Draft Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2019 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease[1]

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Lyme Sections:

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Abstract

This evidence-based guideline for the prevention, diagnosis, and treatment of Lyme disease was prepared by a multidisciplinary panel representing the Infectious Diseases Society of America, the American Academy of Neurology, and the American College of Rheumatology. The scope of this guideline includes prevention of Lyme disease, and the diagnosis and treatment of early Lyme disease, its neurologic, cardiac, and rheumatologic complications, and Lyme disease complicated by coinfection. This guideline does not include comprehensive recommendations for babesiosis and tick-borne rickettsial infections, which are published separately (IN PRESS). The target audience for this guideline includes primary care physicians and specialists caring for this condition such as infectious diseases specialists, emergency physicians, internists, pediatricians, neurologists, rheumatologists, cardiologists and dermatologists.

Introduction

Lyme disease is a tick-borne infection caused by spirochetes in the *Borrelia burgdorferi* sensu lato complex and transmitted to humans by the bite of *Ixodes* species ticks. It is the most common vector-borne infectious disease of humans in the temperate northern hemisphere, affecting hundreds of thousands of people annually in North America and Eurasia. In the United States, Lyme disease is found predominantly in three expanding regions: the northeastern states from Virginia to eastern Canada; the upper Midwest, particularly Wisconsin and Minnesota; and in northern California.

Lyme disease is a clinically complex infection, and there can be a wide range of clinical latency after the infecting tick bite. Presentations include an early localized skin lesion at the site of the tick bite, and disseminated disease resulting in neuropathy, meningitis, cardiac conduction abnormalities, and arthritis. Clinical disease can manifest as early as days and as late as many months following an infectious tick bite. Interpretation of diagnostic tests for Lyme disease presents additional challenges. Finally, treatment options, including the drug, route, and duration of treatment differ for different disease manifestations.

Scope

This guideline encompasses the prevention, diagnosis, and treatment of Lyme disease, as well as Lyme disease complicated by simultaneous coinfection with other tick-borne pathogens. In contrast to prior guidelines, this guideline only addresses anaplasmosis and babesiosis in the context of a coinfection. Anaplasmosis is now addressed in the rickettsial disease guidelines authored by the Centers for Disease Control and Prevention [1], and babesiosis recommendations can be found in its own IDSA guideline (IN PRESS).

This guideline is primarily intended for medical practitioners in North America, although many recommendations will be applicable to patients in Europe and Asia. As uniquely Eurasian manifestations of Lyme disease occasionally are imported into North America, this guideline includes recommendations for the evaluation and treatment of borrelial lymphocytoma and acrodermatitis chronica atrophicans.

Guideline Authorship

This guideline is preceded by guidelines by the American Academy of Neurology (AAN) [2] and the Infectious Diseases Society of America (IDSA) [3]. As such, this guideline is a collaborative effort by AAN, IDSA, as well as the American College of Rheumatology (ACR). Recognizing that Lyme disease is evaluated and treated by physicians from different subspecialties in varied clinical settings, this

guideline has official representation from numerous organizations including scientific, primary care, and medical specialties.

Methodology

Clinical Practice Guidelines

Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health care for specific clinical circumstances. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [4]. The "IDSA Handbook on Clinical Practice Guideline Development" provides more detailed information on the processes followed throughout the development of this guideline [5].

Guideline Panel Composition

Each of the three sponsoring organizations elected a co-chair to lead the guideline panel (P.M.L. representing Infectious Diseases Society of America, J.A.R. representing American Academy of Neurology, and L.K.B. representing American College of Rheumatology) with a fourth co-chair selected for his expertise in guideline methodology (Y.F.Y. representing the U.S. GRADE Network). A total of 36 panelists comprised the full panel. The panel included infectious diseases specialists representing IDSA, neurologists representing AAN, rheumatologists representing ACR, as well as representatives from the American Academy of Family Physicians (AAFP), American Academy of Pediatrics - Committee on Infectious Diseases (AAP-COID), American Academy of Pediatrics - Section on Emergency Medicine (AAP-EM), American College of Physicians (ACP), Association of Medical Microbiology and Infectious Diseases - Canada (AMMI-CA), Child Neurology Society (CNS), Pediatric Infectious Diseases Society (PIDS), Entomological Society of America (ESA), and European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Members representing the disciplines of cardiology, microbiology, pathology, and a

methodologist with expertise in GRADE were also included. Finally, the panel included three patient representatives and one healthcare consumer representative. Both academic and community practitioners were included. Guideline methodologists (Y.F.Y. and V.L.), oversaw all methodological aspects of the guideline development. A technical review team from Tufts Medical Center (R.B., M.O. and E.V) performed the systematic reviews of the literature, identified and summarized the scientific evidence using the "PICO" format (Patient/Population[P]; Intervention/Indicator[I]; Comparator/Control[C]; Outcome[O]) questions. IDSA staff (G.D.), in collaboration with AAN (S.M.) and ACR (A.T.) staff, oversaw all administrative and logistic issues related to the guideline panel.

Disclosure and Management of Potential Conflict of Interest (COI)

The Lyme conflict of interest (COI) review group consisting of two representatives from IDSA, AAN, and ACR were responsible for reviewing, evaluating and approving all disclosures. All members of the expert panel complied with the IDSA/AAN/ACR agreed- upon process for reviewing and managing conflicts of interest, which required disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict, regardless of relevancy to the guideline topic. Thus, to provide transparency, IDSA/AAN/ACR required full disclosure of all relationships. The assessment of disclosed relationships for possible COI by the IDSA/AAN/ACR review group was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). For more information on allowable and prohibited relationships, please review Table 1 and Table 2. In addition, the IDSA/AAN/ACR adhered to Section 7 of the Council for Medical Specialty Societies' "Code for Interactions with Companies"[6]. The COI review group ensured that the majority of the panel and each co-chair was without potential relevant

(related to the topic) conflicts (see Table 3). Each of the co-chairs and all members of the technical team were determined to be unconflicted. See Table 3 for disclosures reported to IDSA/AAN/ACR.

Clinical Questions and Evidence Review

An initial list of relevant clinical questions for these guidelines was created by the whole panel for review and discussion. The final set of clinical questions was approved by the entire committee. All outcomes of interest were identified *a priori* and explicitly rated for their relative importance for decision making. Each clinical question was assigned to a pair of panelists.

The technical team, consisting of three experts in systematic reviews from Tufts Medical Center (R.B., M.O. and E.V) who did not have any conflicts of interest, designed the literature searches to address every clinical question. Searches were limited to studies published in English. There was no restriction on the year of publication. The following electronic databases were searched: Ovid Medline, Cochrane database, Google Scholar, Scopus, and EMBASE. The initial literature searches were performed in March 2016, then updated in August 2017. A review of the literature will be conducted again in 2019 and new studies pertinent to this guideline will be incorporated into the final guideline. To supplement the electronic searches, the panelists had the option of manually searching journals, conference proceedings' reference lists, and regulatory agency websites for relevant articles. The Tufts technical team screened titles and abstracts of all identified citations, and all potentially relevant citations were subjected to a full-text review, using predefined inclusion and exclusion criteria that were tailored to meet the specific population, intervention, and comparator of each clinical question. Abstracts and conference proceedings, letters to the editor, editorials, review articles, and unpublished data were excluded. The panel made a priori decision to only include sufficiently peer-reviewed articles to avoid serious risk of bias associated with a lack of editorial oversight. The results of the literature search were thoroughly reviewed by the technical team for the final selection of the relevant articles. Panel members reviewed

for accuracy. Since it is typical that some studies may be initially included to avoid arbitrary exclusion despite meeting borderline inclusion criteria, rereview was necessary to ensure proper final selection of studies. Once the articles were selected, the technical team in conjunction with panelists and methodologists decided if a qualitative and/or a quantitative analysis were appropriate.

Evidence summaries for each question were prepared by the technical team from Tufts Medical Center. The risk of bias was assessed by the technical review team using the Cochrane risk of bias tool for randomized controlled trials [7], the Newcastle-Ottawa scale (NOS) for non-randomized studies [8] and QUADAS-2 tool for diagnostic test accuracy studies [9]. The certainty in the evidence was initially determined for each critical and important outcome, and then for each recommendation using the GRADE approach for rating the confidence in the evidence [10, 11] (see Figure 1). Evidence profile tables and quality of evidence were reviewed by the guideline methodologists (Y.F.Y. and V.L.) The summaries of evidence were discussed and reviewed by all committee members and edited as appropriate. The final evidence summaries were presented to the whole panel for deliberation and drafting of recommendations. Literature search strategies, PRISMA flow diagrams detailing the search results (will be made available in the published guidelines and will detail information from the 2019 literature update), data extraction and evidence profiles tables, and additional data, such as meta-analysis results when appropriate, can be found in the supplementary materials (see supplementary materials).

Ranking of the outcomes by importance for decision-making was determined by consensus for each PICO question. In situations where a PICO question was comparing the use of an antibiotic regimen to no antibiotics (either as a treatment or prophylaxis), if the beneficial effects of the antibiotic regimen were uncertain, undesirable outcomes would usually be ranked higher in importance than if benefits were certain (i.e., ranked as critical for decision-making rather than important). Moreover, in situations where a PICO question compared the use of a specific antibiotic regimen to another antibiotic regimen (either regarding specific molecules, classes of antibiotics, route of administration, or duration of therapy) and

the beneficial effects of the two regimens were similar, then the undesirable outcomes could be ranked as critical for decision-making, but several other considerations might have also been taken into account such as stewardship issues, costs, etc.

Development of Clinical Recommendations

All recommendations were labeled as either "strong" or "weak" according to the GRADE approach [11] (see Figure 1). The words "we recommend" indicate strong recommendations and "we suggest" indicate weak recommendations. Figure 1 provides the suggested interpretation of strong and weak recommendations for patients, clinicians, and healthcare policymakers. For recommendations where the comparators are not formally stated, the comparison of interest is implicitly referred to as "not using the intervention" (either not using a specific treatment or diagnostic test). High-quality evidence was lacking for several recommendations. According to GRADE guidance, strong recommendations in the setting of lower-quality evidence were only assigned when the panelists believed they conformed to one or several paradigmatic conditions. As per GRADE guidance on discordant recommendations [12], two paradigmatic situations presented in the development of this guideline: 1) low-quality evidence suggested benefit in a life-threatening situation (with evidence regarding harms being low or high), and 2) when low-quality evidence suggested benefit and high-quality evidence suggested harm. For recommendations pertaining to good practice statements, appropriate identification and wording choices were followed according to the GRADE working group [13]. A good practice statement represents a message perceived by the guideline panel as necessary in regard to actual heath care practice, is supported by a large body of indirect evidence difficult to summarize and indicates that implementing this recommendation would clearly result in large net positive consequences. Although there is an arguably ongoing need for research on virtually all of the topics considered in this draft guideline, "Research Needs" were noted for recommendations in which the need was believed by the panelists to be particularly relevant.

After 3 years of gathering and evaluating evidence, the entire panel met for a two-day face-to-face meeting in Arlington, VA in January 2017 for the presentation of evidence summaries and the development of the recommendations. All members of the panel participated in the preparation of the draft guideline and approved the recommendations.

Revision process

Public comment allows for key stakeholders to review and identify gaps in a draft guideline before its finalization and publication. In 2015, the guideline panel held a 60-day public comment period requesting input on its project plan that laid the groundwork for new Lyme Disease Guidelines. In June 2019, the panel will hold a second 45-day public comment period requesting feedback on the full draft guideline. The panel will review the feedback from the public comment phase and update the draft if needed.

Feedback will also be obtained from external peer reviews (PENDING). The draft guideline will be reviewed for approval by the IDSA Standards and Practice Guidelines Committee (SPGC), AAN's Guidelines Development, Dissemination, Implementation Sub-Committee and Practice Committee, ACR's Clinical Practice Guidelines Subcommittee and Quality of Care Committee as well as both organizations' respective Board of Directors (PENDING).

Revision for currency schedule

Approximately every two years and more frequently if needed, IDSA, AAN and ACR will determine the need for revisions to the guideline by an examination of the current literature and the likelihood that any new data will have an impact on the recommendations. If necessary, the entire expert panel will be reconvened to discuss potential changes. Any revision to the guideline will be submitted for review and approval to the appropriate Committees and Boards of IDSA, AAN and ACR.

General principles

Diagnostic Testing for Lyme Disease

Based on performance characteristics and practical considerations, antibody tests are first-line for the laboratory diagnosis of Lyme disease. Serum antibody (serologic) testing is highly sensitive in patients with non-cutaneous manifestations of the infection, as these manifestations typically develop after weeks to months of infection [14, 15]. IgG seronegativity in a patient with prolonged symptoms (months to years) essentially rules out the diagnosis of Lyme disease, barring laboratory error or a rare host immune deficiency affecting humoral immunity. Serologic testing is also highly specific when performed and interpreted according to current guidelines [15, 16]. Serum antibody tests should be performed using a two-tiered testing protocol employing clinically validated assays [17, 18]. Predictive value is increased when results are correlated with clinical features, patient history and risk factors.

As an indirect detection method, antibody testing for Lyme disease has some important limitations. Results can be falsely negative in the first days to weeks following initial exposure because a detectable antibody response takes time to develop [15, 19, 20]. This is often the case in patients with erythema migrans, the early localized manifestation of Lyme disease, who are tested less than two weeks after development of the skin lesion [15, 19, 20]. When paired (acute- and convalescent-phase) sera are analyzed in patients with erythema migrans, seroconversion can be documented in approximately 60-70% of treated cases [15, 19-23]. Seroconversion after antimicrobial therapy can be detected at higher rates using modified two-tiered testing protocols [14, 23, 24], which involve the sequential or concurrent use of two different enzyme immunoassays without the use of immunoblots [25, 26].

In a seropositive patient, it can be difficult to determine whether antibody reactivity is due to past infection, active/current infection, or both. In part, this is because both IgM and IgG *B. burgdorferi*-

specific antibody responses can persist for years or even decades after the infection is eradicated [21, 27, 28]. Furthermore, patients can be infected multiple times, as the immune response is not always protective, especially if the initial infection is adequately treated at an early stage and an expanded humoral immune response does not develop. If there is a known or suspected past history of Lyme disease in a seropositive patient with new symptoms, the diagnosis may be primarily reliant on clinical features and exclusion of alternative diagnoses. To supplement the clinical assessment, it may be helpful to analyze paired serum samples, collected at least 4 weeks apart, testing them in the same assay run using immunoblots or similar assays that indicate the breadth of the antibody response. Here, the goal is to determine whether the antibody response is expanding, retracting, or unchanged. In early, untreated infection, the antibody response is expected to expand between paired samples, whereas in patients with untreated late infection, the response is already expanded and should be largely unchanged between paired samples [15, 28, 29]. In patients with past infection, the antibody response may be expanded or limited, depending on several factors including when treatment occurred and initial disease presentation; however, the response should remain largely unchanged between paired samples or should retract. Seroreversion (a change from seropositive to seronegative) or a waning antibody response is not always demonstrable after adequate treatment for Lyme disease, and may take many months to years to occur; thus, analysis of serially collected serum samples is not a reliable “test of cure.”

To address these limitations, numerous direct and non-antibody indirect methods have been proposed or developed. At present, only a few such assays are useful for clinical diagnosis, and these are only useful as adjunctive tests in select clinical scenarios when two-tiered serologic testing is positive. As a rule, an assay should only be used for diagnostic purposes if its analytical and clinical validity has been demonstrated, reproducibly, in comparison to an appropriate reference standard. In the United States, the Food and Drug Administration (FDA) regulates the marketing of diagnostic tests, ensuring their

safety and effectiveness. Currently, the only FDA-cleared or -approved diagnostic assays for Lyme disease are antibody tests. The use of FDA-cleared or -approved assays, performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories, assures quality, safety, and effectiveness. U.S. laboratories with CLIA certification for high complexity testing may also perform non-FDA-cleared or -approved "laboratory developed tests" (LDTs), provided that adequate performance has been established. Before requesting LDTs for diagnostic purposes, providers are strongly encouraged to (1) verify that the diagnostic laboratory offering the LDT is certified under CLIA for high-complexity diagnostic testing, and (2) ensure that validation studies, whether published or unpublished, confirm analytical and clinical performance that is substantially equivalent in comparison to an appropriate reference standard. In making this assessment, consultation with an independent clinical laboratory director with experience in Lyme disease diagnostics is advised. In some cases, the Centers for Disease Control and Prevention (CDC) may serve as a resource for this assessment [30]. Some commercially-available laboratory testing methods including non-standard serology interpretation, urine antigen or DNA testing, or the use of a lymphocyte transformation test [31] or a quantitative CD57 lymphocyte assay [32], should be avoided for clinical use due to lack of systematic, independent, reproducible validation studies [33].

Treatment of Lyme disease

Lyme disease is treated with antimicrobials with activity against *B. burgdorferi* (see Table 4 and Table 5). The goals of treatment are the resolution of objective signs and symptoms of infection with prevention of relapsed active infection or new complications of infection. *B. burgdorferi* is susceptible to antimicrobials from several classes, including doxycycline, penicillin, amoxicillin, cefuroxime, ceftriaxone, and azithromycin. Under most circumstances, oral therapy is effective and preferred over intravenous

therapy due to equivalent efficacies, tolerability, and cost. However, indications for intravenous therapy, such as treatment in the hospitalized patient, are discussed in this guideline.

