al*. was improvement in QoL, as measured by gains in the 36-item short-form health survey (SF-36) mental and physical component summary scores [18]. A biostatistical review of those trials noted that the minimal clinically important difference (MCID) in SF-36 scores have not been established for Lyme disease and it demonstrated that the designated treatment effect sizes for categorizing subjects as 'improved' likely exceeded the MCIDs of the SF-36 scores by several-fold [126].

The enrollment criteria and subsequent data analysis of the trials by Klempner *et al*. also raise the possibility of a type II error [127]. Subjects were not required to meet a specific level of symptom severity, which allowed for the recruitment of subject groups with baseline heterogeneity on the primary end point. Due to outcome averaging, studies failing to account for such baseline heterogeneity in their sample population are more apt to report no treatment effect. Of the four trials, only the trials by Klempner *et al*. failed to address baseline heterogeneity issues and these were the only trials which failed to find a treatment effect on any end point. In contrast, the subjects in the study by Krupp *et al*. were homogeneous with regard to fatigue and the *post hoc* analysis of Fallon *et al*. addressed baseline heterogeneity on this end point as well, with both trials finding a positive treatment effect on fatigue [16,17].

Delayed processing speed was not an inclusion criterion for the trial by Krupp *et al*. and subjects had minimal baseline deficits on this end point. The designated treatment effect, which was based on earlier studies of Lyme patients [128], called for an increase in processing speed that was unrealistically high for this group of subjects in that meeting the designated treatment effect would have required the subjects' processing speed to exceed healthy population norms [126]. Thus, the trial was biased on this end point [126].

All four trials enrolled subjects who had previously received extensive antibiotic treatment for Lyme disease yet remained ill. The presence of treatment refractory subjects biased the trials against finding treatment to be effective.

Krupp *et al*. also investigated an experimental biologic marker of current disease, namely, the presence of outer surface protein A (OspA) in the cerebrospinal fluid of Lyme patients. Although the trial was designed with clearance of OspA from the cerebrospinal fluid as a primary end point [17], only 16% of the subjects had OspA in their baseline cerebrospinal fluid [17], making it impossible to demonstrate a treatment effect in 84% of the subjects. Accordingly, this trial failed to validate the use of OspA as a surrogate marker and the trial was biased against finding treatment to be effective on this end point.

Results can be biased if unmasking occurs. Although they had no direct evidence that this occurred, Krupp *et al*. raised the concern that masking in their study may have been compromised as subjects in the ceftriaxone arm were more likely to correctly guess their treatment group than the placebo subjects. However, two reviews of the NIH-sponsored retreatment trials noted that the correct guesses could reflect that the subjects in the ceftriaxone arm were feeling better and, therefore, properly attributed this change to being on active therapy [126,127].

Precision

Sample sizes in the individual trials were small, ranging from 37 to 78 [16–18]. Small sample sizes are susceptible to random chance and small study bias [97–99].

The trial by Fallon *et al.* was underpowered. It enrolled 37 patients, yet its design required 45 subjects to achieve at least 80% power to detect an effect size of 1.1 with a two-sided test with $\alpha < 0.05$ [16]. The mental processing speed end point in the trial by Krupp *et al.* was designed with only 74% power [17].

Although the trials by Klempner *et al.* were sufficiently powered, the trials called for an unrealistically large treatment effect that likely exceeded the MCID for changes in the SF-36 scores of Lyme disease patients [126]. The selection of a smaller, and more appropriate, effect size would have required significantly larger sample sizes to achieve sufficient statistical power [126].

Consistency

Krupp *et al.* found retreatment provided a clinically meaningful reduction in severe fatigue and the *post hoc* analysis by Fallon *et al.* corroborated this finding [16,17]. In the treatment response rates in the trial by Krupp *et al.*, 64% improved in the treatment arm versus 18.5% in the placebo arm ($p < 0.001$) was similar to the response rates of Fallon *et al.*, where 66.7% of treated subjects improved versus 25% of the placebo group ($p < 0.05$) [16,17].

Cognitive benefits were evaluated by Krupp *et al.* and Fallon *et al.* [16,17]., but consistency cannot be judged because the trial by Krupp *et al.* was inadequately designed for this end point (see bias and precision sections above).

The trials by Klempner *et al.*, in contrast to those of Krupp *et al.* and Fallon *et al.*, reported finding no benefit from antibiotic retreatment [18]. As discussed above, the trials by Klempner *et al.* were inadequately designed, calling for a treatment effect that likely exceeded the MCID [126]. As such, the absence of a treatment benefit in these trials is uninformative.

Directness (generalizability)

The directness (generalizability) of the evidence is limited because entrance criteria led to the enrollment of subjects who are not representative of the full clinical spectrum of patients with persistent symptoms. Trial subjects had been ill for prolonged periods of time and had received extensive antibiotic treatment prior to enrollment [16–18]. Subjects in the antibiotic arms of the trials by Klempner *et al.* and Fallon *et al.* had been ill, on average, for 4.7 and 9.0 years, respectively [16,18]. Thirty-three percent of the subjects in the trials by Klempner *et al.* had been treated with 30 days of iv. ceftriaxone and subjects in the trial by Krupp *et al.* had received, on average, 7.2 weeks of antibiotic therapy, with 47.3% having been previously treated with a minimum of 2 weeks of iv. ceftriaxone [17,18]. Prior antibiotic treatment in the subjects by Fallon *et al.* was significantly higher. The average duration of therapy was 9.5 months, which included 2.3 months of iv. ceftriaxone use [16].

