



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

<http://www.guideline.gov/content.aspx?f=rss&id=49320&osrc=12>

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

Description of Methods Used to Collect/Select the Evidence

The Medline database was used to locate articles published between June 1976 and March 5, 2013 that are relevant to the prevention, assessment, and treatment of Lyme disease for all age groups. The query was restricted to articles published in the English language. Priority was given to publications reporting original research, review articles, and, results of previous guidelines.

RCT and meta-analyses

The panel conducted a Medline search on March 5, 2013 for randomized controlled trials (RCTs) and meta-analyses, which investigated using a single dose of doxycycline for antibiotic prophylaxis of *Ixodes scapularis* (*I. 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 U.S. and two meta-analyses involving some or all of those trials were identified and reviewed. 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. 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 erythema migrans (EM) rash at the bite site.

Prospective randomized clinical trials

The panel conducted a Medline search on March 5, 2013 for prospective randomized clinical trials investigating the effectiveness of 5 to 20 days of oral azithromycin, cefuroxime, doxycycline, phenoxymethylpenicillin or amoxicillin for the treatment of EM. The search used this 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 51 trials. However, 42 were excluded because they investigated antibiotic treatment of non-EM presentations (23); were primarily interested in disseminated disease (3); did not involve any of the antibiotics of interest (1); were 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, 9 trials met the requirements for this Grading of Recommendations, Assessment, Development and Education (GRADE) analysis and were evaluated in detail.

RCTs investigating the effectiveness of antibiotic retreatment in patients with persistent manifestations of Lyme disease

The panel conducted a Medline search on March 5, 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. Six randomized-controlled trials were identified but two had non-completion rates in excess of 20% and were excluded on that basis.

Grade scheme

The Grading of Recommendations Assessment, Development and Evaluation (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 dose-response gradient.

Description of the Methods Used to Analyze the Evidence

The working group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scheme to analyze the quality of the available evidence and summarize its findings. The group chose to include only evidence from randomized controlled trials (RCTs) and meta-analyses in its assessment. GRADE classifies the quality of the available evidence, in aggregate, as either high, moderate, low, or very low. In assessing individual studies, RCTs are typically rated as being of high quality but this rating may be downgraded due to limitations in design or execution. The working group's assessment of the overall quality of the relevant evidence was based on the quantity, consistency, precision, generalizability and biases of the studies under consideration. The evidence for each of the three clinical questions had several limitations; therefore, the working group determined the evidence was of very low quality.

Description of Methods Used to Formulate the Recommendations

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.

The guidelines were developed by a three-member working group which met every other week over a period of two years. The working group included an epidemiologist/physician, a physician educator, and a patient advocate. This group reported back to the full guidelines panel, which consisted of the board of directors of ILADS. The working group identified three questions for the guidelines to address, anticipating that additional questions related to Lyme disease would be addressed in future guidelines. The working group assessed the available evidence for each question using the GRADE process. A literature search using PubMed and question-specific criteria was performed for each question; search criteria are set forth listed in the guidelines. The working group a) assessed the quality of the available evidence, b) performed a risk/benefit assessment for each question, and c) evaluated whether the role of patient preferences and values for each question was low, moderate or high. Recommendations were made based on these assessments, followed by a discussion of scientific and clinical factors concerning the recommendations.

A preliminary draft of the guidelines was distributed to the full guideline panel for comments and the guidelines were then refined by the working group and resubmitted to the full guidelines panel for additional comments and approval. In addition, for each recommendation, each member of the full

guidelines panel was polled to determine whether they agreed with the recommendation to assure consensus. Copies of these documents have been retained by ILADS administration.

Rating Scheme for the Strength of the Recommendations

Given the low quality of the evidence, the panel rated the strength of each recommendation based on the extent to which the risk-benefit assessment favored a particular course of action and aligned with the unique circumstances and values of most patients. The guidelines make a "strong recommendation" in instances where risk-benefit analyses favor a particular intervention such that most patients would choose it. When the risks and benefits of an intervention are balanced or less clear, the panel determined that the choices of individual patients are likely to diverge due to their unique circumstances and values. In these instances the guidelines make a "recommendation" that identifies treatment options and emphasizes the need for shared medical decision-making.

Description of Method of Guideline Validation

The guidelines were reviewed by internal reviewers, external reviewers (including researchers and patients) and the peer reviewers selected by the editor of the publishing journal. The recommendations were also compared to those of the Infectious Diseases Society of America and that information was included as an appendix to the published manuscript (see supplementary material in the "Availability of Companion Documents" field).