The choice of antibiotic depends on a number of factors that include include age, the presence of extracutaneous manifestations of Lyme disease, such as neurologic Lyme disease; drug allergy, side effect profile, or tolerability; frequency of administration; sun exposure (sun exposure will increase the risk of photosensitivity skin reactions associated with doxycycline); likelihood of co-infection with *Anaplasma phagocytophilum* or *Ehrlichia muris eauclairensis* (formerly known as *Ehrlichia muris*-like agent), which, if suspected, would favor the use of doxycycline [1]; whether there is consideration of cellulitis vs. erythema migrans in the differential diagnosis; and cost.

Doxycycline has traditionally been avoided in children under 8 years of age, in pregnancy, and in breastfeeding women because of possible staining of cosmetically important primary teeth. This concern is primarily based on experience with tetracycline, not with doxycycline. Subsequent research, albeit mostly observational and of limited sample size, casts doubt on an association between doxycycline and tooth staining. A growing consensus accepts the safety of doxycycline use in young children for at least up to 14-days duration [34-38]. That said, for pediatric patients regardless of age, amoxicillin will usually be preferred over doxycycline in large part due to its much more common use in pediatrics. For some Lyme disease treatment decisions, most notably Lyme meningitis, doxycycline is the only oral option known to be effective, and the alternative of parenteral therapy has additional risks. For patients with a history of severe beta-lactam allergy, the uncertainties about doxycycline may be preferable to the dangers of re-challenge with a beta-lactam antibiotic or antibiotic desensitization. The safety of doxycycline in pregnancy and breastfeeding has not been systematically studied, and thus the choice to use doxycycline in these patients should be individualized to the likely risks and benefits of alternative antibiotics.

Several antibiotics and antibiotic classes are not indicated to treat Lyme disease due to a variety of considerations, including lack of *in vitro* activity, the absence of supportive clinical data, potential toxicity, and an unnecessarily broad spectrum of antimicrobial activity. Drugs and drug classes that are not indicated for the treatment of Lyme disease include first-generation cephalosporins, fluoroquinolones, aminoglycosides, pyrazinamide, vancomycin, tigecycline, metronidazole, tinidazole, rifampin, hydroxychloroquine, or fluconazole. Additionally, drugs with antibabesial activity such as clindamycin, quinine, and atovaquone should only be used in recommended combinations for the specific treatment of babesiosis, if present. There is no clinical evidence to support regimens intended to treat fastidious states of *B. burgdorferi* infection, such as morphologic variants [39] (aka "cyst" forms, "round" bodies, or "L-forms"), or to treat biofilms.

Tick bites prevention and prophylaxis of Lyme disease

Lyme disease and other tick-borne diseases can be prevented by avoiding tick exposure. Therefore, knowing when and where infectious ticks are most likely to be active can help people take proper precautions to prevent tick bites, to prevent infection from tick bites, to help guide recommendations on the utility of antibiotic prophylaxis following a tick bite, and to provide patients with anticipatory guidance about the signs and symptoms of a tick-borne infection [Table 6].

In North America, the blacklegged (deer) tick (Ixodes scapularis) and western blacklegged tick (I. pacificus) are the tick species responsible for transmitting the agents of Lyme disease, B. burgdorferi sensu stricto (hereafter referred to as B. burgdorferi), and less commonly, B. mayonii [40], to humans [41]. Larval ticks are born free of infection and cannot transmit B. burgdorferi [42], but larval ticks can acquire the organism while feeding on reservoir hosts, such as white-footed mice, and then transmit it in a subsequent life stage. Both nymphal and adult ticks can transmit B. burgdorferi. Nymphs, however, are more likely to transmit B. burgdorferi to humans than adult ticks due to their smaller size, greater

abundance, and their seasonality, which coincides with high levels of human outdoor activity [41]. Human cases of Lyme disease, therefore, temporally correlate with the nymphal host-seeking activity period, typically during late spring and summer (see Figure 2) [40, 41]. While adult ticks play a much less important role in transmission than nymphs, Lyme disease cases do occur during the spring and fall when primarily adult ticks are active.

Ixodes scapularis is responsible for the overwhelming majority of B. burgdorferi transmission in North America [41]. Although the geographic range of I. scapularis encompasses much of the eastern U.S., the risk of Lyme disease is not uniform, with the distribution of Lyme disease cases closely corresponding to the distribution of B. burgdorferi-infected, questing I. scapularis nymphs [43]. Fourteen states in the northeastern and north-central US, where infected questing nymphs are abundant, accounted for 95.2% of all cases of Lyme disease reported to the Centers for Disease Control and Prevention (CDC) during 2008-2015 (see Figure 3) [40]. In regions to the south, however, the risk of exposure to B. burgdorferi-infected ticks is much lower [43, 44], due in part to behavioral differences of the nymphal life stage [45, 46].

The geographic risk of exposure is expanding, however, as northern populations of I. scapularis continue to spread into new areas [47] followed by concomitant increases in disease both in the northern [48, 49] and southern [50, 51] U.S. Thus, physicians and the public should consult state health departments and the CDC to obtain the most current information on the areas of existing and emerging Lyme disease risk (https://www.cdc.gov/lyme/datasurveillance/maps-recent.html). Within the geographic range of their distribution, I. scapularis may exist in urban, suburban, and rural landscapes in a variety of habitats.

I. Which measures should be used to prevent tick bites and tick-borne infections?

A) Personal protective measures

Recommendation:

1. In potentially exposed individuals, personal protective measures should be implemented to reduce the risk of tick exposure and infection with tick-borne pathogens **(good practice statement).**

Summary of the evidence: Several personal protective measures can reduce the risk of tick exposure and infection with tick-borne pathogens. Recommended measures include wearing light-colored clothing with long sleeves and long pants, tucking pants into socks, and conducting thorough tick checks following outdoor activities [41, 52-54]. Bathing within two hours of outdoor activity can significantly reduce the risk of Lyme disease [55]. After outdoor activities, placing clothes in a dryer on high heat for at least six minutes is highly effective for killing I. scapularis, though up to 60 min may be required for other tick species [56, 57]; washing clothes in hot, but not cold nor warm water, will also kill I. scapularis [56]. Because pets that spend time outdoors may bring unattached ticks into the home, even if they are treated with tick control products, they should also be checked regularly for ticks to prevent subsequent tick attachment to humans [58].

Rationale for recommendation: Although there is little systematic evidence supporting some of these measures for prevention of Lyme disease, they may offer potential benefits with little effort or risk.

B) Repellents to prevent tick bites

Recommendation:

1. For the prevention of tick bites, we recommend N,N-Diethyl-meta-toluamide (DEET), picaridin, ethyl-3-(N-n-butyl-N-acetyl) aminopropionate (IR3535), oil of lemon eucalyptus, or permethrin **(strong recommendation, moderate-quality evidence).**

Summary of the evidence: In laboratory and field experiments involving human subjects, the use of DEET, picaridin, IR3535, oil of lemon eucalyptus, or permethrin reduced the number of ticks detected crawling on or attached to subjects compared with controls. Other commercially available products, including

botanical agents and essential oils (e.g., essential oils of rosemary, cinnamon leaf, lemongrass, geraniol [59], nootkatone, and carvacrol [60]) cannot be recommended due to insufficient evidence.

DEET, picaridin, IR3535, and oil of lemon eucalyptus are applied directly to skin, except for the face or hands. Different concentrations and preparations affect their efficacy and duration of activity. Repellents should only be applied to exposed skin or clothing and should not be applied under clothing. Products with higher concentrations provide greater and/or longer periods of efficacy compared with lower concentrations. Studies indicate that products with ≥ 20% DEET [61-63, 64], ≥ 10% picaridin [61, 62], ≥ 10% IR3535 [61, 62], and 30% p-menthane-3,8-diol (PMD) (the synthetic derivative of oil of lemon eucalyptus) [65] effectively repel ticks. Products containing >50% DEET are not recognized to offer a meaningful increase in protection time over lower concentrations. Permethrin (0.5%) kills ticks on contact, but must be applied to clothing. Field studies indicate that clothes sprayed with permethrin or made with pre-treated, permethrin-impregnated material provide highly effective protection against tick bites [64, 66-68] and are more effective compared with clothes treated with DEET [64, 66].

To improve efficacy and safety, repellents should always be applied according to the manufacturer's instruction. Despite public concern over the use of DEET, decades of use show there is a very low risk of adverse effects when used as labeled [69-77]. Some reported cases of encephalopathy following DEET application were likely due to improper application, an excessive dose, or unintentional ingestion [69, 70, 73]. Despite hundreds of millions of annual applications of DEET, reports of encephalopathy are rare and may not differ from the background rate in the general population [70, 71]. Because of a lack of safety data, the American Academy of Pediatrics and the Environmental Protection Agency do not recommend DEET for infants <2 months of age. The use of products that combine sunscreen and DEET is discouraged, because frequent re-application of the sunscreen may lead to greater-than-recommended exposure to the repellent. Furthermore, sunscreen may increase the absorption of DEET through the skin [78]. Consequently, the FDA recommends that sunscreen be applied before DEET.

IR3535 and PMD are both EPA-registered as biopesticides (derived from natural materials), that are available for people who prefer an alternative to conventional synthetic repellents. For people with frequent occupational or recreational exposure to tick habitats, a feasible option would be to wear permethrin-treated clothing, and then selectively apply a repellent to exposed skin if additional protection is desired.

Rationale for recommendation: Because ticks often attach and complete blood meals without being noticed, repellents with proven efficacy may prevent tick-borne diseases.

Research needs: Properly designed studies performed with human subjects under natural conditions are required to test the efficacy and safety of additional options for repellents. For example, a small field study [60] indicated that clothes sprayed with natural-product based repellents (nootkatone, carvacrol, geraniol) can effectively repel ticks, but before these products can be recommended larger studies are needed to confirm these results. Further studies to address adverse effects of repellents are needed.

C) Removal of Attached Ticks

Recommendations:

1. We recommend promptly removing attached ticks by mechanical means using a clean tweezer (or a comparable device) inserted between the tick body and the skin (**good practice statement**).
2. We recommend against burning an attached tick (with a match) or applying noxious chemicals or petroleum products to coax its detachment (**good practice statement**).

Summary of the evidence: Duration of tick attachment is among the most important predictors of subsequent Lyme disease. Experimental studies in animals have established that there is a time delay between the onset of tick feeding and transmission of B. burgdorferi, and that the probability of transmission increases the longer the tick is attached. Thus, performing tick checks after exposure and promptly removing any attached Ixodes ticks, is a potentially effective means to prevent Lyme disease. Proper removal requires grasping and pulling the mouthparts at the closest point of attachment to the

skin (see Figure 4). If the mouthparts cannot easily be removed from the skin, they should be left alone and permitted to fall out.

In laboratory experiments in animals, the time between tick attachment and transmission of I. scapularis-borne pathogens varies. For B. burgdorferi, rarely were animals infected within 24 hours of tick attachment [79]; a low percentage of animals exposed to infected nymphs became infected within 24-36 hours [80]; and the majority of animals became infected ≥ 48 hours [80-83]. In contrast, Powassan virus may be transmitted within 15 minutes of attachment [84]; Anaplasma phagocytophilum [81] and B. miyamotoi [85] within 24 hours; and B. mayonii [86] and Babesia microti [87] mainly after 48 hours of attachment.

Rationale for recommendation: Prompt detection and removal of an attached tick can reduce the likelihood of pathogen transmission and therefore disease. Proper removal of the intact tick is best achieved by mechanical means. Saving the tick and showing it to the health care provider may provide guidance as to the type of tick (i.e., species and life stage) and potentially enable an assessment of the degree of blood engorgement. Such determinations are best achieved through a qualified expert or laboratory assessment. Knowing tick characteristics may be helpful for anticipatory guidance or in determining if antibiotic prophylaxis to prevent Lyme disease is appropriate.

II. Which diagnostic tests should be used following a tick bite?

A) Diagnostic tick testing

Recommendation:

1. We recommend against testing for B. burgdorferi in an Ixodes tick following a bite (**strong recommendation, moderate-quality evidence**).

   Comment: The presence or absence of B. burgdorferi in an Ixodes tick does not reliably predict the likelihood of clinical infection.

Summary of the evidence: Studies from the U.S. and Europe have shown that detecting Lyme Borrelia in Ixodes ticks poorly predicts either subsequent disease (0-12.4%) [88-94] or seroconverting asymptomatically (0-4.7%) [89, 90, 92, 94, 95]. This is likely due to a variety of factors that influence the likelihood of transmission and the observation that most ticks discovered by patients have been attached for under 48 hrs [96, 97].

Rationale for recommendation: Even in areas that are highly endemic for Lyme disease, patients presenting with an Ixodes tick bite have a low probability of developing Lyme disease, regardless of whether the tick tests positive for B. burgdorferi. Testing ticks may lead to unnecessary antibiotic prescriptions in patients who would not go on to develop Lyme disease. Anticipatory guidance is recommended so that a prompt diagnosis of Lyme disease (as well as other relevant Ixodes tick transmitted infections) can be made should a patient develop symptoms.

Research needs: Although we recommend against testing ticks for pathogens, having the tick identified by a qualified expert or laboratory may inform patient counseling about early signs of infection and aid in diagnosis because different tick species transmit different pathogens. However, this can be challenging for physicians and the public [98]. Further research is needed to understand the capacity of practicing physicians to identify ticks accurately, and the feasibility and success of provider education in tick identification merits further study as well. Additionally, further study is needed to evaluate whether accurate tick identification improves patient outcomes.

B) Diagnostic testing of asymptomatic patients following tick bites

Recommendation:

1. We recommend against testing asymptomatic patients for exposure to B. burgdorferi following an Ixodes tick bite (**strong recommendation, moderate-quality evidence**).

Summary of the evidence: Following a recent tick bite, asymptomatic patients should have negative serologic tests for B. burgdorferi unless the patient had a prior infection. Notably, the background

seroprevalence of B. burgdorferi in a highly endemic Lyme disease area was 5% in the mid-1990s [99] and may now be even higher given the increase in disease incidence [40, 41]. While follow-up testing 4-6 weeks after the tick bite could detect an asymptomatic infection, this is not recommended as antibiotic treatment is not indicated for asymptomatic seroconversion.

Rationale for recommendation: Serologic testing of asymptomatic patients following a tick bite does not help with treatment decisions. There is currently insufficient evidence that asymptomatic patients with positive serologic tests should receive antibiotic therapy. Available data suggest that patients with asymptomatic seropositivity are much less likely to develop disseminated Lyme disease than untreated patients with erythema migrans [100-102].

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

Recommendation:

1. We recommend that prophylactic antibiotic therapy is given only to adults and children within 72 hours of removal of an identified high-risk tick bite, but not for bites that are equivocal or low risk (**strong recommendation, high-quality evidence**). **Comment**: A tick bite is considered to be high-risk only if it meets the following three criteria: the tick bite was from a) an identified Ixodes tick; b) it occurred in a highly endemic area (i.e., the prevalence of a B. burgdorferi-infected tick ≥ 20%); and c) the tick was engorged and attached for ≥ 36 hours. If the tick bite cannot be classified with a high level of certainty as a high-risk bite, a wait-and-watch approach is recommended.

Summary of the evidence: The likelihood of Lyme disease following a tick bite is associated with several factors, including the infection prevalence of B. burgdorferi among questing nymphal I. scapularis ticks in the region of exposure [103]. In highly endemic areas of the northeastern, middle Atlantic, and north-central United States the nymphal infection prevalence may exceed 20% [43, 104, 105]. To determine

whether an Ixodes tick bite comes from a highly endemic area, medical professionals can consult state health agency Lyme disease risk maps if they exist and/or up-to-date summaries of Lyme disease cases reported to the CDC that will indicate states with high Lyme incidence, states that are neighboring high incidence states (and thus with presumed elevated risk), or states with low incidence [40]. The infection prevalence among I. pacificus ticks often is less than 20% [105, 106] and their bites are therefore generally not considered high-risk. However, medical professionals should consult state public health agency Lyme disease risk maps as some areas with > 20% infection prevalence in nymphal I. pacificus do occur.

The duration of tick attachment (see Figure 5) is among the most important predictors of subsequent Lyme disease. Unengorged ticks do not pose a significant risk for B. burgdorferi transmission. The likelihood of transmission increases with duration of attachment in both laboratory mice and patients, with the majority of transmission occurring after 36 hours of attachment [79-83]. Clinical studies [93, 107] have described a positive association between duration of tick attachment (over vs. under 72 hours) and clinical signs of Lyme disease or seroconversion. In this high-risk scenario, the likelihood of subsequent Lyme disease has varied across studies, but the risk may exceed 20% when a tick has been attached for ≥72 hours [93]. A meta-analysis of four studies [108], pooling both high- and low-risk tick bites reported that administration of prophylactic antibiotics within 72 hours of removal of an attached tick reduced the risk of subsequent Lyme disease from 2.2% to 0.2%. After a lower risk exposure, such as brief duration of tick attachment (i.e., <36 hrs) or exposure in regions with low Lyme disease incidence, the absolute risk of Lyme disease will be lower, and therefore the benefit of prophylactic antibiotics will be lower as well.