The trials also excluded patients with characteristics commonly seen in clinical practice. All four trials excluded patients with co-infections or confounding illnesses/conditions [16–18]. Fallon excluded patients who were negative on current ELISA and western blot testing and Krupp *et al.* excluded those who lacked both a history of a physician-documented EM and serologic confirmation of late manifestations [16,17]. However, seronegative status would not necessarily deter clinicians from offering antibiotic therapy [87,75]. Once subjects were enrolled, trial designs restricted the investigators' ability to prescribe non-antibiotic therapy to subjects, which is a common clinical practice. For example, the need for pain medication resulted in one subject being dropped from the trial by Fallon *et al.* [16]. Investigators' primary responsibility is to the trial and not potential enrollees, while clinicians are chiefly concerned with providing care to ill patients and thus they may choose to employ broader treatment criteria. Highly selective research entry criteria and treatment restrictions, like those employed in the four retreatment trials, serve the purpose of ensuring internal validity, but may do so at the expense of external validity, undermining the generalizability of the results to the population of patients clinicians see in practice.

Evidence quality, in aggregate

The quality of the evidence regarding the effectiveness of antibiotic retreatment in patients with persistent symptoms following standard and appropriate antibiotic therapy for Lyme disease is very low (Table 6), implying that the true effectiveness of retreatment is likely to be substantially different from the effectiveness rates seen in the four NIH-sponsored retreatment trials.

Benefits

Retreatment with ceftriaxone was effective in two of the four trials (Table 7). Krupp *et al.* found that 28 days of ceftriaxone was more effective than placebo (64 vs 18.5%; $p < 0.001$) for producing a clinically significant reduction in severe fatigue, a primary outcome [17]. The effect size was moderate to large [127]. Fallon *et al.* found that subjects treated with 70 days of iv. ceftriaxone achieved a moderate improvement (effect size = 0.81) in generalized cognitive function at 2 weeks post-therapy compared with those in the placebo arm (effect size = 0.30) ($p = 0.053$), although the preferential effect of drug versus placebo was not sustained at 14 weeks post-therapy [16]. The mechanisms leading to the subsequent loss of the cognitive gains are unknown; however, this long-term outcome may indicate that the offered therapy was incomplete. A planned secondary analysis demonstrated an interaction effect between baseline impairments and treatment, such that the ceftriaxone effect increased with higher baseline severity; this was demonstrated for the measures of pain and physical dysfunction at week 12 and sustained to week 24 [16]. On *post hoc* analysis, Fallon *et al.* also demonstrated a positive treatment effect on severe fatigue. Of the subjects in the trial by Fallon *et al.*, who met the fatigue entrance criteria of the trial by Krupp *et al.*, those who received ceftriaxone experienced significant

Table 6. Quality of the evidence, in aggregate, that supports antibiotic retreatment in patients with persistent symptoms of Lyme disease.

No. of studies	Limitations	Precision	Consistency	Indirectness	Evidence quality
4	Designated treatment effects were excessive [17,18] Unsupported design assumptions [17,18] Lack of pertinent inclusion criteria [17] Enrollment of treatment-refractory subjects	Small sample sizes (range 37–78) [16–18] Underpowered trial/end point [16,17]	Consistent finding of treatment effectiveness on fatigue in the trials by Krupp *et al*. and Fallon *et al*. [16,17]. Inconsistent findings on treatment effectiveness between the trials by Krupp *et al*., Fallon *et al*. and Klempner *et al*. [16–18].	Subjects had prolonged illnesses [16,18] Subjects had a history of extensive antibiotic treatment [16–18] Excluded subjects with co-morbidities and medication use commonly seen in practice [16–18] Restricted use of non-antibiotic medications, limiting practice [16–18]	Very low

reductions in the level of their fatigue compared with those who received placebo (66.0 vs 25.0%; $p < 0.05$).

Harms

The NIH-sponsored retreatment trials described 15 serious adverse events among the 221 subjects (6.8%) [16–18]. Each event was associated with ceftriaxone itself or the need for venous access; 60 days of oral doxycycline therapy was not associated with any significant adverse event. Six individuals experienced allergic reactions [16–18], including one case of anaphylaxis [17]. Seven events were related to the iv. line [16–18], four cases involved line-related infections (all on placebo) [16,17], two cases involved thrombi [16] and one subject developed a pulmonary embolus [18]. Additionally, there was one case of cholecystitis [16] and one case of gastrointestinal bleeding with fever and anemia [18].

Risk–benefit assessment

The clinical population of patients with persistent manifestations of Lyme disease is heterogeneous; therefore, the risk–benefit assessment needs to be done on an individualized basis, taking into account the severity of an individual's persistent disease, their responsiveness to treatment, their ability to tolerate side effects associated with additional and potentially long-term treatment as well as their willingness to accept the risk associated with antibiotic treatment or, conversely, the level of their desire to avoid treatment-associated risk.

