Clinical Infectious Diseases

IDSA FEATURES

Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease

Paul M. Lantos,[1] Jeffrey Rumbaugh,[2] Linda K. Bockenstedt,[3] Yngve T. Falck-Ytter,[4] Maria E. Aguero-Rosenfeld,[5] Paul G. Auwaerter,[6] Kelly Baldwin,[7] Raveendhara R. Bannuru,[8] Kiran K. Belani,[9] William R. Bowie,[10] John A. Branda,[11] David B. Clifford,[12] Francis J. DiMario Jr,[13] John J. Halperin,[14] Peter J. Krause,[15] Valery Lavergne,[16] Matthew H. Liang,[17] H. Cody Meissner,[8] Lise E. Nigrovic,[18] James (Jay) J. Nocton,[19] Mikala C. Osani,[8] Amy A. Pruitt,[20] Jane Rips,[21] Lynda E. Rosenfeld,[3] Margot L. Savoy,[22] Sunil K. Sood,[23] Allen C. Steere,[11] Franc Strle,[24] Robert Sundel,[18] Jean Tsao,[25] Elizaveta E. Vaysbrot,[8] Gary P. Wormser,[26] and Lawrence S. Zemel[13]

[1]Duke University School of Medicine, Durham, North Carolina, USA, [2]Pathway Neurology, Tampa, Florida, [3]Yale University, New Haven, Connecticut, USA, [4]Case Western Reserve University, VA Northeast Ohio Healthcare System, Cleveland, Ohio, USA, [5]New York University School of Medicine, New York, New York, USA, [6]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [7]Geisinger Medical Center, Danville, Pennsylvania, USA, [8]Tufts Medical Center, Boston, Massachusetts, USA, [9]Childrens Hospital and Clinical of Minnesota, Minneapolis, Minnesota, USA, [10]University of British Columbia, Vancouver, British Columbia, Canada, [11]Massachusetts General Hospital, Boston, Massachusetts, USA, [12]Washington University School of Medicine, St. Louis, Missouri, USA, [13]Connecticut Children's Medical Center, Hartford, Connecticut, USA, [14]Atlantic Health System, Summit, New Jersey, USA, [15]Yale School of Public Health, New Haven, Connecticut, USA, [16]University of Montreal, Montreal, Quebec, Canada, [17]Brigham and Women's Hospital, Boston, Massachusetts, USA, [18]Boston Children's Hospital Boston, Massachusetts, USA, [19]Medical College of Wisconsin, Waowatosa, Wisconsin, USA, [20]University of Pennsylvania, Philadelphia, Pennsylvania, USA, [21]Consumer Representative, Omaha, Nebraska, USA, [22]Temple University, Philadelphia, Pennsylvania, USA, [23]Northwell Health, Manhattan, New York, USA, [24]University Medical Centre Ljubljana, Ljubljana, Slovenia, [25]Michigan State University, East Lansing, Michigan, USA, and [26]New York Medical College, Valhalla, New York, USA

This evidence-based clinical practice guideline for the prevention, diagnosis, and treatment of Lyme disease was developed by a multidisciplinary panel representing the Infectious Diseases Society of America (IDSA), the American Academy of Neurology (AAN), and the American College of Rheumatology (ACR). The scope of this guideline includes prevention of Lyme disease, and the diagnosis and treatment of Lyme disease presenting as erythema migrans, Lyme disease complicated by neurologic, cardiac, and rheumatologic manifestations, Eurasian manifestations of Lyme disease, and Lyme disease complicated by coinfection with other tick-borne pathogens. This guideline does not include comprehensive recommendations for babesiosis and tick-borne rickettsial infections, which are published in separate guidelines. 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, family physicians, neurologists, rheumatologists, cardiologists and dermatologists in North America.

Summarized below are the 2020 recommendations for the prevention, diagnosis, and treatment of Lyme disease. The panel followed a systematic process used in the development of other IDSA, AAN, and ACR clinical practice guidelines, which included a standardized methodology for rating the certainty of the evidence and strength of recommendation using the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation) (see Figure 1). A detailed description of background, methods, evidence summary and rationale that support each recommendation, and knowledge gaps can be found online in the full text.

I. WHICH MEASURES SHOULD BE USED TO PREVENT TICK BITES AND TICK-BORNE INFECTIONS?

(A) Personal Protective Measures

Recommendation:

1. Individuals at risk of exposure should implement personal protective measures to reduce the risk of tick exposure and infection with tick-borne pathogens *(good practice statement)*.