Rationale for Recommendation: For high-risk tick bites, we have weighed the likelihood of disease and the effectiveness of prophylactic doxycycline therapy to be higher than the potential risks of the antibiotic. For ticks that have not been identified as Ixodes or are Ixodes but do not meet high-risk criteria, antibiotic prophylaxis may not benefit and may lead to adverse reactions. Because of uncertainty about the safety of doxycycline in pregnancy, we advise pregnant women to have an

informed discussion with their physicians about the risks, benefits, and uncertainties of antibiotic treatment versus observation.

Regardless of whether antibiotic prophylaxis is given, clinicians should counsel patients about the symptoms and signs of the regional Ixodes-borne infections. Moreover, patients should be advised to seek medical attention if they develop an expanding erythematous lesion at the site of the tick bite or other skin sites, fever or any other unexplained illnesses, particularly within 30 days of the tick bite. There is currently no systematic data supporting post-exposure antibiotic prophylaxis to prevent other I. scapularis-borne diseases including anaplasmosis, ehrlichiosis, or babesiosis.

Research needs: A limitation of this recommendation is the reliable and timely determination of whether a tick bite meets all three criteria of a high-risk tick bite. An examination of the scutal index, a measure of engorgement used to calculate duration of attachment, of Ixodes ticks attached to patients in a highly endemic region over a 17-year period found that >40% did not meet the high-risk criteria [109]. Prescription of an antibiotic would not be indicated for these bites. Accurate identification of a tick species may be challenging, especially as the tick engorges, but in particular, the duration of attachment of an identified Ixodes tick can only be reliably determined by a qualified expert (e.g., by measuring the scutal index), because the certainty about the timing of the bite by history is often unreliable. Thus research is needed to develop methods to deliver reliable and timely information about the tick bite to the clinician. This could include feasibility of training laboratory personnel in measurement of the scutal index. These research needs will likely become more significant in the future as blacklegged tick populations are increasing, and the geographic distributions of blacklegged and other tick species are increasingly overlapping.

Infection prevalence, as well as strain diversity, of B. burgdorferi among I. scapularis ticks, can be locally and regionally variable [43, 104, 105]. This contributes to considerable variability in the risk of Lyme disease following a tick bite, with the expected benefit of antibiotic prophylaxis to be greatest in areas

with high disease risk and to diminish with decreasing risk. Longitudinal disease and tick surveillance, therefore, are needed to monitor how disease risk is changing over time, especially as infected tick populations continue to spread into areas without known previous disease risk [40, 43, 47]. Clinical studies to evaluate the utility of chemoprophylaxis to prevent other I. scapularis-borne pathogens also are needed.

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

Recommendation:

1. For high-risk Ixodes bites, we recommend the administration of a single dose of oral doxycycline within 72 hours of tick removal over observation (**strong recommendation, moderate-quality evidence). Comment:** Oral doxycycline dosing is 200 mg for adults and 4.4 mg/kg up to a maximum dose of 200 mg for children.

Summary of Evidence: Four placebo-controlled clinical trials, all conducted in areas endemic for Lyme disease, were included for review (see Evidence Profile Tables IV) [108]. Most of the included trials recruited both adults and children; one trial recruited only children [110]. Two potential dosing alternatives have been studied in this setting - a single dose of doxycycline (200 mg x 1 dose) [107] and multiple doses for 10 days of other antibiotics, including tetracycline (1,000 mg/day) [110], penicillin (1,000 mg/day) [89] and amoxicillin (1,000 mg/day) [92]. There has been no direct comparison between β-lactams and tetracyclines; each has been compared to a placebo. Among 1082 randomized subjects, the risk of developing Lyme disease in the placebo group was 3.0%. Antibiotic prophylaxis significantly reduced the risk of developing Lyme disease compared with placebo (relative risk: 0.27, 95%CI (0.10, 0.75); absolute risk: 22 fewer per 1,000, (95%CI: 27 to 7 fewer per 1,000)). Although there were no serious adverse effects from the antibiotics in any of the studies, drug rashes and gastrointestinal side effects were observed.

Rationale for recommendation: Doxycycline is preferred over alternative antibiotics in this setting, since it can be taken as a single dose with a relatively low risk of side effects (see Introduction to Treatment for a more detailed discussion). Single doses of other alternative antibiotics have not been studied and longer courses may result in additional toxicity. In addition, none of the other antibiotics were shown to be more effective than placebo, but this was likely due to insufficient enrollment of subjects in these studies. There is currently insufficient data to recommend topical antibiotics to prevent Lyme disease [111, 112].

Research needs: Additional research is needed to evaluate whether brief courses of amoxicillin and other antibiotics are comparable to doxycycline for the prophylactic treatment of tick bites. Further research is also needed to evaluate whether topical antibiotics can reliably prevent Lyme disease.

Early localized Lyme disease (erythema migrans)

The most common clinical manifestation of Lyme disease is an expanding, erythematous, often annular skin lesion referred to as erythema migrans (EM) [3, 113-115]. EM occurs at the site of inoculation of *B. burgdorferi* into the skin by the bite of an infected *Ixodes* species tick. Patients with EM may have concomitant constitutional symptoms such as fatigue, arthralgias, myalgias, and headache [3, 113-115]. After deposition into the skin, in untreated patients, the spirochetal bacteria may disseminate to other anatomic sites leading to regional lymphadenopathy, additional EM skin lesions, certain neurologic and cardiac manifestations, and/or arthritis [113, 115].

V. What is the preferred diagnostic testing strategy for erythema migrans?

Recommendation:

1. In patients with skin lesions compatible with erythema migrans, we recommend clinical diagnosis over laboratory testing. **(Strong recommendation, moderate quality evidence).**

Comment: The clinical diagnosis of erythema migrans assumes that a patient has had plausible exposure to infectious ticks in a region endemic for Lyme disease.

2. In patients with one or more skin lesions suggestive of, but atypical for erythema migrans, we suggest antibody testing performed on an acute-phase serum sample (followed by a convalescent-phase serum sample if the initial result is negative) rather than currently available direct detection methods such as polymerase chain reaction (PCR) or culture performed on blood or skin samples ***(weak recommendation, low-quality evidence).*** **Comment:** If needed, the convalescent-phase serum sample should be collected at least 2 to 3 weeks after collection of the acute-phase serum sample.

Summary of the evidence: Most patients with localized, cutaneous Lyme disease are seronegative at the time of initial presentation. Among untreated patients with microbiologically-confirmed, solitary erythema migrans lesions, fewer than 20% are seropositive using conventional two-tiered antibody testing (EIA or IFA followed by immunoblotting), performed on a single, acute-phase serum sample collected within 1 week of noticing the lesion [20, 116, 117]. Acute-phase sensitivity is comparatively higher if the lesion has been present for longer without treatment [20, 116, 118], reaching 86% in the 4th week of symptoms [116], or in patients presenting with multiple erythema migrans lesions [15, 116, 119].

In patients with erythema migrans who are treated within 2 weeks or so after first recognition of the lesion, the diagnostic sensitivity of serologic testing conducted at least 2-3 weeks after initiating therapy improves compared with baseline testing [20]. Using the conventional two-tiered testing protocol, sensitivity is approximately 53-66% after therapy [15, 120, 121] and is substantially higher if the lesion was present for longer before treatment [20]. Compared with conventional two-tiered antibody testing, higher diagnostic sensitivity may be achieved in patients with erythema migrans during the acute- or convalescent-phase of illness using a modified two-tiered serologic testing algorithm, in which two different EIAs are applied sequentially or concurrently, without the use of immunoblots [14, 23, 24, 120].

The extent of improvement depends on the particular enzyme immunoassays used in the modified two-tiered testing approach.

In a study directly comparing antibody testing with various direct detection methods in patients with a clinical diagnosis of solitary or multiple erythema migrans (mean duration of illness >1 week), the most sensitive method in the acute-phase of illness, prior to antibiotic administration, was real-time PCR performed on skin biopsy samples of the lesion (80.9%), followed by conventional two-tiered antibody testing performed on convalescent-phase serum samples (66%) [121]. The least sensitive method was conventional two-tiered antibody testing performed on acute-phase serum samples (40.4%). Intermediate sensitivity was demonstrated using culture of 2mm skin biopsy samples (51.1%) and high-volume (≥9 mL) plasma culture with growth detection by microscopy (44.7%). Subsequent investigations demonstrated that the sensitivity of high-volume plasma culture might exceed 70% if growth detection is performed using real-time PCR [122, 123].

Studies involving skin biopsy culture of untreated erythema migrans lesions have typically reported diagnostic sensitivity of approximately 40-60% [121, 123-132] with some reporting lower yield [133-136] and a few reporting sensitivity exceeding 70% [137-140]. When skin biopsy culture has been directly compared with PCR performed on skin biopsy samples, the latter has generally been more sensitive, although this depends on the exact methods used and the reverse has also been reported [121, 123, 125, 127, 129-135].

The yield of plasma or whole-blood PCR is comparable to the yield of high volume plasma culture using growth detection by microscopy, with reported sensitivities in the 30-50% range [123, 133, 141-143], although substantially lower yields have been reported [144, 145]. PCR sensitivity varies according to the specific technique, and the application of multiple PCR assays to the same sample can improve sensitivity [123].

Rationale for the recommendation: In untreated patients with erythema migrans of short duration (2 weeks or less), none of the currently-available serologic or direct detection tests for Lyme disease is sufficiently sensitive for accurate diagnostic use, necessitating clinical diagnosis. However, in patients with skin lesions that are atypical for erythema migrans, laboratory testing may aid in the diagnostic assessment. In such cases, if the patient will not be treated empirically with antimicrobial therapy, the most practical approach is to perform serologic testing on paired samples collected at least 2-3 weeks apart. An alternative (or supplement) to paired serologic testing is to attempt direct detection of *B. burgdorferi* in the skin lesion or blood. These methods offer the possibility of a more timely diagnosis in true cases; direct detection methods are generally more sensitive at the time of initial clinical presentation with erythema migrans, compared with acute-phase (single sample) serologic testing. However, practical matters limit their use and availability; recognition of these limitations has informed our testing recommendations.

Research needs: None of the currently available direct or indirect detection methods is optimally sensitive in patients with acute erythema migrans at the time of initial clinical presentation; more sensitive diagnostic methods are needed.

VI. What are the preferred antibiotic regimens for the treatment of erythema migrans (EM)?

Recommendation:

1. For patients with EM, we recommend using oral antibiotic therapy with doxycycline, amoxicillin, cefuroxime axetil or phenoxymethylpenicillin over other antimicrobials ***(strong recommendation; moderate quality of evidence).*** **Comment:** For patients unable to take both doxycycline and beta-lactam antibiotics, azithromycin is preferred. Due to a lack of evidence on the efficacy of higher dosage amoxicillin administered twice daily, the conventional dose divided three times daily is preferred (see Table 7).

Summary of evidence: Although EM will resolve without antibiotic treatment, evidence indicates that the currently used antibiotic regimens will lead to faster resolution of the skin lesion and associated symptoms and will effectively prevent the development of disseminated manifestations of Lyme disease (e.g., Lyme arthritis) [101, 146, 147]. Based on clinical trial data and on in vitro susceptibility testing data, the three widely used oral antibiotics in the United States, doxycycline, amoxicillin, or cefuroxime axetil, appear to have similar efficacy for the treatment of patients with EM (see Evidence Profile Tables VI) [148-155]. Azithromycin has also been found to be effective clinically and of comparable efficacy to comparators for patients with EM in all clinical trials conducted to date except for one (see Evidence Profile Tables VI) [150, 156-163]. The explanation for the worse outcomes reported in one trial comparing azithromycin with amoxicillin is unclear [156]. This trial was a randomized, double-blind study, and no similar study on the efficacy of azithromycin for EM has been conducted subsequently in the U.S. Methodologic issues may explain the differences in results, particularly because 14% of the enrolled subjects may have had STARI rather than Lyme disease [164]. Although the authors stated that exclusion of these particular subjects did not affect the overall response rates for each treatment group, they did not provide results of these sensitivity analyses [156]. Because of results from that study, however, azithromycin is often considered to be a second line agent to be used for patients who cannot safely take beta-lactam or tetracycline antibiotics [113, 115].

Rationale for recommendation: Given the comparable efficacy of doxycycline, amoxicillin and cefuroxime axetil, factors other than efficacy should be considered in the selection of which oral antibiotic should be prescribed for the treatment of patients with EM. The American Academy of Pediatrics recommends that doxycycline, amoxicillin or cefuroxime axetil may be used to treat EM in children of any age (including those less than 8 years). Other clinicians, however, given the limited data on dental safety of doxycycline, along with the methodologic and inferential concerns of the available data [165] would only prescribe doxycycline for young children with EM if the patient is unable to tolerate beta-lactam

antibiotics. The decision to use doxycycline to treat EM in young children, pregnant women, and breastfeeding women who wish to continue breastfeeding and have no contraindication to beta-lactam antibiotics, should be individualized and made with careful deliberation (see discussion in the Introduction to the Treatment Section).

Research needs: Additional studies in the United States on the efficacy of azithromycin for EM and studies comparing twice daily with three times daily dosing of amoxicillin are warranted. Further study is needed to establish the safety profile of doxycycline in children and in pregnant and lactating women.

VII. How long should a patient with EM be treated?

Recommendation:

1. We recommend that patients with EM be treated with either a 10-day course of doxycycline or a 14-day course of amoxicillin, cefuroxime axetil or phenoxymethylpenicillin rather than longer treatment courses ***(strong recommendation, moderate quality of evidence).*** **Comment:** If azithromycin is used, the preferred duration is 7 days.

Summary of evidence: Different durations of antibiotic therapy have been evaluated in the treatment of patients with EM ranging from a short, 5-day a course of therapy to more than 21 days (See Evidence Profile Tables VII) [113, 114, 146, 148-163, 166-177]. No difference in outcomes has been associated with duration of therapy, as demonstrated by several studies comparing the same antibiotic used for different durations. A prospective, randomized, double-blind, placebo-controlled clinical trial of patients with EM showed equivalent efficacy of 10 days compared with 20 days of doxycycline therapy [171]. Another prospective study showed similar efficacy of a 10 days course compared with 15 days of doxycycline treatment for patients with EM [170]. The shorter course of azithromycin therapy is recommended because the drug has a prolonged tissue half-life.

Rationale for recommendation: Shorter durations of antibiotic exposure may reduce adverse effects and cost.

Research needs: Further studies in the United States on the efficacy of even shorter courses of antibiotic therapy are warranted.

VIII. Should patients with Southern Tick-Associated Rash Illness (STARI) be treated with antibiotics?

Recommendation:

1. In patients who develop an EM-like skin lesion following the bite of the lone star tick (*Amblyomma americanum*), an illness referred to as Southern Tick-Associated Rash Illness (STARI), we make no recommendation for or against the use of antibiotics ***(no recommendation; knowledge gap).*** **Comment:** In certain geographic regions both STARI and Lyme disease are endemic [178]. Distinguishing EM due to Lyme disease from STARI may not be possible clinically unless the responsible tick has been identified [179]. When STARI cannot be distinguished from Lyme disease-associated EM in areas endemic for both conditions, antibiotic therapy directed towards Lyme disease is indicated.

Summary of evidence: STARI has been reported predominantly in the southeastern and south-central United States, where the lone star tick is the most abundant human-biting tick. Lone star ticks are not able to transmit *B. burgdorferi* [180-184]. To date no infectious agent has been identified in STARI patients [164, 185-189], except in one instance, where *B. lonestari* was detected by PCR in a sample of the skin lesion and also detected in the lone star tick that had bitten the patient [190]. Recent data suggest that STARI and Lyme disease-associated EM produce different host metabolic biosignatures [191]. There are no known extracutaneous sequelae associated with STARI, though few untreated patient case histories have been reported [192]. It remains unknown whether antibiotic treatment of STARI patients affords clinical benefit, and if so which antibiotics would be useful.

In geographic areas where Lyme disease is rare or non-endemic and there are abundant lone star ticks, physicians and patients may choose observation rather than antibiotic treatment for EM [178, 192]. This decision should be guided by both patient and physician preferences. The decision to observe should be accompanied by patient counseling about the manifestations of disseminated Lyme disease, and the importance of prompt evaluation should any of these manifestations arise.

Rationale for recommendation: There are insufficient data to provide a recommendation for or against antibiotic treatment for a proven case of STARI, an illness of unknown etiology.

Research needs: Additional studies are needed to determine the etiology of STARI and to establish whether or not antibiotic therapy improves the rate of resolution of the skin lesion and associated symptoms.

Neurologic Lyme disease

It is helpful to consider nervous system Lyme disease (Lyme neuroborreliosis, LNB) in two dimensions – anatomic and temporal. Anatomically, disorders may affect the peripheral (PNS) or central (CNS) nervous systems. PNS involvement includes cranial neuritis, radiculoneuritis, plexopathies, mononeuropathy and mononeuropathy multiplex. CNS disorders can be divided into those affecting the subarachnoid space (meningitis, raised intracranial pressure) and the parenchyma of the brain or spinal cord (encephalitis, myelitis). It is important to note that patients with Lyme disease, but without parenchymal CNS infection with *B. burgdorferi* may, as in many other systemic inflammatory disorders, have associated alterations of concentration, memory and cognitive function, a state referred to as Lyme encephalopathy. In the absence of focal CNS abnormalities clinically or on imaging studies, this is generally not indicative of encephalitis.

Temporally, the most common manifestations of LNB (meningitis, cranial neuritis, radiculoneuritis) and more rarely encephalomyelitis, typically have an abrupt onset and occur in the first

few months of infection; these manifestations are often termed early LNB. Later in infection, LNB may similarly involve the PNS or CNS but have a more indolent evolution. From a pathophysiologic perspective, there is probably little difference between early and late LNB.