The scientific evidence regarding potential etiologic mechanisms for the development of persistent manifestations of Lyme disease continues to evolve. Proposed mechanisms include immune dysregulation of various types, tissue injury, infection-induced secondary conditions, unrecognized or undertreated co-infections and persistent infection [129,130]. Of these, we think the weight of the evidence supports persistent infection, although other mechanisms may co-exist and the exact etiology for persistent manifestations may vary from patient to patient. Given this uncertainty, the panel concluded that the evidence at hand regarding persistent infection and the potential benefits of retreatment are adequate to support those who wish to treat but is not overwhelming enough to mandate treatment.

The panel also determined that there is no compelling evidence to support routinely withholding antibiotic retreatment from ill patients. While antibiotics are not always effective, the importance of providing patients with the opportunity to receive an adequate trial of antibiotic therapy is heightened by the lack of other effective treatment approaches. Palliative care may be helpful in addressing some symptoms in some cases, but it is important to bear in mind that palliative interventions also carry risks. Additionally, clinicians must not assume that palliative interventions would provide adequate treatment in the face of an underlying persistent infection. Therefore, in the panel's judgment, antibiotic retreatment will prove to be appropriate for the majority of patients who remain ill and thus it is inappropriate to constrain clinicians from exercising their clinical judgment.

In making these determinations, the panel considered the strength of the evidence addressing the effectiveness of antibiotic retreatment, the burden of disease and the risks associated with various antibiotic options. The panel weighed each in light of the marked heterogeneity within this patient population.

Potential benefits include the restoration of health, improved QoL and prevention of further decline in health status. While complete restoration of health was not identified in any of the four retreatment trials, the moderate-to-large treatment effect on severe fatigue demonstrated in the trial by Krupp *et al*. and the sustained interaction effects between baseline severity and improvements in pain and physical functioning seen in the trial by Fallon *et al*. suggested to the panel that retreatment may improve the QoL of some patients.

Others have reached a similar conclusion. In a recent review of the four retreatment trials, Fallon *et al*. make the point that guidelines restricting the use of antibiotics in patients with persistent manifestation of Lyme disease are based on the erroneous dismissal of the treatment efficacy demonstrated in two of

Table 7. Summary of findings regarding the effectiveness of antibiotic retreatment in patients with persistent manifestations of Lyme disease.

Assessment[†]	Trial	N	Measure	Outcome		Comments	Ref.
				Treatment	*Placebo*		
Impairment: fatigue							
FSS[‡]	Krupp *et al.*	55	% improved	64%	18.5%	*Ad hoc* success	[17]
FSS[‡]	Fallon *et al.*	37	% improved	66.7%	25%	*Post hoc* success in the subset of subjects who had a baseline FSS-11 score of 4.0 or higher	[16]
Impairment: pain							
MPQ[§]	Fallon *et al.*	37	Mean drop	5.2	5.6	Secondary analysis – Patients with more joints in pain at baseline had a preferential improvement with ceftriaxone on measures of pain ($p = 0.07$) at week 24	[16]
VAS[¶]	Fallon *et al.*	37	Mean drop	1.4	0.9		
Impairment: neurocognitive dysfunction							
Index[#]	Fallon *et al.*	37	Mean gain index	1.1	0.72	Secondary analysis – Patients with more joints in pain at baseline had a preferential improvement with ceftriaxone on cognitive index measures at week 24 ($p = 0.04$)	[16]
A-A[††]	Krupp *et al.*	48	N/total (%)	2/26 (8)	2/22 (9)	The authors noted that baseline cognitive deficits 'were relatively mild which may have contributed to the lack of a treatment effect on cognition'.	[17]
*****Impairment: QoL physical functioning***							
SF-36 PCS[‡‡]	Klempner *et al.*, seropositive	78	N/total (%)	11/35 (31%)	10/25 (29%)	Due to design deficiencies, the lack of a demonstrable treatment effect is uninformative	[18]
SF-36 PCS[§§]	Klempner *et al.*, seronegative	51	N/total (%)	9/22 (41%)	5/23 (22%)	Due to design deficiencies, the lack of a demonstrable treatment effect is uninformative	[18]
SF-36 PCS[¶¶]	Fallon *et al.*	37	Mean gain	4.9	3.3	Secondary analysis – sustained improvement in physical functioning to week 24 could also be seen when baseline severity of impairment was not included as a covariate ($p = 0.09$) at week 24	[16]
Impairment: QoL mental health							
SF-36 MCS[‡‡]	Klempner *et al.*, seropositive	78	N/total (%)	11/35 (31%)	16/35 (46%)	Due to design deficiencies, the lack of a demonstrable treatment effect is uninformative	[18]

[†]Outcome for measures described in Table 1.
[‡]The FSS assesses the impact of fatigue on everyday functioning [210].
[§]The MPQ estimates the sensory and affective elements of pain, both qualitatively and quantitatively.
[¶]VAS [16].
[#]Neurocognitive dysfunction index
[††]A-A
[‡‡]The PCS on the SF-36 measure of QoL is a measure of physical health, role physical, bodily pain and general health [209].
[§§]The MCS on the SF-36 measure of QoL is a measure of mental health, role emotional, social function and vitality [209].
FSS: Fatigue severity scale; GI: Gastrointestinal; MCS: Mental component of health; MPQ: McGill Pain Questionnaire; PCS: Physical component of health; VAS: Visual analog scale; QoL: Quality of life.