(B) Repellents to Prevent Tick Bites

Recommendation:

1. For the prevention of tick bites, we recommend N,N-Diethyl-meta-toluamide (DEET), picaridin,

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Correspondence: P. M. Lantos, Duke University School of Medicine, Durham, North Carolina (paul.lantos@duke.edu).

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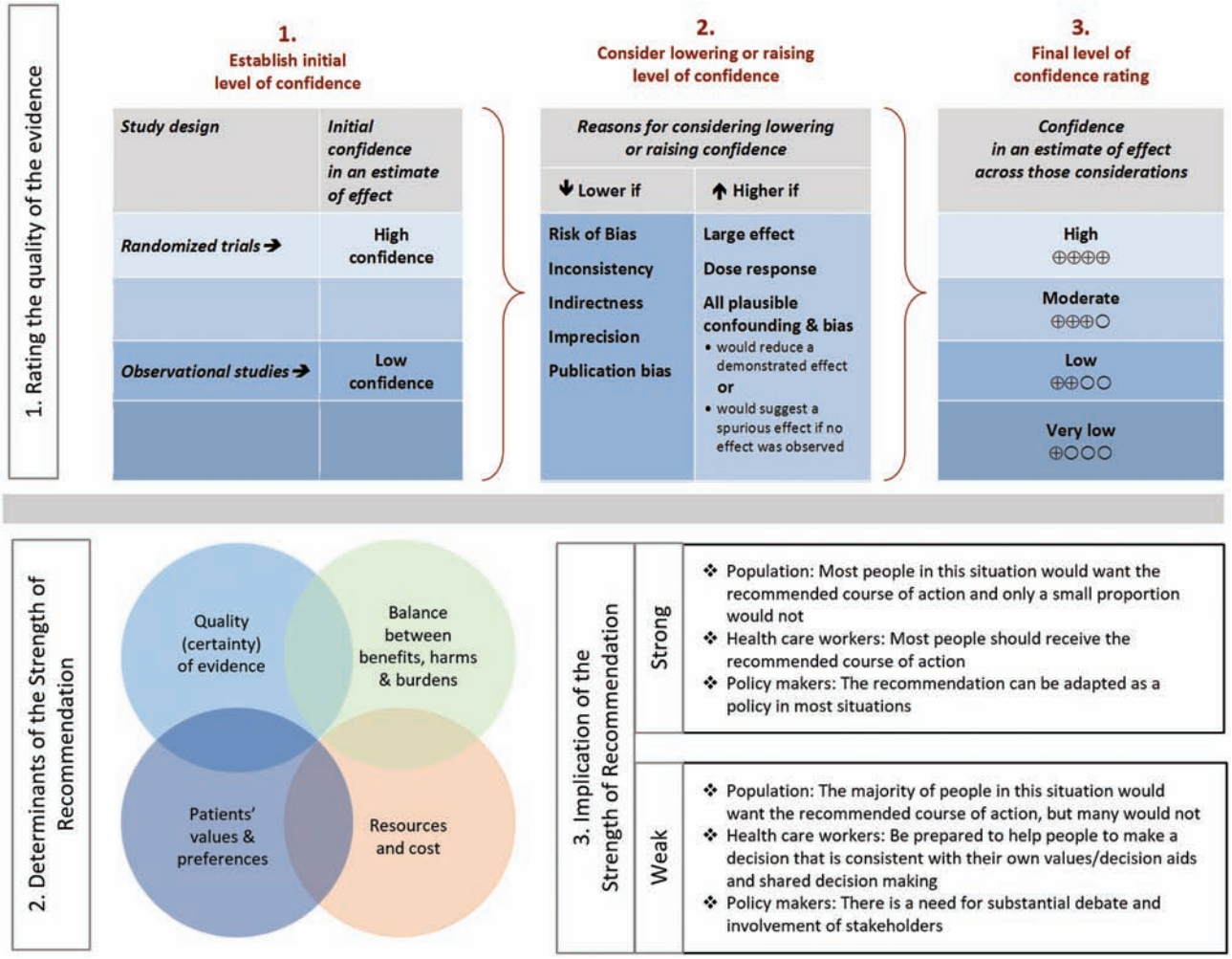

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the US GRADE Network) [1, 2]. Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

ethyl-3-(N-n-butyl-N-acetyl) aminopropionate (IR3535), oil of lemon eucalyptus (OLE), p-methane-3,8-diol (PMD), 2-undecanone, or permethrin *(strong recommendation, moderate-quality evidence).*

(C) Removal of Attached Ticks

Recommendations:

1. We recommend promptly removing attached ticks by mechanical means using a clean fine-tipped 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 other heat device) or applying noxious chemicals or petroleum products to coax its detachment (*good practice statement*).