IX. What is the preferred diagnostic testing strategy for Lyme neuroborreliosis?

Recommendations:

1. When assessing patients for possible Lyme neuroborreliosis involving either the peripheral or central nervous system, we recommend serum antibody testing rather than PCR or culture of cerebrospinal fluid (CSF) or serum ***(strong recommendation, moderate-quality of evidence).***
2. If CSF testing is performed in patients with suspected Lyme neuroborreliosis involving the CNS, we (a) recommend obtaining simultaneous samples of CSF and serum for determination of the CSF:serum antibody index, carried out by a laboratory using validated methodology, (b) recommend against CSF serology without measurement of the CSF:serum antibody index, and (c) recommend against PCR or culture of CSF or serum **(strong recommendation, moderate-quality of evidence).**

Summary of the evidence: Several studies have demonstrated that most patients with early Lyme neuroborreliosis are seropositive by conventional two-tiered testing at the time of initial clinical presentation [15, 119, 193-195]. Neurological manifestations typically develop several weeks after initial infection, which is usually sufficient time for the development of a detectable serum antibody response. Occasionally, patients with early Lyme neuroborreliosis are seronegative at the time of initial clinical presentation [195]. In some - but not all - of these cases, antibody reactivity is detectable using a first-tier test (EIA or IFA), but the antibody response has not yet expanded enough to meet Western blot interpretive criteria for a positive second-tier result. Such patients are often seropositive using modified

two-tiered testing protocols [23, 24, 120, 196]. Infected patients who are initially seronegative are typically strongly seropositive on repeat testing several weeks later.

Demonstration of intrathecal antibody production directed against *B. burgdorferi*, with an elevated CSF:serum antibody index, is a highly specific finding for Lyme neuroborreliosis with CNS involvement. The index, however, may remain elevated for years following successful treatment [197-199]. Diagnostic sensitivity in U.S. patients with Lyme meningitis exceeded 85% in several small studies [200, 201], but most studies have exclusively involved European patients, potentially limiting generalizability. Reported sensitivity in European cases of early Lyme neuroborreliosis ranges from 56% to 79% [202-204]. A limitation of intrathecal antibody testing is that methods are not standardized and vary among laboratories. Providers are cautioned to seek intrathecal antibody testing only at experienced laboratories using well-validated methods. Western immunoblots performed on paired serum and CSF samples, or CSF samples alone, are not recommended outside the research setting to evaluate for intrathecal antibody production [205] [145].

Direct detection of *B. burgdorferi* in cerebrospinal fluid, by PCR or culture, is usually not possible in patients with Lyme neuroborreliosis. A meta-analysis including both U.S and European studies demonstrated PCR sensitivity of 17% when applied to CSF in patients with acute Lyme neuroborreliosis, although some patients did not have meningitis [206]. In a study of U.S. patients with Lyme meningitis, PCR sensitivity was only 5% [207]. As with CSF PCR, the sensitivity of CSF culture is poor [208, 209].

Similarly, direct detection of *B. burgdorferi* in blood by PCR or culture is seldom helpful in patients with Lyme neuroborreliosis, with reported sensitivities between 1 and 28% in patients with otherwise verifiable infection [208, 210, 211]. CXCL13, a chemokine, has been proposed as a biomarker for Lyme neuroborreliosis. Elevated levels of CSF-CXCL13 in the CSF correlate well with intrathecal *B. burgdorferi*-specific antibody responses in patients with acute Lyme meningitis [212-216]. However, CSF CXCL13

concentrations may be elevated in numerous other infectious, inflammatory, and neoplastic conditions [213-220]. Studies to date have used different threshold concentrations to define significantly elevated CSF CXCL13 levels. As standardized upper limits and interpretive criteria are lacking, clinical performance characteristics are unclear. Notably, CSF CXCL13 concentration can fall rapidly with effective treatment; while this may make it a useful marker of treatment efficacy, it limits its diagnostic utility if first measured following initiation of antibiotic therapy.

Rationale for the recommendations: Serum antibody testing is the most sensitive diagnostic test in early Lyme neuroborreliosis, whereas culture or PCR tests performed on blood or CSF lack acceptable clinical sensitivity. An elevated CSF:serum antibody index can support the diagnosis of CNS Lyme neuroborreliosis, but a normal antibody index value does not exclude the diagnosis. Measurement of CXCL13 has not been sufficiently studied or standardized to recommend at present.

Research needs: Large-scale studies of U.S. patients are needed to determine the performance characteristics of CSF:serum antibody index determinations and to standardize this testing. Studies are needed to determine the predictive value of CSF CXCL13 and, if useful, to determine an appropriate threshold above which values are considered informative for clinical diagnostic purposes.

X. Under what circumstances will CSF examination alter the treatment of patients with Lyme neuroborreliosis?

CSF examination in patients with suspected neuroborreliosis can serve four purposes. First, if meningitis is suspected, it permits the exclusion of bacterial, viral or other etiologies, besides Lyme neuroborreliosis. Second, and particularly in children, if there is any reason to suspect raised intracranial pressure (ICP), it permits ICP measurement, and subsequent management if elevated. Third, it permits more definitive diagnosis of CNS neuroborreliosis, particularly when there is parenchymal brain or spinal fluid inflammation and if intrathecal antibody production is present. Fourth, if a CSF pleocytosis is evident,

it provides a metric for treatment efficacy. Since CSF pleocytosis in meningitis typically improves after appropriate treatment but takes an extended period to resolve completely, having a baseline value can be useful as a basis for comparison. Since the recommended treatment for neuroborreliosis may be the same whether meningitis is present or not, the decision to perform a CSF examination must be individualized.

XI. For which neurological presentations should patients be tested for Lyme disease?

Recommendations:

1. In patients presenting with one or more of the following acute disorders: meningitis, painful radiculoneuritis, mononeuropathy multiplex, acute cranial neuropathies (particularly VII, VIII, less commonly III, V, VI and others) and with epidemiologically plausible exposure to ticks infected with *B burgdorferi*, we recommend testing for Lyme disease ***(strong recommendation, moderate-quality evidence).***
2. In patients with typical amyotrophic lateral sclerosis, relapsing-remitting multiple sclerosis, Parkinson's disease, dementia or cognitive decline, or new-onset seizures, we recommend against routine testing for Lyme disease ***(strong recommendation, low-quality evidence****).*
3. In patients with neurological syndromes other than those listed in (1) or (2), in the absence of a history of other clinical or epidemiologic support for the diagnosis of Lyme disease, we recommend against screening for Lyme disease ***(strong recommendation, low-quality evidence)***
4. In patients presenting with nonspecific MRI white matter abnormalities confined to the brain in the absence of a history of other clinical or epidemiologic support for the diagnosis of Lyme disease, we recommend against testing for Lyme disease ***(weak recommendation, low-quality evidence).***

Summary of the evidence: Association of Lyme disease with meningitis, cranial neuritis, radiculoneuritis and other forms of mononeuropathy multiplex is well-established. Although the VIIth cranial nerve is the most common, involvement of the nerves to the extraocular muscles, the trigeminal nerve and occasionally the acousticovestibular nerve [221] occur as well.

The few systematic studies that have been performed have failed to identify consistent associations between Lyme disease and amyotrophic lateral sclerosis [222-224], multiple sclerosis [225, 226] Alzheimer's disease [227] or Parkinson's disease [222-224]. Seizures appear to be quite uncommon in Lyme neuroborreliosis. While some early studies in hyperendemic regions supported an association between ALS and serologic evidence of exposure to *B. burgdorferi* [228-230], subsequent studies have not confirmed this observation [231, 232].

Radiographic white matter changes have been described in numerous case series. The largest systematic study [233] of brain imaging in patients with confirmed Lyme neuroborreliosis found rare patients with contrast enhancing parenchymal abnormalities, but non-specific white matter abnormalities were no more common than in controls.

Rationale for recommendation: These recommendations place a high value on avoiding false positive Lyme disease test results, which can delay appropriate medical evaluations and treatment of other disorders, and lead to unnecessary antibiotic exposure and potential side effects. Screening neurologic patients with a low *a priori* likelihood of Lyme disease – i.e., without a history of tick bite, EM, or other more typical manifestations, would result in far more false positive than true positive results [234].

Lyme disease can very rarely cause focal inflammation in the brain or spinal cord (i.e., parenchymal CNS disease or encephalomyelitis), with typical inflammatory imaging characteristics that could be confused with the first episode of demyelinating disease. Testing may be informative in this setting. In contrast, small MRI-detected cerebral white matter T2 hyperintensities occur very commonly in individuals with vascular risk factors and migraineurs, becoming increasingly frequent with age. Consequently, MRI

findings of non-specific T2 white matter hyperintensities are not generally useful to diagnose Lyme neuroborreliosis. "Treating the MRI scan" could lead to misattribution of unrelated chronic symptoms to Lyme disease and overuse of antibiotics with under-emphasis on treatable vascular risk factors.

Research Needs: Rigorous epidemiologic research is needed to understand both the prevalence of Lyme disease in patients with select neurologic diseases and the prevalence of various neurologic disorders among patients with confirmed Lyme disease. Prospective studies of white matter abnormalities in patients with positive serological tests for Lyme disease, stratified by age and vascular risk factors, could delineate patterns that are particularly suggestive of Lyme disease.

XII. Should adult patients with psychiatric illnesses be tested for Lyme disease?

Recommendation:

1. In patients with psychiatric illness, we recommend against testing for Lyme disease ***(strong recommendation, low-quality evidence).***

Summary of the evidence: No studies suggest a convincing causal association between Lyme disease and any specific psychiatric conditions [235-238]. There is no controlled prospective evidence that treatment for Lyme disease is effective for any specific psychiatric disease. While studies have found evidence of exposure to tick-borne infections in some psychiatric populations, there has not been clear etiologic evidence linking the psychiatric disease to infection.

Rationale for recommendation: While Lyme disease can co-occur with psychiatric illness, as it may with any other illness, there is no systematic evidence supporting a causal relationship that would warrant routine Lyme disease screening of patients with either ongoing or newly diagnosed psychiatric illness. Given the lack of an association between Lyme disease and *specific* psychiatric disorders, testing should be limited to patients with a reasonable *a priori* likelihood of Lyme disease based on exposure and clinical compatibility of their illness. Indiscriminate testing may result in misattribution of symptoms to Lyme disease with potential delays in appropriate care and unnecessary antibiotic exposure.

XIII. Should children with developmental, behavioral or psychiatric disorders be tested for Lyme disease?

Recommendation:

1. In children presenting with developmental, behavioral or psychiatric disorders, we suggest against routinely testing for Lyme disease ***(weak recommendation, low-quality evidence).***

Summary of the evidence: There are no data to support a causal relationship between tick-borne infections and childhood developmental delay or behavioral disorders (such as attention deficit-hyperactivity disorder, autistic spectrum disorders, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), learning disabilities, or psychiatric disorders). As with many acute medical illnesses, Lyme disease could worsen behavioral or psychiatric symptoms in children who are predisposed to these. There are no data that associate Lyme disease and developmental or behavioral childhood disorders.

Because there is a low pre-test probability (prevalence) of Lyme disease in this population, broadly testing all such children will lead to a high proportion of false positive results. Misattribution of symptoms to Lyme disease may lead to delays in care and unnecessary antibiotic exposure.

Rationale for recommendation: There is no evidence to support a causal relationship between Lyme disease and developmental or behavioral disorders in children. Low probability testing is expected to produce disproportionate false positive results, potentially causing harm.

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

Recommendation:

1. In patients with Lyme disease-associated meningitis, cranial neuropathy, radiculoneuropathy or with other PNS manifestations, we recommend using parenteral ceftriaxone, cefotaxime or

penicillin, or oral doxycycline over other antimicrobials **(strong recommendation, moderate-quality evidence)**. **Comment:** Decisions about the choice of antibiotic among these, including the route of administration, should primarily be made based on individual factors unrelated to effectiveness. Treatment route may be changed from parenteral to oral during treatment. The preferred antibiotic duration is 14-21 days.

Summary of the evidence: All studies have used antimicrobials that achieve therapeutic levels against *B. burgdorferi* within the central nervous system. Treatment was effective using meningitis-dosing of penicillin, cefotaxime, ceftriaxone, or oral doxycycline, with no statistically significant differences in either response rate or relative risk of adverse effects (see Evidence Profile Tables XIV). In two studies, 14-day courses of oral doxycycline (200 mg/day), IV penicillin, and IV ceftriaxone were equally effective [239, 240]. While adverse effects were more frequent with parenteral treatment, relative risk (RR) confidence intervals were broad (RR IV vs. PO 1.29 [CI 0.83-2.01]). In most studies, 14-day courses of treatment have proved highly efficacious. While some studies have used 21 days, none directly compare the efficacy of 14 vs. 21 days in patients with nervous system infection, and none has found that courses longer than this are more effective. All listed antibiotics appear to be equally effective.

Treating LNB patients with 100 days of oral amoxicillin [241] following 3 weeks of parenteral ceftriaxone did not improve response (RR with vs. without 100 days 1.06 [CI 0.89-1.25]), but significantly increased the incidence of adverse effects (RR 3.70 [CI 1.29-10.61]) (see Evidence Profile Tables XIV). Studies comparing the efficacy of oral and parenteral regimens for acute neurological manifestations of Lyme disease have all been performed in European patients. Although the *Borrelia* strains prevalent in Europe (primarily *B. afzelii* and *B. garinii*) differ from *B. burgdorferi* sensu stricto, the strain responsible for Lyme disease in the U.S., antimicrobial sensitivities are generally identical, and antibiotic pharmacokinetics should not differ. Other than small case series [242] and unpublished observations, no

high-level studies have addressed this in U.S. patients, potentially diminishing the applicability to North American patients.

Rationale for the recommendation: Factors to consider include the apparent therapeutic equivalence of oral and IV administration, the improved convenience and lower cost with oral administration, and the risk of potentially serious adverse events associated with IV administration. In light of recent evidence demonstrating a low risk of adverse effects of doxycycline in young children and risks associated with IV catheters [36], oral doxycycline may be considered over IV treatment in children of all ages who can tolerate oral antibiotics.

The choice of initial antibiotic regimen will be heavily influenced by factors other than toxicity and efficacy. For example, oral doxycycline may be suitable for mildly ill patients who can be treated as outpatients. Patients who are more acutely ill, seen in an inpatient or emergency department setting, may tolerate oral medication less well and have IV access, making initial IV therapy preferable.

While the evidence supports the use of oral doxycycline in patients with nervous system Lyme disease, suppurative bacterial meningitis and other neuro-inflammatory disorders may have other causes that require consideration of initial empiric parenteral treatment (see guidelines for management of bacterial meningitis [243] and encephalitis [243]). Once these alternative diagnoses are excluded, or the diagnosis of Lyme neuroborreliosis is confirmed, treatment with oral doxycycline may be considered.

Research needs: A study confirming the therapeutic equivalence of oral and parenteral treatment in North American patients is needed.

XV. Should patients with Lyme disease-related parenchymal involvement of the brain or spinal cord be treated with oral or parenteral antibiotics?

Recommendation:

1. In patients with Lyme disease-associated parenchymal involvement of the brain or spinal cord, we recommend using parenteral over oral antibiotics ***(strong recommendation, moderate-quality evidence).***

Summary of the evidence: Lyme disease-related parenchymal involvement of the brain or spinal cord, evident by MRI imaging or focal findings on neurologic examination, is exceedingly rare. Treatment in this population has never been systematically studied. Incidence seems even less today than it was 30 years ago when this aspect of Lyme disease was first described. No studies have compared different durations of treatment. Typically, 2 to 4-week courses have been used successfully in these patients.

Rationale for recommendation: By analogy to most other parenchymal CNS bacterial infections, including neurosyphilis, parenteral antibiotics with good CNS penetration are recommended. Given the rarity of this disorder, it is unlikely the question will be amenable to systematic study.

Research Needs: Further study is unlikely to be feasible.

XVI. Should patients with Lyme disease and facial nerve palsy receive corticosteroids in addition to antimicrobial therapy?

Recommendation:

1. In patients with Lyme disease-associated facial nerve palsy, we make no recommendation on the use of corticosteroids in addition to antibiotics ***(no recommendation; knowledge gap)***. **Comment:** In patients age 16 or older presenting with acute facial nerve palsy but without other objective clinical or serologic evidence of Lyme disease, corticosteroid treatment should be administered within 72 hours in accordance with current facial nerve palsy guideline recommendations.

Summary of the evidence: Facial nerve palsies, both idiopathic and in association with Lyme disease, are thought to occur due to swelling of the facial nerve in its narrow bony canal, resulting in compression, demyelination and potentially nerve ischemia, a mechanism that could be partially mitigated by corticosteroids. The data in idiopathic facial nerve palsy strongly support corticosteroid use [197, 244].

While some studies in Lyme disease associated facial nerve palsy suggest benefit, others raise the possibility of harm [245]; this body of research is small and methodologically limited [198, 199, 246]. Although theoretical concerns about the potential immunosuppressive effects of corticosteroids in infections are quite understandable, no high-level studies address this question in Lyme neuroborreliosis. Given that the diagnosis of Lyme neuroborreliosis is often not obvious at the time of presentation with a facial nerve palsy and given that corticosteroids are most effective in idiopathic facial nerve palsy if given within the first 72 hours after onset, steroids should be instituted immediately in patients in whom the diagnosis of Lyme disease is not immediately evident. When the diagnosis of Lyme disease becomes apparent the decision regarding stopping corticosteroids that have already been started or starting them in a patient initially presenting with acute Lyme disease associated facial palsy, is a matter of patient preference and clinical judgment.