Table 7. Summary of findings regarding the effectiveness of antibiotic retreatment in patients with persistent manifestations of Lyme disease (cont.).

Assessment[†]	Trial	N	Measure	Outcome		Comments	Ref.
				Treatment	*Placebo*		
Impairment: QoL mental health (cont.)							
SF-36 MCS[§§]	Klempner *et al.*, seronegative	51	N/total (%)	8/22 (36%)	6/23 (26%)	Due to design deficiencies, the lack of a demonstrable treatment effect is uninformative	[18]
SF-36 MCS[¶¶]	Fallon *et al.*	37	Mean gain	2.9	6.6		[16]
Adverse events							
	Klempner *et al.*, Krupp *et al.* and Fallon *et al.*	221	Fifteen serious adverse reactions among the 221 subjects (6.8%) [16–18]. Six subjects experienced allergic reactions [16–18], including one case of anaphylaxis [17]; four developed line-related infections (all on placebo) [16,17], two developed thrombi [16] and there was one case of each of the following: pulmonary embolus [18], cholecystitis [16], GI bleed with fever and anemia [18]				[16–18]

[†]Outcome for measures described in Table 1.
[‡]The FSS assesses the impact of fatigue on everyday functioning [210].
[§]The MPQ estimates the sensory and affective elements of pain, both qualitatively and quantitatively.
[¶]VAS [16].
[#]Neurocognitive dysfunction index
[††]A-A
[‡‡]The PCS on the SF-36 measure of QoL is a measure of physical health, role physical, bodily pain and general health [209].
[§§]The MCS on the SF-36 measure of QoL is a measure of mental health, role emotional, social function and vitality [209].
FSS: Fatigue severity scale; GI: Gastrointestinal; MCS: Mental component of health; MPQ: McGill Pain Questionnaire; PCS: Physical component of health; VAS: Visual analog scale; QoL: Quality of life.

the trials [127]. The authors state that such guidelines 'are not helpful to clinicians and patients' [127].

In addition to the NIH-sponsored retreatment trials, retreatment was also shown to be beneficial in clinical trials of EM treatment and in a case series involving the treatment of late neurologic disease. Investigators in seven of the nine EM trials discussed above retreated subjects who failed initial therapy [47,48,53,74,88,91,92]. Decisions to retreat were often based on symptoms alone and investigators frequently reported on the success of retreatment. In three trials, biopsy specimens from the EM site were culture-positive for *B. burgdorferi* 1–3 months post-treatment [47,48,92]. In two of these, subjects were retreated with oral antibiotics and follow-up cultures 3 [47] or 4 months later [92] were negative. Thus, these trials simultaneously demonstrated persistent infection following standard therapy and the value of retreatment.

In a study by Logigian *et al.*, one subject relapsed at 8 months post-treatment, was retreated, became well once again and remained so for the remainder of the study [33]. Several observational studies also demonstrated benefits from antibiotic retreatment [87,109,110,131].

The panel also considered the risk of withholding antibiotics from patients with a potentially treatable *B. burgdorferi* infection. Currently available laboratory tests are unable to confirm or deny persistent infection on a routine basis yet persisting infection has been demonstrated in patients with Lyme disease by PCR and culture [47,113,132–136]. A recently published xenodiagnostic study in humans demonstrated positive results in one of eight subjects with post-treatment manifestations of Lyme disease; a subsequent xenodiagnostic specimen obtained from the same subject 8 months later was also positive [137]. Animal studies have corroborated the human findings, documenting bacterial persistence by culture, PCR and histopathologic testing of post-treatment necropsy specimens and by xenodiagnosis [76,138,139]. Given these realities, withholding antibiotic retreatment risks allow an infection to continue unchecked.

The panel weighed the burden of chronic illness that Lyme disease imposes on patients. In the four retreatment trials analyzed here, the subjects' QoL was consistently worse than that of control populations and reductions in employment or educational activities were common [16–18]. A community-based trial of antibiotic retreatment found the QoL of its subjects was the same or worse as that of individuals with depression, diabetes, heart disease, osteoarthritis and rheumatoid arthritis [87]. Surveys of Lyme disease patients further document the negative impact of persistent manifestations. One survey of openly recruited Lyme disease patients identified 2424 patients whose initial clinical diagnosis of Lyme disease was confirmed with positive serology and who had persistent manifestations of Lyme disease despite antibiotic treatment [140]. Of this cohort, 25% had received public support or disability benefits and the majority of respondents in this subset received these payments for 2 or more years. A second online survey identified 1087 respondants diagnosed with Lyme disease (based on the presence of an EM rash or positive two-tier testing that used the CDC interpretive criteria) who had ongoing manifestations of Lyme disease for 6 or more months [119]. Using a CDC metric of health-related QoL, the survey found that this group averaged 19.6 and 15.5 days/month of poor physical and mental health days, respectively. Not surprisingly, 71.6% rated their health as fair or poor. This

rate is higher than that seen in other chronic diseases including congestive heart failure, fibromyalgia, post- stroke and post-myocardial infarction status, diabetes and multiple sclerosis and the survey findings corroborate those of the community-based retreatment trial mentioned above. By comparision, in a general population with an average age of 46, only 16% rated their health as fair or poor [119]. The respondants also reported significant economic impacts – 39.4% stopped working and an additional 28.3% reduced their work hours or role; 37.3% spent at least US$5000 in out-of-pocket Lyme-related expenses.