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

Recommendation 1a

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

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 mg to 200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis (Recommendation, very low-quality evidence).

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* (*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).

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

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).

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. Initial antibiotic therapy should employ 4 to 6 weeks of amoxicillin 1500 mg to 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 mg to 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 mg/kg/day to 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 mg/kg to 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, 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).

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).

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 in the original guideline document) (Recommendation, very low-quality evidence).

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 quality of life (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 below). 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).

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).

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

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 Grading of Recommendations Assessment, Development and Evaluation [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).

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 to 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).

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 to 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 to 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).

Definitions

Rating of Evidence

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 dose-response gradient.

Rating of Recommendations

Given the low quality of the evidence, the panel rated the strength of each recommendation based on the extent to which the risk-benefit assessment favored a particular course of action and aligned with the

values of most patients. The guidelines make a "strong recommendation" in instances where risk-benefit analyses favor a particular intervention such that most patients would choose it. When the risks and benefits of an intervention are balanced or less clear, the panel determined that the choices of individual patients are likely to diverge. In these instances the guidelines make a "recommendation" that identifies treatment options.

Potential Harms

Adverse events related to antibiotic agents and route of delivery include allergic reactions, drug eruptions, serious photosensitivity reaction, nausea and vomiting, diarrhea, *Clostridium difficile* infections, cholecystitis, intravenous (iv.) line-related infections, thrombi, pulmonary embolus, gastrointestinal (GI) bleed with fever, and anemia.

Although the panel did not consider a Jarisch–Herxheimer reaction an adverse event, four erythema migrans (EM) trials reported a Jarisch–Herxheimer reaction in 60 of 351 subjects (17.1%) (range 12.1% to 18.7%).

International Lyme and Associated Diseases Society (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.

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.

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. ILADS encourages clinicians to consider the specific details of an individual patient's situation when determining an appropriate treatment plan.

Implementation of the Guideline

These guidelines will be widely disseminated through the August 2014 edition of the journal *Expert Review of Anti-infective Therapy*, the International Lyme and Associated Diseases Society (ILADS) Web site at www.ILADS.org and the National Guideline Clearinghouse. Dissemination will be achieved by announcement at professional conferences, opportunities for continuing education, and press releases. Some of the tools that will be developed to help implement the guideline include specially designed resources, such as slide presentations and training. The guidelines have been endorsed by LymeDisease.org (LDo), a national non-profit with extensive engagement and communications reach in the Lyme patient community. LDo will distribute information regarding the guidelines on its Web site and through its social media platforms. In addition, LDo will distribute the executive summary of the guidelines through its print journal, *The Lyme Times*.

Guideline Consensus Committee Members: Robert Bransfield, MD, DFAPA, Riverview Medical Center, New Jersey; Daniel Cameron, MD, MPH, Mt. Kisco, New York; Andrea Gaito, MD, Basking Ridge, New Jersey; Christine Green, MD, San Francisco, California; Lorraine B. Johnson, JD, MBA, LymeDisease.org, Chico, California; Judith Leventhal, PhD, Manhattan, New York; Tom Moorcroft, DO, Berlin, Connecticut; Leo Shea, PhD, Rusk Institute Manhattan, New York; Samuel Shor, MD, FACP, George Washington University Health Care Sciences, Reston, Virginia; Raphael Stricker, MD, San Francisco, California

Members of the working group and the full guidelines panel were asked to declare all interests and activities potentially resulting in a conflict of interest (COI) with development of the guidelines, by written disclosure. The disclosure form reflected all current and planned commercial interests. Written conflict of interest forms were completed and are on file at the International Lyme and Associated Diseases Society (ILADS). Although the panel determined that payments to physicians that are inherent in the provision of healthcare did not disqualify experienced clinicians from serving on the guideline panel or working group, other forms of financial relationships exceeding \$10,000 that were not intrinsic to medical practice and accordingly were avoidable were taken into account. No panel members held such financial conflicts-of-interest of \$10,000 or more. All members of the panel were members of ILADS and none reported any other potential institutional conflicts. To ensure clinical expertise, the panel included clinicians who treat Lyme disease; 7 of 10 panel members are physicians who treat patients with Lyme disease.

Several panel members, including members of the working group, serve on non-profit boards related to Lyme disease. The panel did not consider these interests sufficient to exclude participation by these panel members.

Financial and Competing Interests Disclosure

DJ Cameron is the President of the International Lyme and Associated Diseases Society. LB Johnson is Executive Director of LymeDisease.org. EL Maloney is a provider of continuing medical education courses on tick-borne diseases. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Writing assistance from A DeLong was utilized in the production of this manuscript.