Research needs: A controlled, randomized prospective trial of antibiotics with and without corticosteroids in Lyme-associated facial palsy is needed in adult and pediatric patients.

XVII. Should patients with Lyme disease and papilledema be treated with techniques to reduce intracranial pressure?

As in any situation with potentially elevated intracranial pressure, the risk of herniation must be weighed against the value of the information to be gained by lumbar puncture. Since herniation has never been reported in Lyme neuroborreliosis, the risk in these circumstances is presumably related to other diagnoses under consideration. Raised intracranial pressure and papilledema should be treated regardless of etiology. Lyme neuroborreliosis has been associated with raised intracranial pressure, which can compromise vision. All but two of the reported cases have been in children [247, 248]. Although data in Lyme disease are only anecdotal, as in all other circumstances, raised ICP with papilledema should be treated with techniques to lower ICP to prevent visual loss.

Lyme carditis

Lyme carditis is a manifestation of early disseminated infection with *B. burgdorferi* and typically occurs within several days to seven months (average 21 days) after the initial illness/infection, most often in the summer and fall [249]. Initial studies suggested that 4-10% of untreated patients developed carditis [250, 251], though more recent data indicate that this number may be significantly lower [252, 253]. Epidemiologic studies suggest that only about 40% of patients recall the characteristic erythema migrans lesion[252]. Peak incidence is seen in childhood and middle age [252], most typically in young adult and middle-aged men [252, 253]. It is not known if the male predominance is the result of greater exposure or specific pleiotropism [253]. While *B. burgdorferi* infection can affect all parts of the heart, it most typically presents as atrioventricular nodal block, often with rapidly fluctuating complete heart block [147, 250, 254, 255]. Atrial and ventricular arrhythmias may be seen and there may be involvement of the sinus node and distal conduction system [256-259]. *B. burgdorferi* infection may also present as pericarditis and acute myocarditis with associated ventricular dysfunction [260]. The role of *B. burgdorferi* infection in chronic cardiomyopathy is less certain [261-263]. Although recovery from Lyme carditis with supportive care and antibiotic treatment is the norm, deaths have been reported [252].

XVIII. Should all patients with early Lyme disease receive an electrocardiogram to screen for Lyme carditis?

Recommendation:

1. We suggest performing an ECG only in patients with signs or symptoms consistent with Lyme carditis ***(weak recommendation, low-quality evidence)***. **Comment:** Symptoms of cardiac involvement in Lyme disease include dyspnea, edema, palpitations, lightheadedness, chest pain, and syncope.

Summary of the evidence: Numerous studies have demonstrated that patients with early Lyme disease have a relatively high prevalence of nonspecific ECG changes [250, 254, 264-267]. Clinically significant

findings, however, are uncommon in patients who lack signs or symptoms of carditis. Patients with other early manifestations of Lyme disease should be asked specifically if they have experienced symptoms compatible with cardiac involvement.

Rationale for recommendation: In the absence of symptoms suggesting Lyme carditis, severe ECG abnormalities are uncommon and minor/nonspecific abnormalities are relatively common. Obtaining ECGs on all patients with Lyme disease, therefore, may result in more harm than benefit.

XIX. Which patients with Lyme carditis require hospitalization?

Recommendation:

1. In patients with significant PR prolongation, other arrhythmias, or clinical manifestations of myopericarditis, such as symptoms of left ventricular dysfunction, we recommend hospital admission with continuous ECG monitoring ***(strong recommendation, very low-quality evidence).***

   Comment: Clinical manifestations of Lyme carditis include exercise intolerance, lightheadedness, palpitations, syncope, pericarditic pain, evidence of pericardial effusion or elevated biomarkers (such as troponin), while symptoms of left ventricular dysfunction may include edema, or shortness of breath.

Summary of the evidence: Lyme carditis has been associated with death, often sudden, as the result of heart block, tachyarrhythmias or myocardial failure. No study has systematically compared inpatient to outpatient management. Several case series report that a PR interval longer than 300 milliseconds is associated with an increased risk of sudden higher grade heart block requiring pacing [147, 255, 257]. Thus, a PR interval of 300 milliseconds or greater is generally regarded as a reason for admission in a patient with a presentation consistent with Lyme disease. The need for intensive ECG and vital sign monitoring and supportive care in the setting of heart failure and other arrhythmias [250, 264] is also an indication for admission.

Rationale for recommendation: We recommend hospitalization in these settings despite the very low-quality evidence because of the potential for life-threatening arrhythmias, bradycardia, heart failure and death.

Research Needs: Research is needed to more clearly define the risk factors for the development of the life-threatening cardiac manifestations of Lyme disease.

XX. What pacing modality should be used for the management of Lyme carditis?

Recommendation:

1. For patients with symptomatic bradycardia due to Lyme carditis that cannot be managed medically, we recommend temporary pacing modalities over routinely implanting a permanent pacemaker ***(strong recommendation, moderate-quality evidence).***

Summary of the evidence: Temporary pacing may be lifesaving in patients with Lyme disease associated heart block. Virtually all patients recover over a period of 3-7 days, however, and therefore permanent pacemakers are not routinely needed [146, 147, 255, 264, 268]. This recommendation is consistent with the 2012 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Rhythm Society (HRS) focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm disorders in which the potential harms of permanent pacemakers are to be avoided in patients in whom recovery is expected [269]. The ability to reliably temporarily pace patients for the period necessary to permit recovery may be enhanced by using externalized screw-in pacing leads.

Rationale for recommendation: Although temporary and permanent pacing have similar immediate benefits, we recommend temporary pacemakers to avoid unnecessary harms from permanent pacemakers.

XXI. What are the preferred antibiotics regimens for the treatment of Lyme carditis?

Recommendations:

1. In outpatients with Lyme carditis, we suggest oral antibiotics over IV antibiotics **(*weak recommendation, very low-quality evidence).***
2. In the hospitalized patient with Lyme carditis, we suggest initially using IV ceftriaxone over oral antibiotics until there is evidence of clinical improvement, then switching to oral antibiotics to complete treatment ***(weak recommendation, very low-quality evidence).***
3. For the treatment of Lyme carditis, we suggest 14 to 21 days of total antibiotic therapy over longer durations of treatment. (***weak recommendation, very low-quality evidence)***. **Comment:** Oral antibiotic choices for Lyme carditis are similar to other non-neurologic manifestations of Lyme disease: doxycycline, amoxicillin, cefuroxime axetil, and azithromycin.

Summary of the evidence: Antibiotic treatment options, including drug choice, route, and duration, have not been subjected to a high-quality trial for patients specifically with Lyme carditis. Our recommendation is based on heterogeneous studies that include small numbers of carditis patients [172, 241], as well as observational data [270]. One randomized controlled trial [172] compared oral doxycycline to IV ceftriaxone in patients with acute disseminated *B. burgdorferi* infection without meningitis. Of the patients in the trial, 6.5% presented with carditis. This study showed similar efficacy for both antibiotic therapies, but significantly more gastrointestinal adverse events with IV ceftriaxone (see Evidence Profile Table XXI). Numerous case descriptions further report rapid and permanent resolution of arrhythmias upon initiation of antibiotics, which suggests that carditis can be treated similarly to other disease manifestations. Cumulative clinical experience is greatest with doxycycline, and there have been no comparative data evaluating whether other oral antibiotics have similar efficacy in the treatment of Lyme carditis.

Rationale for recommendation: Antibiotic treatment is indicated for both the resolution of Lyme carditis and to prevent further progression of infection in other tissues. As it is recommended that patients with, or at risk for severe cardiac complications of Lyme disease be hospitalized, initial IV antibiotic treatment

is reasonable at this time. However, there is greater potential toxicity associated with IV therapy, particularly with prolonged courses, and IV antibiotics have not been shown to be superior to oral antibiotics in the treatment of Lyme carditis. Thus, patients initially treated with IV antibiotics should be converted to oral therapy to complete their treatment course once they begin to improve.

XXII. Should patients being evaluated for acute myocarditis/pericarditis or chronic cardiomyopathy of unknown cause be tested for Lyme disease?

Recommendation:

1. In patients with acute myocarditis/pericarditis of unknown cause in an appropriate epidemiologic setting, we recommend testing for Lyme disease ***(strong recommendation, low-quality evidence).***
2. In patients with chronic cardiomyopathy of unknown cause, we suggest against routine testing for Lyme disease (***weak recommendation, low-quality evidence).***

Summary of evidence: There are reports of patients with a clinical scenario consistent with acute Lyme disease, positive Lyme serologies, and acute myocardial dysfunction or pericarditis who have improved after appropriate antibiotic therapy [260, 263]. However, we recognize that *B. burgdorferi* infection is an unusual cause of acute myocarditis/pericarditis and other etiologies should be sought as well.

In studies from the United States and the United Kingdom an inconsistent or absent response to specific antibiotic therapy has been demonstrated among patients with chronic dilated cardiomyopathy and objective evidence of *B. burgdorferi* infections [271, 272]. In contrast, there is some suggestion that in eastern Europe similar patients may have a higher prevalence of positive Lyme serologies than controls [273] and may respond to specific treatment for Lyme disease [262]. Because attribution of chronic cardiomyopathy is uncertain and antibiotic therapy is not known to be helpful in the United States, testing such patients for Lyme disease is unlikely to be of clinical benefit.

Rationale for recommendation: In geographic regions where there is a high prevalence of Lyme disease, testing patients with acute myocarditis/pericarditis of unknown cause in the appropriate clinical setting (rash, recent onset of symptoms of myocarditis/ventricular dysfunction, tick bite, etc.) is recommended. Although the quality of evidence supporting such testing is low, appropriate antibiotic treatment may be lifesaving. By contrast, demonstrating seropositivity to Lyme disease is of unlikely benefit in patients with chronic cardiomyopathy, and may result in unnecessary antibiotic exposure without expectation of improvement.

Research Needs: Randomized controlled trials are needed to determine the optimal route, drug, and duration of antibiotic therapy for Lyme carditis, particularly with respect to the rate of resolution of clinical disease and long-term outcomes. It remains unknown whether and which patients with Lyme carditis might benefit from the anti-inflammatory effects of aspirin or corticosteroid therapy. It is also uncertain whether nonspecific inflammatory biomarkers, such as the erythrocyte sedimentation rate and C reactive protein, are useful point-of-care diagnostic tests to aid in decisions to defer permanent pacing or initiate antibiotic treatment in patients whose serologic testing is not yet available.

Lyme arthritis

While historically arthritis was reported to occur in 60% of patients with untreated erythema migrans [101], surveillance data over the past 15 years document a much lower annual incidence of only 30%. Recognition and treatment of the infection in its earliest stages may explain this decline. The percentage of Lyme disease patients with arthritis may be even lower as joint pain (arthralgia) may erroneously be equated with joint inflammation (arthritis).

Lyme arthritis typically presents with marked swelling of one or a few large joints, most often the knee, with less pain than expected based on the degree of swelling [274]. In young children Lyme arthritis may mimic septic arthritis, with fever and a painful swollen joint, especially with hip involvement,

necessitating evaluation for a possible alternative bacterial joint infection [275]. Untreated Lyme arthritis can be intermittent, with spontaneous resolution of joint inflammation after a few weeks or months. Adult patients most often report minimal if any symptoms of a tick-borne infection in the months preceding the onset of Lyme arthritis. Knee swelling may create a popliteal cyst which can rupture and cause a pseudo-thrombophlebitis of the calf. Overall, fewer than 5 joints are typically affected in untreated Lyme arthritis and most often only a single joint is involved. Small joint involvement of the hands and feet is very unusual and should prompt consideration of other diagnoses.

In Lyme endemic areas, such as New England, the Mid-Atlantic states, and the upper Midwest, there is a greater likelihood that acute infectious monoarthritis is the result of Lyme disease rather than septic arthritis. Predictors of Lyme arthritis include history of tick bite, isolated knee involvement, and lack of fever. Predictors for septic arthritis include a peripheral blood absolute neutrophil count greater than 10,000, sedimentation rate of greater than 40, hip involvement, and pain with short arc motion [275, 276]. There is considerable overlap between Lyme arthritis and septic arthritis in children in the following instances: presence of fever, elevated acute phase reactants, and the inability to bear weight (especially when the hip is involved). Previously published Kocher criteria distinguished septic arthritis from transient synovitis of the hip, but should not be employed in distinguishing septic arthritis from Lyme arthritis [277]. When there is any doubt, joint fluid should be obtained for culture for routine causes of septic arthritis.

XXIII. What is the preferred diagnostic testing strategy for Lyme arthritis?

Recommendations:

1. When assessing for possible Lyme arthritis, we recommend serum antibody testing over PCR or culture of blood or synovial fluid/tissue ***(strong recommendation, moderate quality of evidence).***
2. In seropositive patients for whom the diagnosis of Lyme arthritis is being considered but treatment decisions require more definitive information, we recommend PCR applied to synovial

fluid or tissue rather than Borrelia culture of those samples ***(strong recommendation, moderate quality of evidence).***

Summary of the evidence: Lyme serology, particularly IgG seroreactivity, is invariably positive in people presenting with Lyme arthritis but results are not available in the acute setting. The decision to perform arthrocentesis is therefore dependent on clinical judgment. The majority of patients with septic arthritis are febrile and have monoarthritis, but fever may also accompany acute Lyme arthritis, especially in children. If synovial fluid analysis is performed, the majority of patients with septic arthritis have at least 70,000 WBCs, with a mean of 128,000 cells, while the mean cell count in Lyme arthritis ranges from ~46,000 – 60,000 [278-280] in children and tends to be lower in adults [117]; however, there are occasional instances of Lyme arthritis synovial fluid having greater than 100,000 WBCs [279]. Both septic and Lyme arthritis synovial fluids have neutrophil predominance [117, 278-280]. In adults, concomitant crystal-associated arthropathy could alter the presentation of Lyme arthritis, particularly when the afflicted joint is painful. In this situation, arthrocentesis may be informative as both conditions should be treated.

Numerous studies and meta-analyses have demonstrated that the sensitivity of serum antibody testing in the diagnosis of Lyme arthritis, using conventional two-tiered testing with Western immunoblotting, is very high—in the range of 95-100% [15, 118, 119, 193, 281]. Notably, seropositive patients with Lyme arthritis almost uniformly have an expanded IgG response, with at least 5 of 10 specific bands on *B. burgdorferi* IgG immunoblots using standardized scoring criteria [15, 281]. The diagnosis of Lyme arthritis should be questioned in patients with only IgM seroreactivity but not IgG seroreactivity, or in those with only limited IgG seroreactivity (<5 of 10 IgG immunoblot bands).

Modified two-tiered testing algorithms, which make use of two different enzyme immunoassays either sequentially or concurrently, provide similarly high sensitivity compared with conventional two-

tiered testing with immunoblotting [14, 23, 24, 120, 282]. A limitation of this approach for the diagnosis of Lyme arthritis or other late manifestations of Lyme borreliosis, is that many enzyme immunoassays are polyvalent tests, meaning that they detect multiple immunoglobulin isotypes, and do not separately detect IgM and IgG. When polyvalent enzyme immunoassays are used in modified two-tiered testing algorithms, one cannot determine whether reactivity in the assays is due to IgM or IgG, or both. Furthermore, one cannot determine whether an IgG response is expanded or limited, even if enzyme immunoassays capable of separately detecting IgM and IgG immunoassays are used.

In patients with Lyme arthritis, direct detection methods applied to blood or blood components have a low yield. One European study demonstrated that *Borrelia* culture of plasma in patients with Lyme arthritis had a sensitivity of 7.7% sensitive [210]. Authors of a U.S. study including 11 patients with Lyme arthritis reported that 5 (45%) were positive using a PCR assay applied to serum samples [283].

Several investigations have demonstrated moderate to high diagnostic accuracy with the use of *B. burgdorferi* PCR assays applied to synovial fluid or synovial tissue collected from patients with Lyme arthritis prior to administration of antimicrobial therapy. Reported sensitivity ranges from 71-100% [137, 281, 283-287]. In contrast to *B. burgdorferi* PCR, other direct detection methods applied to synovial fluid or synovial tissue are poorly sensitive. In a study directly comparing synovial fluid PCR with synovial fluid culture in patients with untreated Lyme arthritis, sensitivity was 86% with synovial fluid PCR, and 0% with synovial fluid culture [288]. Another study documented 0% sensitivity using culture of synovial tissue, synovial fluid and cartilage [289]. When various *B. burgdorferi* PCR assays were applied to culture-negative synovial fluid samples from 18 patients with Lyme arthritis, some PCR primer sets yielded positive results in all samples (100%) [285]. An evaluation of direct microscopic examination of synovial tissue in untreated patients with Lyme arthritis demonstrated that spirochetes could be visualized in only 2 of 17 cases (12%) [290].

Antibody testing applied to synovial fluid is not a clinically validated method and may lead to misdiagnosis of Lyme arthritis [291].