Given the severity of the QoL impairments, the panel viewed the need for clinical intervention as high.

Additionally, the panel considered that antibiotic risk varies by agent and route of administration. Although all of the regimens in the NIH-sponsored retreatment trials incorporated iv. ceftriaxone, the use of iv. antibiotics is discretionary and should be based on an individualized risk–benefit assessment. The risks associated with iv. antibiotics have two main origins. The first is the medication itself and includes allergic reactions and other adverse events, such as cholecystitis from ceftriaxone. The second source of risk is the iv. access device.

The risks associated with iv. access are well known. A meta-analysis of the risks associated with iv. access, in general, found that risks varied by access type; peripheral iv. catheters caused 0.5 bloodstream infections per 1000 intravascular device days, while surgically implanted long-term central venous devices – cuffed and tunneled catheters – caused 1.6 infections per 1000 intravascular device days [141].

Combined, there were seven device-related adverse events among the four retreatment trials and approximately 8110 days of device use, yielding 0.86 device-related adverse events per 1000 intravascular device days, which is lower than the rate found in the meta-analysis. Although the risk associated with iv. antibiotics is significant, in situations where the QoL impairments are substantial, retreatment with iv. antibiotics may be wholly appropriate.

There is substantial evidence on the clinical safety of amoxicillin, cefuroxime axetil, doxycycline and azithromycin, which are commonly used to treat Lyme disease [105,106]. In a community-based trial, none of the subjects randomized to amoxicillin experienced a serious adverse event [87]. Similarly, the trials by Klempner *et al*. confirmed the safety of oral doxycycline for longer-term use [18]. Regardless of treatment agent and route of administration, it is expected that the concomitant use of probiotics would reduce the risk of *C. difficile* colitis and antibiotic-associated diarrhea [44,45].

Values: The panel placed a high value on reducing the morbidity associated with chronic Lyme disease and improving the patient's QoL as well as on the need for individualized risk/benefit assessment and informed shared decision-making. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong compelling evidence to the contrary.

Recommendation 3a

Clinicians should discuss antibiotic retreatment with all patients who have persistent manifestations of Lyme disease. These discussions should provide patient-specific risk–benefit assessments for each treatment option and include information regarding *C. difficile* infections and the preventative effect of probiotics (although none of the subjects in the retreatment trials developed a *C. difficile* infection). (Strong recommendation, very low-quality evidence. *Note*: In GRADE, a strong recommendation may be made in the face of very low-quality evidence when the risk–benefit analysis favors a particular intervention such that most patients would make the same choice.)

Role of patient preferences: low

The benefits of educating patients about the potential benefits of retreatment and the risks associated with various treatment options, including not treating, clearly outweigh any attendant risks associated with education.

Recommendation 3b

While continued observation alone is an option for patients with few manifestations, minimal QoL impairments and no evidence of disease progression, in the panel's judgment, antibiotic retreatment will prove to be appropriate for the majority of patients who remain ill. Prior to instituting antibiotic retreatment, the original Lyme disease diagnosis should be reassessed and clinicians should evaluate the patient for other potential causes of persistent disease manifestations. The presence of other tick-borne illnesses should be investigated if that had not already been done. Additionally, clinicians and their patients should jointly define what constitutes an adequate therapeutic trial for this particular set of circumstances.

When antibiotic retreatment is undertaken, clinicians should initiate treatment with 4–6 weeks of the selected antibiotic; this time span is well within the treatment duration parameters of the retreatment trials. Variations in patient-specific details and the limitations of the evidence imply that the proposed duration is a starting point and clinicians may, in a variety of circumstances, need to select therapeutic regimens of longer duration.

Treatment options are extensive and choices must be individualized. Each of these options would benefit from further study followed by a GRADE assessment of the evidence and consideration of associated risks and benefits, but until this information is available, clinicians may act on the currently available evidence.

In choosing between regimens, clinicians should consider the patient's responsiveness to previous treatment for Lyme disease, whether the illness is progressing and the rate of this progression; whether the patient has impaired immune system functioning or has received immunosuppressant corticosteroids [54,114] and whether other co-morbidities or conditions would impact antibiotic selection or efficacy. The possibility of co-infections should be investigated (see Recommendation 2e for discussion regarding co-infections complicating the diagnosis and treatment of Lyme disease).