II. WHICH DIAGNOSTIC TESTS SHOULD BE USED FOLLOWING A TICK BITE?

(A) Diagnostic Tick Testing

Recommendations:

1. We recommend submitting the removed tick for species identification (*good practice statement*).
2. We recommend against testing a removed *Ixodes* tick for *B. burgdorferi (strong recommendation, moderate-quality evidence).* **Comment:** The presence or absence of *B. burgdorferi* in an *Ixodes* tick removed from a person does not reliably predict the likelihood of clinical infection.

(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* spp. tick bite *(strong recommendation, moderate-quality evidence).*

III. WHO SHOULD RECEIVE ANTIBIOTIC PROPHYLAXIS TO PREVENT LYME DISEASE FOLLOWING PRESENTATION WITH A TICK BITE?

Recommendation:

1. We recommend that prophylactic antibiotic therapy be 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 risk or low risk *(strong recommendation, high-quality evidence)*. **Comment**: If a tick bite cannot be classified with a high level of certainty as a high-risk bite, a wait-and-watch approach is recommended. 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* spp. vector species, (b) it occurred in a highly endemic area, and (c) the tick was attached for ≥36 hours.

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* spp. bites in all age groups, 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:** Doxycycline is given as a single oral dose, 200 mg for adults and 4.4 mg/kg (up to a maximum dose of 200 mg) for children.

V. WHAT IS THE PREFERRED DIAGNOSTIC TESTING STRATEGY FOR ERYTHEMA MIGRANS?

Recommendations:

1. In patients with potential tick exposure in a Lyme disease endemic area who have 1 or more skin lesions compatible with erythema migrans, we recommend clinical diagnosis rather than laboratory testing *(strong recommendation, moderate-quality evidence)*.
2. In patients with 1 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 2–3 weeks after collection of the acute-phase serum sample.

VI. WHAT ARE THE PREFERRED ANTIBIOTIC REGIMENS FOR THE TREATMENT OF ERYTHEMA MIGRANS?

Recommendation:

1. For patients with erythema migrans, we recommend using oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil *(strong recommendation, moderate-quality evidence)*. **Comment:** For patients unable to take both doxycycline and beta-lactam antibiotics, the preferred second-line agent is azithromycin.

VII. HOW LONG SHOULD A PATIENT WITH ERYTHEMA MIGRANS BE TREATED?

Recommendation:

1. We recommend that patients with erythema migrans be treated with either a 10-day course of doxycycline or a 14-day course of amoxicillin or cefuroxime axetil rather than longer treatment courses *(strong recommendation, moderate-quality evidence)*. **Comment:** If azithromycin is used, the indicated duration is 5–10 days, with a 7-day course preferred in the United States, as this duration of therapy was used in the largest clinical trial performed in the United States [3].

VIII. SHOULD PATIENTS WITH THE SOUTHERN TICK-ASSOCIATED RASH ILLNESS (STARI) BE TREATED WITH ANTIBIOTICS?

Recommendation:

1. In patients who develop an erythema migrans-like skin lesion following the bite of the lone star tick (*Amblyomma americanum*), an illness referred to as 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 [4]. Distinguishing single erythema migrans due to Lyme disease from STARI may not be possible clinically unless the responsible tick has been identified [5]. When STARI cannot be distinguished from Lyme disease-associated erythema migrans in areas endemic for both conditions, antibiotic therapy directed toward Lyme disease is indicated.

IX. WHAT IS THE PREFERRED DIAGNOSTIC TESTING STRATEGY FOR LYME NEUROBORRELIOSIS?

Recommendations:

1. When assessing patients for possible Lyme neuroborreliosis involving either the PNS or central nervous system (CNS), we recommend serum antibody testing rather than PCR or culture of either cerebrospinal fluid (CSF) or serum *(strong recommendation, moderate-quality 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 routine PCR or culture of CSF or serum *(strong recommendation, moderate-quality evidence)*.