Rationale for the recommendations: The clinical manifestations of Lyme arthritis overlap with several other diseases. Thus, laboratory confirmation of *B. burgdorferi* infection is indicated when Lyme arthritis is suspected. The test of choice is serum antibody testing using a two-tier approach with serum Lyme screening ELISA with reflex to immunoblot, as this approach has consistently yielded high sensitivity in studies of patients with Lyme arthritis and is also highly specific for *B. burgdorferi* infection. The main disadvantage of this approach is that seroreactivity after successfully treated Lyme borreliosis may persist for years [27], complicating test interpretation in patients with known previous exposure and/or in patients from highly endemic areas where background seroprevalence is substantial. In such patients, after seroreactivity has been demonstrated, synovial fluid or synovial tissue *B. burgdorferi* PCR may improve diagnostic specificity. The latter approach is not indicated as a stand-alone diagnostic strategy, as sensitivity is inferior compared with serum antibody testing. Interpretation of the results of synovial fluid or tissue PCR can be complicated since PCR may remain positive for weeks or months after antimicrobial therapy, and therefore positive results do not necessarily equate with active infection [137, 284, 287, 292]. Other direct detection methods (culture or microscopic examination of synovial tissue or fluid, or blood PCR or culture), cannot be recommended because diagnostic accuracy is lower compared with the recommended tests. Antibody testing performed on synovial fluid samples is also not recommended, as it can produce false-positive results [291].

Research needs: Assays are needed that can differentiate active from past infection with greater reliability. Ideally, such assays would be performed on readily available fluid samples, like blood, rather than sample types requiring more invasive collection procedures, such as synovial fluid or tissue.

XXIV. What are the preferred antibiotic regimens for the initial treatment of Lyme arthritis?

Recommendation:

1. For patients with Lyme arthritis, we recommend using oral antibiotic therapy for 28 days ***(strong recommendation, moderate-quality evidence)***

Summary of Evidence: Early randomized controlled studies established that parenteral antibiotics were effective in treating Lyme arthritis when compared to placebo [293, 294]. Two studies showed the superiority of IV cephalosporins over IV penicillin in leading to improvement and resolution of arthritis [295, 296]. Subsequent studies demonstrated the efficacy of oral therapy for Lyme arthritis. One randomized controlled trial (RCT) [297] reported resolution of arthritis within 1-3 months in approximately 90% of participants (adults and children) treated with a 30-day course of either oral doxycycline (100 mg orally twice daily) or amoxicillin plus probenecid (500 mg orally every 6 hours). In this report, no statistically significant difference in the development of neuroborreliosis was noted between groups. Note that the dosing regimen for doxycycline differs from that studied for neuroborreliosis (200 mg orally once daily). Although not statistically significant, a trend toward more allergic reactions and more gastrointestinal adverse events occurred in the amoxicillin group (see Evidence Profile Tables XXIV). No studies directly assess the efficacy of cefuroxime axetil versus other oral antibiotics or placebo in the treatment of Lyme arthritis. Evidence is inferred from studies of its efficacy in the treatment of early manifestations of Lyme disease and in the prevention of late disease.

Rationale for recommendation: Oral antibiotics are easier to administer than IV antibiotics, are associated with fewer serious complications and are less expensive. Because of comparable efficacy, other factors should be considered in the selection of a particular antibiotic for the treatment of Lyme arthritis and these factors are discussed elsewhere. Oral antibiotic regimens indicated for the treatment of Lyme arthritis are doxycycline, amoxicillin or cefuroxime axetil for 28 days. Rarely patients treated with oral antibiotics for Lyme arthritis have subsequently manifested clinical evidence of neurologic disease [297].

This may be related to the dosing regimen and choice of antibiotics. Recommendations for treatment of neurologic complications in patients presenting with Lyme arthritis can be found in the Neurologic Lyme disease section.

Research Needs: Studies evaluating a shorter course of antibiotic therapy appear warranted for treatment of Lyme arthritis in the United States. Prospective studies that compare the response of Lyme arthritis treated initially with oral antibiotics only versus oral antibiotics in combination with non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular steroids are lacking. Such studies should assess the rate of arthritis resolution as well as recurrence of arthritis or other manifestations of Lyme disease.

XXV. What are the approaches to patients in whom Lyme arthritis has not completely resolved?

Recommendations:

1. In patients with Lyme arthritis with partial response (mild residual joint swelling) after a first course of oral antibiotic, we make no recommendation for a second course of antibiotic versus observation ***(no recommendation, knowledge gap*****). Comment:** Consideration should be given to medication compliance, duration of arthritis prior to initial treatment, degree of synovial proliferation versus joint swelling, patient preferences, and cost. A second course of oral antibiotics for up to 1 month may be a reasonable alternative for patients in whom synovial proliferation is modest compared to joint swelling and for those who prefer repeating a course of oral antibiotics before considering IV therapy.
2. In patients with Lyme arthritis with no or minimal response (moderate to severe joint swelling with minimal reduction of the joint effusion) to an initial course of oral antibiotic, we suggest a 2 to 4-week course of IV ceftriaxone over a second course of oral antibiotics ***(weak recommendation, low-quality evidence).***

Summary of the evidence: The rate of resolution of Lyme arthritis after an initial course of oral antibiotics can vary, with 90% of patients responding within 1-3 months [297]. In patients who exhibit an initial partial response during the treatment period, joint swelling may take weeks to resolve completely. A minority may resolve completely but have a relapse of arthritis months later. Others may have minimal to no response of the joint inflammation to the initial course of oral therapy or may develop inflammation in another joint during a course of therapy.

Patients who are treated with IV ceftriaxone for Lyme arthritis have the resolution of all signs and symptoms in 59-83% of cases, although complete resolution may take many months to over a year. The resolution rate after treatment with a third-generation cephalosporin is higher than that with IV penicillin. The rate of resolution with 14- and 28-day courses of IV ceftriaxone overlap, however, as do adverse event and discontinuation rates [298]. Data regarding effectiveness of IV ceftriaxone courses longer than 28 days are not available.

Studies of IV antibiotics for Lyme arthritis include patients who have previously received oral antibiotics and those who have not received an initial course of oral antibiotics [297, 299, 300]. Third-generation cephalosporins tend to have a lower failure rate at 6 and 12-month follow-ups, although no high-quality trials directly compare IV ceftriaxone with oral doxycycline or IV penicillin in patients who continue to have symptoms of arthritis after completing a course of oral antibiotics.

In one study [137] *B. burgdorferi* spirochetes were moribund or dead in joint fluid even before antibiotic treatment, yet spirochetal DNA apparently persisted after live spirochetes were no longer present. Animal studies demonstrate that *B. burgdorferi* has a predilection for connective tissue, including relatively avascular areas such as tendons and ligaments [301], and an ultrasound study revealed hamstring tenosynovitis in Lyme arthritis patients [302]. It is possible that spirochetes might be present

in joint tissues, such as tendons, without spirochetal DNA being found in joint fluid. Slow resolution of arthritis may be due to spirochete DNA or other remnants of the pathogen that remain within the joint.

Rationale for recommendations: Resolution rates of Lyme arthritis with ceftriaxone tend to be higher than with oral therapy or IV penicillin, therefore this is recommended for patients who continue to have arthritis after a course of oral antibiotics. If spirochetes are present in relatively avascular periarticular tissues such as tendons, it is possible that oral therapy may not have provided sufficient drug levels and tissue penetration for eradication of the organism. For this reason, one course of IV therapy is suggested in a patient with persistent Lyme arthritis who has previously been treated with oral antibiotics. We suggest a 2-week course of IV ceftriaxone that can be extended to 4 weeks if resolution is not complete.

Research needs: Studies are needed to compare treatment with 1) NSAIDs only versus a second course of oral antibiotics in patients with mild residual arthritis after the completion of a first course of oral therapy; and 2) a second course of oral therapy versus IV antibiotic therapy in patients with synovitis who do not respond to a 28-day course of oral antibiotic therapy.

Signs and symptoms of synovitis may persist after a course of antibiotics due to failed eradication of the infection, persistent inflammation despite clearance of the infection, or development of post-infectious-inflammatory arthritis. Reliable tests to distinguish among these causes of persistent arthritis are needed in order to be able to treat patients appropriately with either additional antibiotics or anti-inflammatory medications used for non-infectious forms of inflammatory arthritis.

XXVI. How should post-antibiotic (previously termed antibiotic-refractory) Lyme arthritis be treated?

Recommendation:

1. In patients who have failed one course of oral antibiotics and one course of IV antibiotics, we suggest a referral to a rheumatologist or other trained specialist for consideration of the use of

disease modifying anti-rheumatic drugs (DMARDS), biologic agents, intra-articular steroids, or arthroscopic synovectomy ***(weak recommendation, very low-quality evidence).*** **Comment:** Antibiotic therapy for longer than 8 weeks is not expected to provide additional benefit to patients with persistent arthritis

Summary of Evidence: Most patients with Lyme arthritis respond to antibiotic therapy, although up to 23% may develop persistent synovitis that no longer responds to antibiotic therapy. This form of persistent joint inflammation was previously called "antibiotic-refractory" Lyme arthritis and is now referred to as "post-antibiotic Lyme arthritis" to avoid confusion with antibiotic-resistance. A variety of approaches has been used to treat patients who develop post-antibiotic Lyme arthritis. These include NSAIDs, intraarticular corticosteroids, DMARDs, biologic response modifiers, and synovectomy. Each of these modalities has been associated with successful outcomes.

Specific Studies: In a prospective cohort study [303], 20 patients with post-antibiotic Lyme arthritis were treated with synovectomy. The median duration of arthritis prior to synovectomy was 38 months (range 5-84). 65% (13 of 20) of patients had complete resolution of joint inflammation within 1 month after synovectomy and had a normal joint exam or only minimal decrease in joint range of motion 2-3 years later. 15% (3 of 20) had reduction in inflammation but remained functionally disabled due to muscle atrophy or meniscal or ligament tears. 20% (4 of 20) experienced persistent or recurrent synovitis despite synovectomy. None of the 20 patients subsequently experienced extra-articular manifestations of Lyme disease.

In a retrospective cohort study [299], 62 patients who developed post-antibiotic Lyme arthritis were treated initially with NSAIDS, with or without intraarticular corticosteroids, with the majority responding to this intervention. 72.6% of the patients who failed this therapy resolved arthritis after synovectomy or DMARDs alone or synovectomy followed by DMARDs. Overall, only 3.2% (2 of 62) of the

post-antibiotic Lyme arthritis patients experienced total treatment failure. A similar rate of arthritis resolution was seen in a prospective cohort study [303] of 20 patients with post-antibiotic Lyme arthritis who were treated with synovectomy.

Eight of 32 adult patients (25%) seen at a Lyme arthritis referral clinic who did not respond to oral antibiotics had resolution of arthritis within 1 month of completing IV antibiotic therapy [304]. The remaining 24 patients (75%) had persistent proliferative synovitis despite treatment with oral and IV antibiotics. 23 of the 24 patients (96%) were subsequently treated with DMARDs, including hydroxychloroquine, methotrexate, or TNF inhibitor, and they had marked improvement within months.

In an earlier 10-20-year follow-up study [305], 10 of 42 adult patients with previous Lyme arthritis had findings suggestive of degenerative arthritis in previously affected knees compared with none of 42 patients with previous Lyme disease without Lyme arthritis (P=0.001). As quadriceps atrophy can occur with Lyme arthritis, physical therapy is an important adjunct to antibiotic treatment.

Systemic autoimmune diseases that affect joints, such as rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis, for which antibiotics are of no benefit, have been reported after an episode of Lyme disease, particularly early Lyme disease [304]. These patients typically have polyarthritis, including small joint disease, are male, have high body mass index, have a family history of autoimmunity, and have less IgG reactivity on immunoblot testing compared to patients with Lyme arthritis.

Children

Twenty-three of 99 children (23.2%) seen in a pediatric rheumatology referral center had ongoing evidence of synovitis 3 months after the completion of oral antibiotic therapy (N=8) or IV antibiotic therapy (N=4) or both (N=11) [306]. These children usually achieved remission with NSAIDs or intra-articular corticosteroids. However, 3 children were treated with methotrexate and hydroxychloroquine

or sulfasalazine. All were in complete remission at follow-up one year later. Children may be more likely than adults to regain normal function within 4 weeks after the initiation of antibiotic therapy.

In a retrospective analysis, 29% of children with Lyme arthritis had persistent synovitis requiring second-line therapy [307]. Of these 112 children, 18 received intra-articular (IA) steroids with or without a second round of antibiotics. 17% of the children receiving IA steroids developed post-antibiotic Lyme arthritis, compared to 44% receiving a second course of antibiotics alone (P=0.04). Recovery times were shorter in the steroid treated group [307].

Rationale for recommendation: Patients with persistent joint inflammation after oral and IV antibiotic therapy for Lyme disease exhibit immune-mediated proliferative synovitis that can lead to significant joint damage and dysfunction. Persistent infection has not been documented in this subgroup of patients, who are considered to have post-antibiotic Lyme arthritis (previously termed antibiotic-refractory Lyme arthritis). PCR testing for *B. burgdorferi* DNA in joint fluid has limited utility in determining whether Lyme arthritis patients have persistent infection after they have received at least one course of oral and one course of IV antibiotics. Some patients may respond to NSAIDs alone or in combination with intra-articular steroids; DMARDs (including hydroxychloroquine, methotrexate, and TNF inhibitors) can be considered [299, 305, 306]. Recrudescent Lyme disease has not been demonstrated in patients administered DMARDs, including TNF inhibitors. In responding patients, DMARDs can usually be discontinued after 6-12 months. In patients with incomplete responses to DMARDs, arthroscopic synovectomy is an option, but debridement of synovial tissue down to the cartilage interface is necessary for a successful result [302]. Consultation with a rheumatologist is recommended or other trained specialists to ensure that there is no other potential explanation for joint swelling or synovial proliferation (e.g. underlying osteoarthritis) and that other non-pharmacologic modalities are used such as physical therapy to improve outcomes, especially if atrophy of the quadriceps has developed.

Research Needs: Studies are needed comparing DMARD therapy with NSAIDs or further antibiotic therapy for proliferative synovitis that persists after oral and IV antibiotic therapy for Lyme arthritis.

In addition, the development of predictive biomarkers would permit studies comparing antibiotics alone with simultaneous antibiotic and DMARD therapy for those at risk for developing post-antibiotic persistent synovitis.

Prolonged symptoms following treatment of Lyme disease

The prevalence of persistent symptoms following standard treatment of Lyme disease is a matter of uncertainty, and estimates depend in large part on the patient population and methods of long-term assessment. Some longitudinal studies of patients appropriately diagnosed with and treated for Lyme disease describe either persisting or recurrent fatigue, musculoskeletal pain, neurocognitive and other non-specific subjective symptoms in 10-20% or more 1 year after treatment [308, 309]. Although these symptoms appear to subside over time [310-312], while present they can be quite disabling. Importantly, prospective controlled trials, in which healthy controls were identified at the same time that patients with Lyme disease were treated and both groups were then followed over the ensuing months or years, have found that the frequency of this symptom complex is the same in controls as in treated patients [151, 313-316], raising the possibility that this phenomenon, in whole or in part, represents anchoring bias, in which commonly occurring non-specific symptoms are inaccurately linked to a prior diagnosis of Lyme disease.

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

Recommendation:

1. For patients who have persistent or recurring non-specific symptoms such as fatigue, pain, or cognitive impairment following treatment for appropriately diagnosed Lyme disease, but who lack

objective evidence of reinfection or treatment failure, we recommend against additional antibiotic therapy (**Strong recommendation, moderate-quality evidence**).

Comment: Evidence of persistent infection or treatment failure would include objective signs of disease activity, such as arthritis, meningitis, or neuropathy.

Summary of the Evidence: Several clinical trials have investigated antibiotic re-treatment of patients with disabling symptoms that had persisted-months after standard treatment for documented Lyme disease (see Evidence Profile Tables XXVII).

Klempner et al randomized 78 seropositive and 51 seronegative subjects with well-documented, previously treated Lyme disease but persistent musculoskeletal pain, neurocognitive symptoms, or dysesthesias, often associated with fatigue, to receive 30 days of IV ceftriaxone followed by 60 days of oral doxycycline; these treatments were compared to IV placebo followed by oral placebo [317, 318]. At 30, 60, and 180 days there was no difference between the treatment and placebo arms as assessed by symptom severity and neurocognitive measures. Krupp et al randomized 54 subjects to 28 days of IV ceftriaxone vs IV placebo, assessing a variety of outcome measures including fatigue, pain, and cognitive function [319]. At 6-month follow up there was an improved fatigue score compared with baseline in the treatment arm, though no improvement in the other domains tested; the fatigue scores and their interpretability are limited by methodological and statistical considerations [320]. Fallon et al studied a longer duration of therapy, administering 10 weeks of IV ceftriaxone to 23 subjects and IV placebo to 14 control subjects [321]. A cognitive index score at week 24 did not differ between treatment and control groups. A secondary outcome measure improved at week 12, and was sustained to week 24 for pain and physical functioning, but not fatigue, the opposite of the findings in the Krupp study. In both the Krupp and Fallon studies, fatigue improved over baseline among placebo-treated patients (9.1% and 14.5%, respectively). Finally, Berende et al randomized 281 patients (89% of whom had previously received

antibiotic treatment for the diagnosis of Lyme disease) to receive 14 days of IV ceftriaxone, followed by 12 weeks of either doxycycline, clarithromycin plus hydroxychloroquine, or placebo [322]. At the final observation point, 52 weeks following initiation of therapy, health-related quality of life scores did not differ significantly among the 3 groups.