Clinicians should also weigh the extent to which the illness interferes with the patient's QoL, including their ability to fully participate in work, school, social and family-related activities and the strength of their initial response against the risks associated with the various therapeutic options. Antibiotic selection should also consider medication tolerability, cost, the need for lifestyle adjustments to accommodate the medication and patient preferences.

For patients with mild impairments who had a strong-to-moderate response to the initial antibiotic, repeat use of that agent is favored. Patients with moderate impairments or only a modest response to the initial antibiotic may benefit from switching to a different agent or combination of agents; the latter to include at least one agent that is able to effectively reach intracellular compartments [109,110]. Injectable penicillin G benzathine or iv. agents such as ceftriaxone are other options.

For patients with significant impairments and/or a minimal or absent therapeutic response, a combination of oral antibiotics or injectable penicillin G benzathine or iv. ceftriaxone alone, or in combination with other agents, is preferred. For patients who experienced disease progression despite earlier therapy, treatment with injectable penicillin G benzathine or an iv. agent, such as ceftriaxone, alone or in combination with other antibiotics, is advisable. Additionally, minimal or absent responses and disease progression require a re-evaluation of the original diagnosis. (Recommendation, very low-quality evidence)

Role of patient preferences

High: The heterogeneous nature of the patient population seen in clinical practice, particularly with regard to variations in disease severity, QoL impairments and aversion to treatment-related risk, is likely to affect the risk–benefit assessment. Although many patients will value the opportunity to improve their individual QoL through antibiotic treatment over the risk of adverse events, others may prefer to avoid the risks associated with treatment. Hence, treatment options, including their associated risks and benefits, should be discussed with the patient in the context of shared medical decision-making.

Recommendation 3c

Clinicians should re-assess patients immediately following the completion of the initial course of retreatment to evaluate the effectiveness of retreatment and the need for therapeutic adjustments. Reassessment may need to be done much earlier and with greater scrutiny in patients with severe disease or when the therapeutic intervention carries substantial risk.

For patients who improve yet continue to have persistent manifestations and continuing QoL impairments following 4–6 weeks of antibiotic retreatment, decisions regarding the continuation, modification or discontinuation of treatment should be based on several factors. In addition to the factors listed in Recommendation 3b, the decision to continue treatment may depend on the length of time between the initial and subsequent retreatment, the strength of the patient's response to retreatment, the severity of the patient's current impairments, whether diagnostic tests, symptoms or treatment response suggest ongoing infection and whether the patient relapses when treatment is withdrawn.

In cases where the patient does not improve after 4–6 weeks of antibiotic retreatment, clinicians should reassess the clinical diagnosis as well as the anticipated benefit. They should also confirm that other potential causes of persistent manifestations have been adequately investigated prior to continuing antibiotic retreatment. Decisions regarding the continuation, modification or discontinuation of treatment should consider the factors noted above as well as the definition of an adequate therapeutic trial.

Whenever retreatment is continued, the timing of subsequent follow-up visits should be based on the level of the therapeutic response, the severity of ongoing disease, the duration of current therapy and the need to monitor for adverse events (see remarks section below). (Recommendation, very low-quality evidence).

Role of patient preferences

High: See Recommendation 3b.

Remarks

The lack of pharmaceutical interest and its concomitant funding does not encourage the innovative research that is essential to improving care for patients with Lyme disease. When pharmaceutical interest is lacking, clinical practices often become the source of therapeutic innovation, preceding rather than following clinical trials.

The US FDA recognizes the important role that clinical innovation plays in patient care, stating: 'Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations [142]'. In providing clinicians with therapeutic flexibility, the agency makes room for clinicians to fashion patient-centered care, with treatment decisions being driven by the specific circumstances of an individual's illness. The benefits related to therapeutic flexibility are quite evident in orphan diseases, where an estimated 90% of all prescribed medications represent off-label use and if not for that practice, clinicians would often have no effective therapies to employ [143]. In this respect, patient care in Lyme disease is like that of other research-orphaned diseases, relying heavily on innovative clinicians to develop treatments that improve health and reduce morbidity.

Innovative therapies may employ unconventional dosages of standard medications, novel combinations of currently accepted practices, new applications of standard interventions or may use accepted therapy or approved drugs for non-approved indications [144]. Unlike research, the primary purpose of innovative care is to benefit the individual patient [144]. Clinicians

employing innovative therapies need to verify that the innovation is intended to be in the patient's best interest and recognize that informed consent requires that the patient understand that the recommended therapy is not standard treatment [144]. In this context, the panel concluded that it is necessary for clinicians to provide patients with treatment options and engage in shared medical decision-making.

This determination is in keeping with the approach used by other physician-developed guidelines. The American Academy of Pediatrics guidelines recognize that in the face of low-quality evidence or where the risk–benefit equilibrium is balanced, 'guideline developers generally should not constrain the clinician's discretion [9]'. Guideline developers commonly consider not only RCTs, but also observational trials, animal model studies, expert opinion, clinical experience, patient values and judgments regarding the potential harms of an intervention as well as the potential harms of inaction [19]. Moreover, when the condition in question poses great risk or QoL impairments, guideline panels may recommend an intervention even when the evidence base is uncertain, mixed or incompletely developed [19].

The panel endorses the view that informed choice is the ethical ideal in circumstances involving scientific uncertainty because it recognizes the patient's right to self-determination [19]. Patients with significant QoL or functional impairments may be willing to take on a far greater degree of risk than those who are relatively unaffected by ongoing disease manifestations. However, because the degree of relative risk aversion varies significantly among patients, it is important that patients be given sufficient information to make a meaningful choice regarding treatment options.

The demonstrated persistence of *B. burgdorferi* in specific individuals [42,47,48,133–135,145,146] and animal models [76,138,139,147] suggests a need for treatment regimens which address the mechanisms underlying bacterial persistence yet these mechanisms may not be fully identified and those that have been are not fully understood. Emerging evidence supports potential roles for these mechanisms: immune evasion via physical seclusion of Bb within immunologically protected tissue sites such as the CNS, joints and eyes [147–149], collagen-rich tissues [150], cells [151–154] and biofilms [155]; alterations in Osp profiles through antigenic variation [156–159], phasic variation [160] and alteration in Bb morphology (including cell-wall deficient forms, spherocytes and 'cyst' forms) [161–166]; immune modulation via alterations in complement [167–169], neutrophil and dendritic cell functioning [170,171], and changes in cytokine and chemokine levels [129,172,173] and innate antibiotic tolerance of some *B. burgdorferi* populations [174].

In the absence of a clear scientific understanding of persistent infection, different views regarding whether and how to address potential mechanisms have developed [175,176]. While some clinicians may elect to wait for more definitive answers, other clinicians, given the QoL impairments some patients bear, may elect to provide innovative care based on the information at hand. Antibiotic options for treating persistent manifestations include all agents known to be effective against *B. burgdorferi* [87,54,75,109,110,112]. While the use of agents proven to be effective in clinical research trials may be preferred, clinicians may choose antibiotics based on their clinical experiences and those of others [177–181]. While agents with favorable *in vitro* findings may also merit consideration, antibiotics that were ineffective in clinical trials are best avoided.

Treatment regimens may employ either a sole agent or combinations of antibiotics, depending on which mechanisms of persistence the clinician is attempting to thwart. The delivery method – oral, iv., IM – is dependent on the agents selected, disease severity and patient preferences. It is reasonable to start with dosages examined in clinical trials, but clinicians may decide to adjust dosages in individual patients with the goal of improving outcomes by achieving adequate drug levels in all infected tissues.

Oral antibiotics which demonstrated effectiveness in clinical trials include the cell wall agents amoxicillin [74,91], phenoxymethylpenicillin [46,48] and cefuroxime axetil [88,91,92]. Other cell wall agents may also be clinically useful; however, first-generation cephalosporins are known to be ineffective [182]. Oral agents within the tetracycline and macrolide classes, which disrupt ribosomal function and are capable of entering cellular compartments, are also effective in Lyme disease. Individual agents include doxycycline [53,183–190], tetracycline [109], azithromycin [49,74,190,191] and clarithromycin [110,192]. However, erythromycin, which performed well *in vitro*, was ineffective *in vivo* [50,193] and the macrolide telithromycin has been linked to drug-induced liver injury [194]. Several of the EM trials reviewed earlier in this document used higher antibiotic dosages than suggested by the panel in Recommendation 2b [47–49,74,88]. For example, Luft *et al*. and Weber *et al*. prescribed azithromycin 500 mg/day [74,191]. Strle *et al*. and Barsic *et al*. prescribed azithromycin 500 b.i.d. on day 1 followed by 500 mg daily [47,49]. Nadelman prescribed doxycycline 100 mg t.i.d. [88]. In certain circumstances, clinicians may decide that higher doses are required.

Metronidazole and tinidazole effectively kill cell wall deficient forms of *B. burgdorferi in vitro* [195,196], but their effectiveness *in vivo*, in either oral or iv. form, has not been investigated in clinical trials.

Ceftriaxone, 2 g iv. per day is known to be effective [16,17,32,33,54,112] and iv. cefotaxime [113], another cephalosporin, has also been recommended. Intravenous penicillin is less effective and requires more frequent dosing [114]'. Additional iv. cell wall agents from the carbapenem and monobactam classes were effective *in vitro*, but have not been studied clinically [115].

IM benzathine penicillin is another useful cell wall agent and it avoids the risks associated with gaining iv. access. A case report noted its effectiveness in antibiotic resistant Lyme arthritis [111].

If the initial course of antibiotic retreatment does not produce a complete response, clinicians should consider various options. Patients who had an incomplete response with one

agent may be responsive to another; thus, switching agents may prove successful. Alternatively, combination therapy may be appropriate in select patients. Examples include those with known or suspected co-infections and patients who had incomplete responses to single-agent therapy.

Aside from antibiotics, few therapeutic strategies have been employed to address non-infectious mechanisms of ongoing disease yet individual patients have benefitted from non-antibiotic therapies. For example, some patients with 'antibiotic-resistant' Lyme arthritis obtained a localized (joint-specific) benefit from synovectomy [197,198]. The rationale being that ongoing synovitis is a reflection of an auto-immune process [198]. Additionally, an autoimmune-mediated polyneuropathy that was secondary to a proven *B. burgdorferi* infection of the CNS improved following IVIG therapy, whereas prior antibiotic interventions failed to halt the progression of the polyneuropathy [199]. Other methods of immunomodulation may prove useful in the future, especially if it can be established that immune dysregulation is the specific mechanism underlying an individual's persistent disease. However, unless an ongoing infection can be definitively ruled out, caution is required because immunomodulation could cause an occult infection to flare.