In all studies, subjects improved – but the improvement was also experienced by placebo-treated subjects. Numerous adverse events were reported in all studies, including complications attributed to the antibiotic. One serious antibiotic allergic reaction in occurred in both the Fallon (37 subjects total) and Krupp (55 subjects total) studies. Three patients in the Fallon study had IV line complications, as did 3 in the Krupp study. One patient in the Fallon study required cholecystectomy for ceftriaxone-associated gallbladder pseudolithiasis. In the Krupp study 43% of the patients receiving ceftriaxone reported diarrhea. Despite these studies many patients receive prolonged IV antibiotic therapy for these symptoms – a practice that has been associated with a number of documented deaths [323, 324].

Thus, our current body of clinical literature does not support the hypothesis that persistent symptoms should be interpreted as clinical infection, or that antibiotic re-treatment is safe and effective. A body of literature conducted in animal models has raised hypotheses of microbiologic persistence. However, these studies are methodologically highly heterogeneous, and thus of limited generalizability to natural human infection [320]. Moreover, animal models cannot reproduce the human experiences of fatigue and pain, and it is unlikely that any animal study can give reliable insight into the biology of humans experiencing such symptoms following treatment of Lyme disease.

Rationale for Recommendation: This recommendation places a high value on avoiding harm due to unnecessary antibiotic exposure or to unnecessary IV access devices. The risks of these interventions were not matched by convincing evidence that antibiotics improved patients' symptom experiences or quality of life any better than placebo.

Chronic Lyme Disease

Early work in the field sometimes referred to patients with infection of more than 6 months duration – particularly North American patients with Lyme arthritis or European patients with acrodermatitis chronica atrophicans – as having chronic infection. This term has been largely supplanted by 'late manifestations' as these syndromes often appear after a long period of apparent clinical latency. The term 'chronic Lyme disease' as currently used lacks an accepted definition for either clinical use or scientific study, and it has not been widely accepted in the medical or scientific community. In practice, the term has been applied to a highly heterogeneous patient population, including patients with prolonged and unexplained symptoms who lack objective features of Lyme disease, many of whom prove to have alternative medical diagnoses. In one systematic study, more than half of patients previously given this diagnosis actually had other specific disorders including rheumatoid or osteoarthritis, amyotrophic lateral sclerosis, myasthenia gravis or depression [325]. Regardless of their underlying diagnosis, many patients who receive the diagnoses of chronic Lyme disease are ill, highly symptomatic, and may be quite impaired by their underlying illnesses and symptoms. When evaluating such patients, clinicians should proceed to a thorough and individualized history, physical examination and appropriate laboratory investigation to identify, whenever possible, the best-fitting diagnosis. If an alternative diagnosis is established or suspected, further evaluation, treatment, and, as appropriate, referral should be directed at that diagnosis. The question remains whether patients with these highly heterogeneous symptoms but no alternative diagnoses should be treated as if they had Lyme disease, and, in the opinion of some, treated for an extended period of time. No higher quality studies have addressed this question. However, two considerations are relevant. First, by definition, these patients often have no compelling clinical or laboratory support for the diagnosis of ongoing Lyme disease. Second, the above studies of persistent symptomatology after treatment of verified Lyme disease have found that prolonged antimicrobial therapy is not helpful. From this, one can infer that prolonged antibiotic treatment is unlikely to benefit

individuals who lack a verifiable history of Lyme disease, while at the same time exposing them to significant risk.

Research needs: Although many patients diagnosed with chronic Lyme disease have other diagnosable and potentially treatable disorders, many have 'medically unexplained symptoms' – poorly understood symptom complexes that lack a unifying medical diagnosis. Studies to better understand this disorder or group of disorders, and the development of effective treatment strategies would be highly beneficial.

Cutaneous manifestations of Eurasian Lyme disease

Borrelial lymphocytoma (BL) and acrodermatitis chronica atrophicans are cutaneous manifestations of Lyme disease that have been primarily observed in European patients with *B. afzelii* infection. Consequently, patients evaluated in the U.S. for these conditions will most often have acquired their infection in Europe or in Lyme disease-endemic areas of Central or East Asia. Borrelia lymphocytoma is an inflammatory skin lesion, usually a bluish-purplish nodule, papule, or plaque. Acrodermatitis chronica atrophicans is an atrophic dermatitis affecting extensor surfaces, especially of the hands, and may present months to years after initial infection.

XXVIII. What is the preferred antibiotic regimen for the treatment of borrelial lymphocytoma?

Recommendation:

1. In patients with borrelial lymphocytoma, we suggest oral antibiotic therapy for 14 days (**weak recommendation, low-quality evidence**).

Summary of the evidence: There is no systematic data to indicate a preferred antibiotic, route, or duration for borrelial lymphocytoma. Most patients in published series have been given oral antibiotics that are used for other manifestations of Lyme disease, typically for 2-4 weeks. The lymphocytoma reportedly lasts 2 weeks to 2 months following initiation of therapy.

Rationale for recommendation: Antibiotic therapy is recommended both for resolution of lymphocytoma and to prevent further dissemination of infection to other tissues.

Research Needs: Comparative clinical studies would be needed to determine the optimal duration of therapy.

XXIX. What is the preferred antibiotic regimen for the treatment of acrodermatitis chronica atrophicans?

Recommendation:

1. In patients with acrodermatitis chronica atrophicans, we suggest oral antibiotic therapy for 21 to 28 days over shorter durations (**weak recommendation, low-quality evidence**).

Summary of the evidence: Several observational studies indicate that acrodermatitis chronica atrophicans stops progressing after a 3-4 week course of antibiotic treatment. It is currently unknown whether shorter durations of therapy will be effective. Improvement or resolution may take months to years. Some patients with disease lasting longer than 6 months have been retreated, but it is uncertain whether this is necessary or effective. Two studies comparing IV to oral therapy have produced conflicting results [326, 327].

Rationale for recommendation: Antibiotic therapy is recommended both for resolution of acrodermatitis chronica atrophicans and to prevent further progression of infection to other tissues.

Research Needs: Comparative clinical studies would be needed to determine whether acrodermatitis chronica atrophicans can be reliably treated with shorter courses of antibiotics.

<u>Lyme disease coinfections</u>

Ixodes ticks that transmit *B. burgdorferi* also harbor six other infectious organisms capable of causing human infection at the same time in North America [104, 270, 328-336]. The two most commonly

identified co-infections are caused by *B. burgdorferi* and the rickettsial bacteria *Anaplasma phagocytophilum* and *B. burgdorferi* and the protozoan parasite *Babesia microti* [333, 337-341].

The frequency of coinfection in studies varies depending on location, case definition, enrollment criteria, and laboratory detection methods [104, 330, 331, 333, 339-345]. For *A. phagocytophilum*, the agent of human granulocytic anaplasmosis (HGA), the frequency of co-infection with *B. burgdorferi* varies between 2-11.7% in reported studies [330, 331, 333, 339, 343, 345]. Data have been mixed as to whether Lyme disease and HGA co-infection presents as a more severe illness than early Lyme disease alone [333, 339, 343, 345]. Epidemiologic studies in areas where *B. burgdorferi* and *Babesia microti* are endemic suggest that about 15% (range 2%- 40%) of early Lyme disease patients experience babesiosis coinfection [333, 340, 341, 343, 344, 346]. Co-existing babesiosis may increase the severity and duration of symptoms seen with early Lyme disease [331, 338, 340, 343]. Lyme disease appears to have little impact on the clinical manifestations of babesia infection [340, 343].

Other pathogens potentially co-transmitted with *B. burgdorferi* include *B. miyamotoi, B. mayonii, Ehrlichia muris eauclairensis* (formerly known as *Ehrlichia muris*-like agent) and Powassan virus (also referred to as Deer Tick virus). Although the frequency of *B. burgdorferi* coinfections with these agents is not well established, they appear to be less frequent than those caused by *A. phagocytophilum* and *B. microti* [331, 334-336, 347-349]. Prompt evaluation for co-infection should be considered wherever Lyme disease is transmitted if one or more co-infecting pathogens have been described in the area and clinical features suggest potential coinfection.

Bartonella has not been established as an *I. scapularis* transmitted infection or as a co-transmitted agent with B. burgdorferi [331, 350, 351]. While *I. scapularis* may take blood meals from animals infected with *Bartonella* species, transmission to humans has not been identified [331, 350-353].

Clinicians seeking detailed information about the diagnosis and management of the two most common tick-borne coinfections with Lyme disease should consult other documents. Recommendations for the diagnosis and treatment of babesiosis may be found in the dedicated IDSA Babesia Guideline [IN PRESS] that will suggest blood smear and/or PCR for timely diagnosis. The preferred treatment requires combination therapy with either atovaquone in combination with azithromycin or clindamycin in combination with quinine. Severe babesiosis may require quinine plus clindamycin and possibly red blood cell exchange transfusion. Guidance regarding HGA may be found in the 2016 report from the Centers for Disease Control [1] that recommend diagnostic testing through DNA amplification assays, though a blood smear or buffy-coat preparation may show characteristic morulae. Acute and convalescent serology for *A. phagocytophilum* may also secure the diagnosis but is unhelpful to guide real-time decision making. Treatment of HGA requires using doxycycline.

XXX. Under what circumstances should a patient with Lyme disease be evaluated for co-infection with *A. phagocytophilum* or *B. microti*?

Recommendation:

1. In patients with Lyme disease who have high grade fever or characteristic laboratory abnormalities, clinicians should assess for possible co-infection with *Anaplasma phagocytophilum* and/or *Babesia microti* infection in geographic regions where these infections are endemic ***(good practice statement).*** **Comment:** Coinfection should be investigated in patients who have a persistent fever for greater than one day while on antibiotic treatment for Lyme disease. If fever persists despite treatment with doxycycline, *B. microti* infection is an important consideration. Characteristic laboratory abnormalities include thrombocytopenia, leukopenia, neutropenia, and/or anemia. Evidence of hemolysis, such as elevated indirect bilirubin level,

anemia, and elevated lactate dehydrogenase suggest babesiosis in particular, while neutropenia suggests anaplasmosis.

Summary of evidence: Although increased hepatic enzyme levels and lymphopenia are well-recognized laboratory abnormalities in patients with early Lyme disease, the following are not found and may suggest co-infection: thrombocytopenia, leukopenia, neutropenia, anemia and elevated indirect bilirubin levels [1, 113, 339, 343, 354, 355].

Rationale for recommendation: In the North America, there are six different pathogens besides *B. burgdorferi* that are transmitted by *Ixodes scapularis* ticks [113]. Three of them, *A. phagocytophilum, Babesia microti,* and *Ehrlichia muris eauclairensis* (the latter is only endemic to the Midwest region of the United States [331]) need special treatment considerations in patients presenting with EM. Although doxycycline is highly effective against both *A. phagocytophilum* and *Ehrlichia muris eauclairensis* [1, 331], it is not effective treatment for *B. microti* infections that require antimicrobial regimens that differ from those discussed above for patients with EM [113]. Beta-lactam antibiotics are ineffective for *A. phagocytophilum*, *Ehrlichia muris eauclairensis* and *B. microti* infections [1, 113, 331]. Other potential co-infections include *B. miyamotoi* and *B. mayonii,* which are treated with the same antibiotic regimens as Lyme disease, and Powassan virus/deer tick virus infections for which antibacterials are ineffective.

Research needs: Further studies determining the frequency of *I. scapularis*-transmitted co-infections in different geographic areas of the U.S are warranted. Further investigations are needed to study the cost-effectiveness of multiplex laboratory assays for the simultaneous diagnosis of multiple coinfections.

Notes

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Conflict of Interest Summary. See the Methodology section and Table 3 for approach to COI by the IDSA/AAN/ACR COI Review Panel. The COI Review Panel required disclosure of all possible COI, regardless of relevance to the guideline. See Table 3 for disclosed COI**.**

Tables and Figures

Table 1. Relationships Prohibited

1. Royalties, licensing fees, patents from any product or device related to the topic under consideration. This includes patents, the rights for which have been turned over to an institution but from which the individual benefits.
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4. Any honoraria, gifts, or other payments (includes funds for travel/hotel) directly received from any relevant commercial healthcare-related entity (US and International). This includes participation in speakers bureaus labeled as promotional and/or when any associated presentation is: a. content-restricted in any way, including, but not limited to, the requirement to use only company-provided material; paid for by any mechanism other than an unrestricted educational grant to a CME-approved (or other educational) entity; and/or product-specific.
5. Any activity not sponsored by the research arm of the company will **NOT** be allowed. For example, an advisory board sponsored by the marketing division, even if concentrating on "future research directions," will **NOT** be allowed. In addition, consulting on post-research regulatory issues will **NOT** be allowed.
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Table 2. Relationships Allowed

1. Advisory/consultancies when research-related will be considered as a research activity, even if the company with which you have the relationship, has products related to the guideline. Thus, work with a pharmaceutical or device company involving study design or service on a Data Safety Monitoring Board **WILL** be allowed. ***Exception, Chair(s)***

2. Serving as an investigator on a company-supported or company-sponsored research study. If you are a panel chair and conduct research, IDSA will require a co-chair with no relationships.
3. Presentations at national or international meetings provided that: a. Presentations are non-promotional and there should be no involvement of industry in presentation content. There should be complete intellectual independence with regard to presentation content. b. There is NO direct payment by industry to an individual for his/her participation (any industry support of speaker expenses must be through a third-party organization (e.g, IDSA, ICAAC, ATS, etc), institution, CME, or other educational provider. ***Exception, Chair(s)***

Table 3: Conflict of Interest Disclosures Reported

Conflict of Interest		
Name	**Related to the Topic**	**Unrelated to the Topic**
P. A	• Expert testimony: Lyme disease	• Advisor/Consultant: Medscape, John Hopkins POC-IT ABX Guide, Dynavax (Past), Aradigm (Past), Cempra (Past), bioMerieux, Inc (Past); • Stock: Johnson and Johnson (J&J) • Research grants/contracts: Fisher Center for Environmental ID • Other: Volunteer member of the IDSA and American Lyme Disease Foundation Board of Directors
K.B		• Research grant/contract: National Institutes of Health (NIH)
L.K.B	• L2 Diagnostics (research, past)	• Research grants/contracts: NIH • Other: Jockers Endowed Professorship and The Gordon Llura Gund Foundation
J.B	• Advisor/consultant: T2 Biosystems, DiaSorin	• Research grants/contracts: Alere, Inc, bioMerieux, Inc, DiaSorsin, Immunetics, T2 Biosystems, Bay Area Lyme Foundation • Other: Editorial board for the Journal of Clinical Microbiology

D.C		• Advisor/consultant: Dr. Reddy's Lab, Biogen, Takeda/Millennium Adjudication Committee, Genzyme/Sanofi, Amgen, Genentech, GlaxoSmithKline, Merck, Inhibikas, Shire, Wave, Covance • Research grants/contracts: NIH and the Alzheimer's Association
Y.F.Y		• Other: Evidence Foundation (GRADE Workshops); Chair, American Gastroenterological Association Guideline Committee (Past); Director, Evidence Foundation
J.H	• Expert testimony: Lyme disease	• Stock: Abbott Labs, Abbvie, Merck and J&J • Other: Editorial Board member, NEUROLOGY
P.J.K	• Advisor/consultant: Oxford Immunotec Inc	• Research grants/contracts: Gordon and Llura Gund Foundation, NIH
P.L		• Advisor/consultant: Frederick O'Connor Medical Consultants (Past) • Research grants/contracts: NIH, Duke University, National Cytomegalovirus (CMV) Foundation
M.L		• Stock: J&J • Research grant/contract: Veterans Affairs
L.N		• Research grants/contracts: NIH, Patient Centered Outcomes Research (PCORNet), Boston Children's Hospital Medical Staff Organization, Milton Foundation, Department of Defense
J.N		• Research grants/contracts: Abbvie Laboratories, Bristol-Meyers-Squibb, NIH, Arthritis Foundation • Other: Committee member, American Board of Pediatrics, Pediatric Rheumatology sub-board

A.P		• Research grants/contract: Teva Pharmaceuticals • Other: Member AAN Editorial Board, Neurology Clinical Practice
L.R		• Stock: Abbott, Proctor and Gamble, General Electric • Fellowship support from Abbott Laboratories, Boston Scientific, and Medtronic • Other: Member, Patients and Caregivers Subcommittee and Education Committee, Heart Rhythm Society (Past); Council member, Connecticut American College of Cardiology
J.R		• Speaker's bureau: Teva Pharmaceutical (Past) • Research grants/contracts: Alzheimer's Association and College of Radiology: IDEAS
M.S		• Advisory/Consultant/Teaching: American Association of Family Practice (AAFP) • Other: President, Delaware Academy of Family Physicians; Editor, DelFamDoc Journals; Commission member, AAFP
S.S		• Research grant/contract: NIH
F.S		• Research grants/contracts: Slovenian Research Agency
R.S		• Advisor/consultant: Paul Hastings, LLC • Expert testimony: Conway Homer and Chin-Caplan, P.C • Research grants/contracts: NIH, Pfizer Inc. • Other: Author/Editor, UpToDate; Medical Education Resources lecturer