Reconciling divergent guidelines

The ILADS panel recommendations differ from those of the IDSA. Different guideline panels reviewing the same evidence can develop disparate recommendations that reflect the underlying values of the panel members, which may result in conflicting guidelines [200,201]. The IOM explains that conflicting guidelines most often result 'when evidence is weak; developers differ in their approach to evidence reviews (systematic vs non-systematic), evidence synthesis or interpretation and/or developers have varying assumptions about intervention benefits and harms' [200]. Conflicting guidelines exist for over 25 conditions and there is no current system for reconciling conflicting guidelines [200]. Supplementary Appendix 1 reconciles the differences between the ILADS and IDSA treatment recommendations by clinical situation.

Expert commentary & five-year view

Lyme disease is a complex illness and patients may experience both acute and persistent manifestations. The science regarding disease mechanisms is limited, uncertain and evolving. However, the profoundly negative impact that persistent manifestations exert on patients' wellbeing as measured on validated QoL assessment tools is well documented. Therefore, critical treatment goals include: disease prevention, treating to cure where possible and otherwise improving patient QoL and preventing disease progression. Following the GRADE model, ILADS recommends that patient goals and values regarding treatment options be identified and strongly considered during a shared decision-making process. Because the GRADE process for formulating evidence-based treatment recommendations fosters transparency and recognizes that patient values may play a pivotal role, GRADE is particularly useful when addressing questions marked by significant scientific uncertainty.

Looking forward over the next 5 years, significant advances are expected in both technology and clinical research that may significantly impact the quality of patient care in Lyme disease. Since the discovery of Lyme disease in 1981, researchers have identified more than 15 new tick-borne pathogens. Progress in identifying new tick-borne pathogens and in understanding the clinical ramifications of simultaneous tick-borne diseases may help improve both the diagnosis and treatment of tick-borne diseases. Advances in genomics and proteonomics should permit researchers to identify differences in *B. burgdorferi* species and strains and explore their clinical implications. Significant advances in diagnostic testing may permit clinicians to distinguish the infected from the non-infected and cured and provide clinicians with a laboratory measure of therapeutic progress. Finally, advances in information technology as well as the methodology for conducting large-scale clinically relevant trials will provide evidence that addresses topics that clinicians and patients deem meaningful to improving patient QoL. These fundamental changes may change the clinical landscape and enable optimal care treatment regimens to be established.

Disclaimer

The state of the evidence in the diagnosis and treatment of Lyme disease is limited, conflicting and evolving. Accordingly, the recommendations in these guidelines reflect an evidence-based, patient-centered approach that many clinicians will find helpful; they are not intended to be viewed as a mandate or as a legal standard of care. Guidelines are not a substitute for clinical judgment. The International Lyme and Associated Diseases Society encourages clinicians to consider the specific details of an individual patient's situation when determining an appropriate treatment plan.

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Key issues

- Lyme disease is a complex illness and patients may experience both acute and persistent manifestations.
- Persistent manifestations may produce profound quality-of-life impairments, yet the mechanisms that produce persistent manifestations are poorly understood.
- The available evidence regarding the treatment of known tick bites, erythema migrans (EM) rashes and persistent disease is limited.
- Grading of Recommendations Assessment, Development and Evaluation-based analyses found the evidence regarding these scenarios was of very low quality due to limitations in trial designs, imprecise findings, outcome inconsistencies and non-generalizability of trial findings.
- It is impossible to state a meaningful success rate for the prevention of Lyme disease by a single 200 mg dose of doxycycline because the sole trial of that regimen utilized an inadequate observation period and unvalidated surrogate end point.
- Success rates for treatment of an EM rash were unacceptably low, ranging from 52.2 to 84.4% for regimens that used 20 or fewer days of azithromycin, cefuroxime, doxycycline or amoxicillin/phenoxymethylpenicillin (rates were based on patient-centered outcome definitions and conservative longitudinal data methodology).
- In a well-designed trial of antibiotic retreatment in patients with severe fatigue, 64% in the treatment arm obtained a clinically significant and sustained benefit from additional antibiotic therapy.
- The optimal treatment regimen for the management of known tick bites, EM rashes and persistent disease has not yet been determined. Accordingly, it is too early to standardize restrictive protocols.
- Given the number of clinical variables that must be managed and the heterogeneity within the patient population, clinical judgment is crucial to the provision of patient-centered care.
- Based on the Grading of Recommendations Assessment, Development and Evaluation model, International Lyme and Associated Diseases Society recommends that patient goals and values regarding treatment options be identified and strongly considered during a shared decision-making process.
- Research is needed to better define the disease process, to identify variables associated with poor outcomes and to establish highly effective therapeutic regimens for known tick bites, EM rashes and persistent disease.

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