J.T	• Consult/Teaching: Michigan Lyme Disease Association, Boehringer Ingelheim (Past)	• Research grants/contracts: NIH, National Science Foundation (Past), Centers for Disease Control and Prevention • Other: Associate Editor, Ticks and Tickborne Disease (Past); Subcommittee member, US HHS Tick-borne Disease Working Group (Past)
G.P.W	• Expert Testimony: Lyme disease • Patent Applications: Application Numbers, 15/046, 204, 62/277,252 and Provisional Patent Application 62/725,745.	• Advisor/Consultant: Baxter (Past), Missouri Board of Registration for the Health Arts (Past) • Stock: Abbott/AbbVie • Research grants/contracts: Immunetics, Inc; Quidel Corp; Rarecyte, Inc; Institute for Systems Biology • Other: Board member, American Lyme Disease Foundation

No COI's to report: **M.A., K.B., R.B., W.B., F.D., V.L., C.M., M.O., J.R., A. S., E.V., L.Z**

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network) [290]

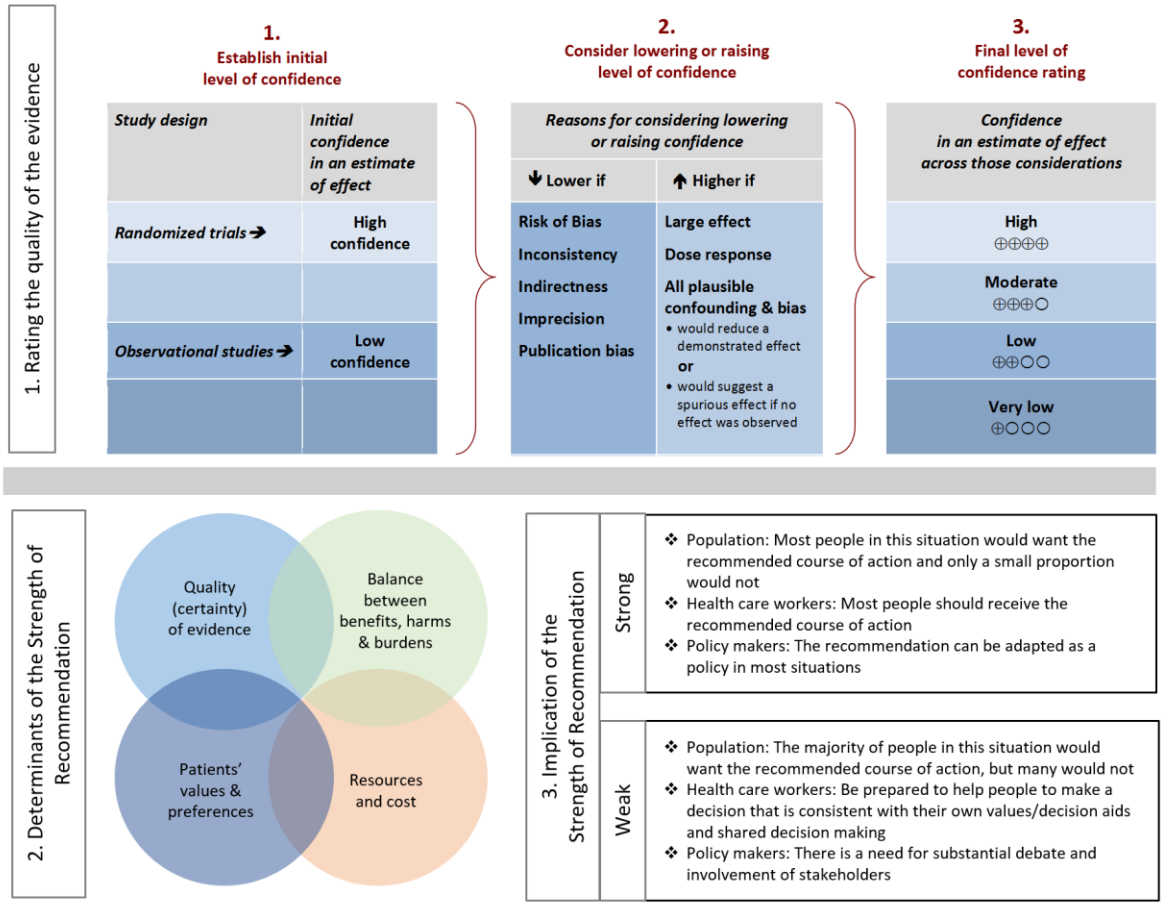


Table 4. Drug Doses

Drug	Dosage for Adults	Dosage for Children
Oral Regimens		
Preferred		
Amoxicillin[c]	500 mg three times daily	50 mg/kg divided three times daily (maximum 500 mg per dose)
Doxycycline[a]	100 mg twice daily or 200 mg once daily[b]	4.4 mg/kg divided twice daily (maximum 200 mg daily)
Cefuroxime axetil[c]	500 mg twice daily	30 mg/kg divided twice daily (maximum 500 mg per dose)
Phenoxymethyl penicillin (penicillin VK)[c]	500 mg four times per day or 1 g three times per day	50-100 mg/kg/day in three divided doses (maximum 1 g per dose)
Alternative		
Azithromycin[d]	500 mg once daily	10 mg/kg once daily (maximum 500 mg per dose)
Intravenous Therapy		
Preferred		
Ceftriaxone[c]	2000 mg once daily	50-75 mg/kg once daily (maximum 2000 mg per dose)
Alternative		
Cefotaxime[c]	2000 mg three times daily	150-200 mg/kg divided 3-4 times daily (maximum 6000 mg daily)
Penicillin G[c]	18-24 million units divided every 4 hours	200,000-400,000 units/kg divided every 4 hours (maximum 18-24 million units daily)

[a] Doxycycline is relatively contraindicated in children under 8 years of age, pregnancy, and lactation

[b] Doxycycline should be given in a single daily dose for Lyme meningitis

[c] Doses of some beta lactam antibiotics (amoxicillin, penicillin, cefuroxime, ceftriaxone, and cefotaxime) may require adjusted dosing for patients with impaired renal function. Ceftriaxone does not require dose reduction in renal failure.

[d] Because of concerns for lower efficacy, macrolide antibiotics including azithromycin are considered second line agents, and should be reserved for patients in whom other antibiotic classes are contraindicated

Table 5. Syndrome Treatment

Disease Manifestation	Route	Medication	Duration, days (range)[a]
Erythema migrans	Oral	Doxycycline	10
		Beta lactam antibiotics[b]	14
		Azithromycin[c]	7
Meningitis or radiculopathy	Oral	Doxycycline	14-21
	Parenteral[d]	Ceftriaxone	14-21
Cranial nerve palsy	Oral	Doxycycline	14-21
Carditis	Oral[e]	Doxycycline	14
		Beta lactam antibiotics[b]	14
	Parenteral[e]	Ceftriaxone	14
Arthritis			
Initial treatment	Oral	Doxycycline	28
		Beta lactam antibiotics[b]	28
Recurrent or refractory arthritis	Oral	Doxycycline	28
		Beta lactam antibiotics[b]	14-28
	Parenteral	Ceftriaxone	14[f]
Acrodermatitis chronica atrophicans	Oral	Doxycycline	21-28
		Beta lactam antibiotics[b]	21-28
Borrelial lymphocytoma	Oral	Doxycycline	14
		Beta lactam antibiotics[b]	14

[a] Ranges are given where different durations have been studied, and the optimal duration remains uncertain.
[b] Oral beta lactam antibiotics include amoxicillin, cefuroxime axetil, and phenoxymethylpenicillin (penicillin VK)
[c] Because of concerns for lower efficacy, macrolide antibiotics including azithromycin are considered second line agents, and should be reserved for patients in whom other antibiotic classes are contraindicated. Azithromycin has not been sufficiently studied for manifestations of Lyme disease other than erythema migrans.
[d] The preferred parenteral agent is ceftriaxone. Cefotaxime and penicillin G are alternatives.
[e] Initial parenteral therapy is recommended for patients requiring hospital admission. Therapy can be completed orally for the same total 14-day duration. Patients with Lyme carditis who do not require hospital admission can be treated orally.
[f] Repeat parenteral therapy can be extended to 28 days if inflammation is not resolving

Table 6. Prevention

Personal Preventive Measures	Wear light colored clothing Wear long sleeves and pants Tuck pants into socks Tick checks after exposure Wash clothing in hot water
Repellents	DEET Picaridin IR3535 Oil of lemon eucalyptus Permethrin[a]
Antibiotic Prophylaxis[b]	Adults: doxycycline 200 mg in a single dose Children: doxycycline 4.4 mg/kg in a single dose

[a] Permethrin is only for application to clothing
[b] Antibiotic prophylaxis is indicated for high risk bites that meet the following criteria:
Prolonged tick attachment (≥ 36 hours) and/or engorgement
Confirmed Ixodes scapularis
Tick bite sustained in area with high Lyme disease prevalence
Antibiotic prophylaxis is not mandatory, and anticipatory guidance with observation is also acceptable.
While single dose doxycycline prophylaxis in children and pregnancy is likely safe, treatment decisions should be individualized in these populations.

Figure 2. Lyme disease- Confirmed cases by month of disease onset, Unites States, 2001-2017 [356]

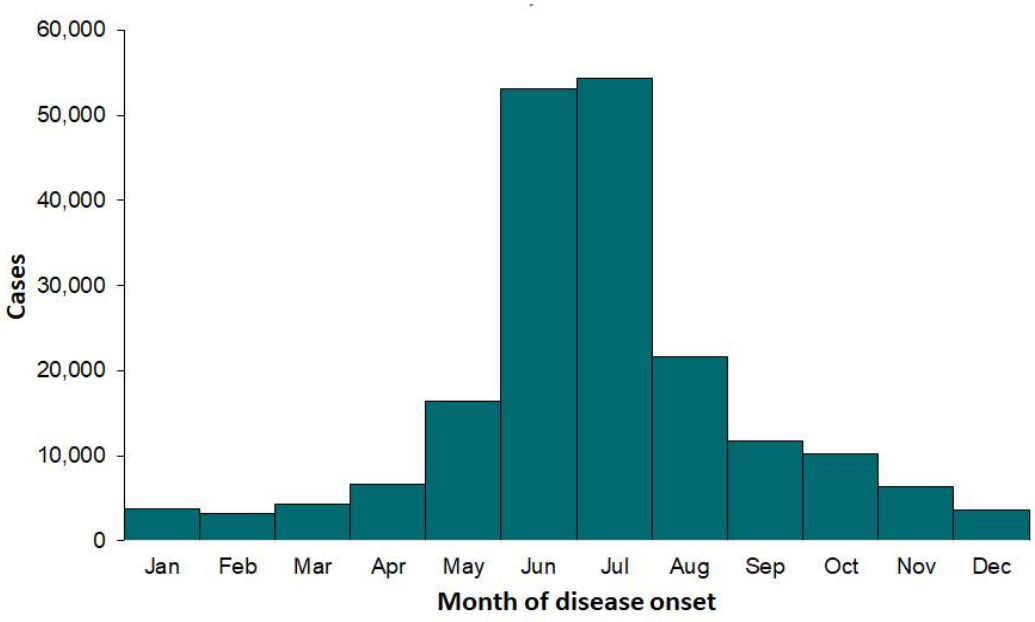


Figure 3. Report Cases of Lyme Disease- United States, 2017 [357]

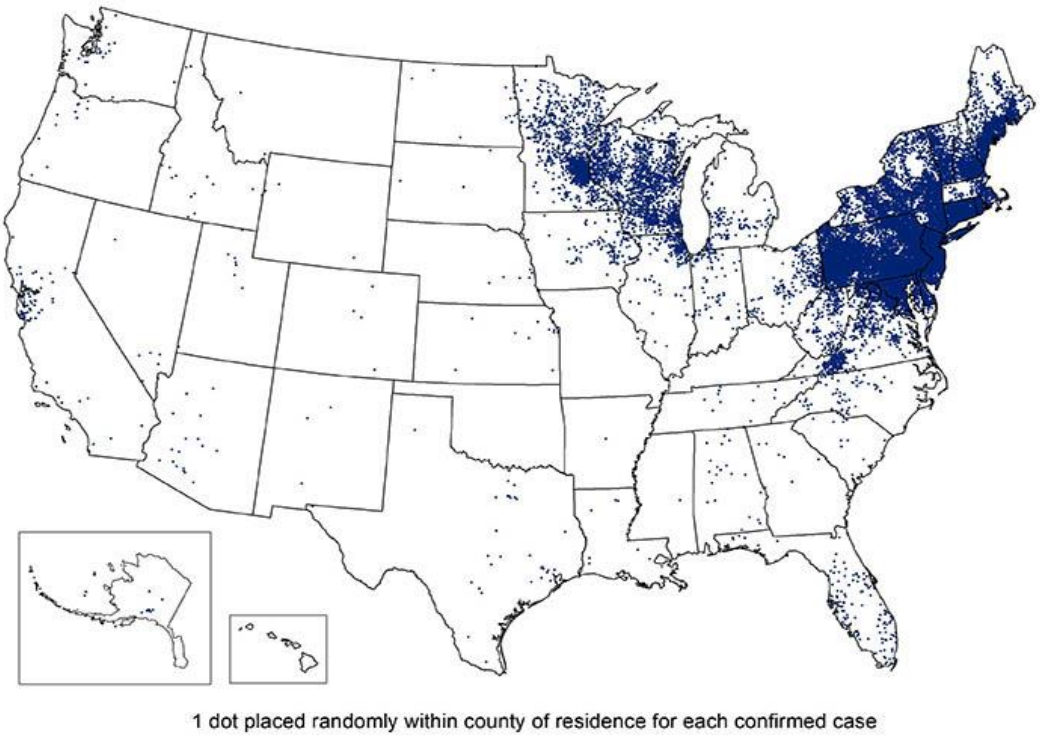


Figure 4. Tick Removal [358]

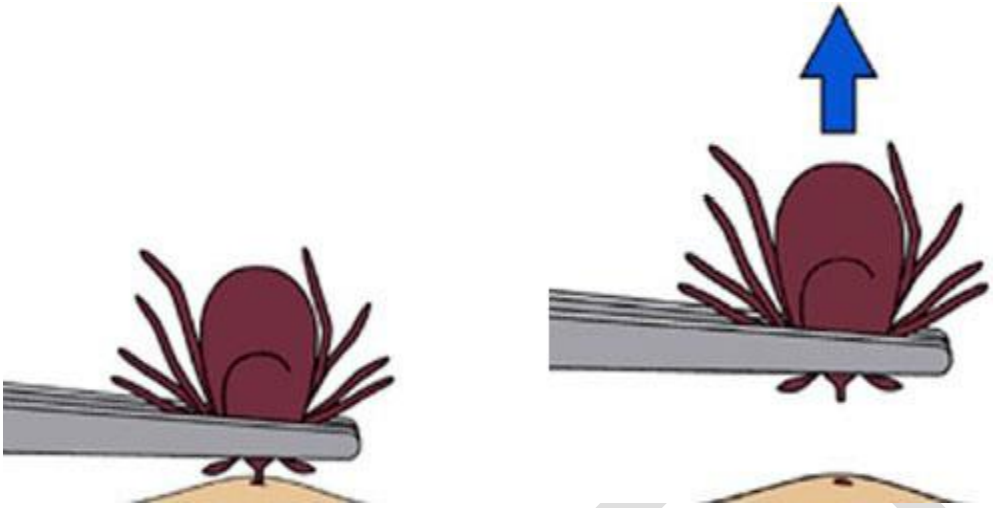
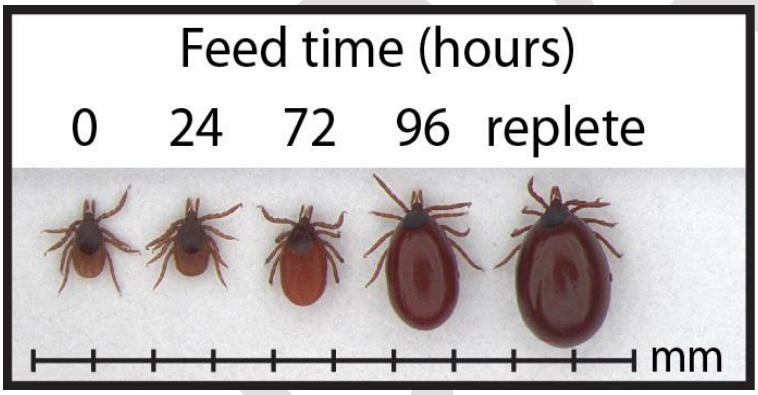


Figure 5. Nymphal Engorgement Scale [359]

A) Engorgement size of blacklegged nymphs (Source CDC)



B) Adult females

**Nymphs feeding for 48 hours and less may not look as red as that depicted in the figure*

Table 7. Dosage and Duration of the Oral Antimicrobial Agents Recommended for Patients with Erythema Migrans

Drug	Adult Dosage	Pediatric Dosage	Duration of Treatment
Amoxicillin	500 mg, three times per day	50 mg/kg per day in three divided doses (maximum, 500 mg per dose)	14 days
Doxycycline	100 mg twice per day	4.4 mg/kg per day in two divided doses (maximum, 100 mg per dose)	10 days
Cefuroxime axetil	500 mg twice per day	30 mg/kg in two divided doses (maximum, 500 mg per dose)	14 days
Phenoxymethylpenicillin	500 mg four times per day; or 1 gm three times per day	50-100 mg/kg/day in three divided doses (maximum 1 g per dose)	14 days
Azithromycin	500 mg once per day	10 mg/kg per day (maximum, 500 mg per day).	7 days

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