X. FOR WHICH NEUROLOGICAL PRESENTATIONS SHOULD PATIENTS BE TESTED FOR LYME DISEASE?

Recommendations:

1. In patients presenting with 1 or more of the following acute disorders: meningitis, painful radiculoneuritis, mononeuropathy multiplex including confluent mononeuropathy multiplex, acute cranial neuropathies (particularly VII, VIII, less commonly III, V, VI and others), or in patients with evidence of spinal cord (or rarely brain) inflammation, the former particularly in association with painful radiculitis involving related spinal cord segments, 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 magnetic resonance imaging (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 suggest against testing for Lyme disease *(weak recommendation, low-quality evidence).*

XI. SHOULD ADULT PATIENTS WITH PSYCHIATRIC ILLNESSES BE TESTED FOR LYME DISEASE?

Recommendation:

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

XII. 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).*

XIII. 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 peripheral nervous system (PNS) manifestations, we recommend using intravenous (IV) ceftriaxone, cefotaxime, penicillin G, 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 such as side effect profile, ease of administration, ability to tolerate oral medication, concerns about compliance unrelated to effectiveness. Treatment route may be changed from IV to oral during treatment. The preferred antibiotic duration is 14–21 days.

XIV. SHOULD PATIENTS WITH LYME DISEASE-RELATED PARENCHYMAL INVOLVEMENT OF THE BRAIN OR SPINAL CORD BE TREATED WITH ORAL OR INTRAVENOUS ANTIBIOTICS?

Recommendation:

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

XV. 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 [6].

XVI. SHOULD ALL PATIENTS WITH EARLY LYME DISEASE RECEIVE AN ELECTROCARDIOGRAM (ECG) 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 and signs of cardiac involvement in Lyme disease include dyspnea, edema, palpitations, lightheadedness, chest pain, and syncope.

XVII. WHICH PATIENTS WITH LYME CARDITIS REQUIRE HOSPITALIZATION?

Recommendation:

1. In patients with or at risk for severe cardiac complications of Lyme disease including those with significant PR prolongation (PR > 300 milliseconds), other arrhythmias, or clinical manifestations of myopericarditis, we recommend hospital admission with continuous ECG monitoring *(strong recommendation, very low-quality evidence).* **Comment:** Clinical manifestations of Lyme carditis include exercise intolerance, palpitations, presyncope, syncope, pericarditic pain, evidence of pericardial effusion, elevated biomarkers (such as troponin), edema, and shortness of breath.

XVIII. WHAT PACING MODALITY SHOULD BE USED IF NEEDED 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 rather than implanting a permanent pacemaker *(strong recommendation, moderate-quality evidence).*

XIX. WHAT ARE THE PREFERRED ANTIBIOTIC 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 14–21 days of total antibiotic therapy over longer durations of treatment *(weak recommendation, very low-quality evidence).* **Comment:** Oral antibiotic choices for Lyme carditis are doxycycline, amoxicillin, cefuroxime axetil, and azithromycin.

XX. SHOULD PATIENTS BEING EVALUATED FOR ACUTE MYOCARDITIS/PERICARDITIS OR CHRONIC CARDIOMYOPATHY OF UNKNOWN CAUSE BE TESTED FOR LYME DISEASE?

Recommendations:

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).*

XXI. WHAT IS THE PREFERRED DIAGNOSTIC TESTING STRATEGY FOR LYME ARTHRITIS?

Recommendations:

1. When assessing possible Lyme arthritis, we recommend serum antibody testing over PCR or culture of blood or synovial fluid/tissue *(strong recommendation, moderate-quality 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 evidence).*

XXII. 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*).

XXIII. 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 exclusion of other causes of joint swelling than Lyme arthritis, medication adherence, 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).*

XXIV. 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, intraarticular 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 if that treatment has included 1 course of IV therapy.

XXV. SHOULD PATIENTS WITH PERSISTENT SYMPTOMS FOLLOWING STANDARD TREATMENT OF LYME DISEASE RECEIVE ADDITIONAL ANTIBIOTICS?

Recommendation:

1. For patients who have persistent or recurring nonspecific symptoms such as fatigue, pain, or cognitive impairment following recommended treatment for 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.

XXVI. 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).*

XXVII. 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 21–28 days over shorter durations *(weak recommendation, low-quality evidence).*

XXVIII. 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 a high-grade fever or characteristic laboratory abnormalities, clinicians should assess for possible coinfection with *Anaplasma phagocytophilum* and/or *B. 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 >1 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 found in both anaplasmosis and babesiosis include thrombocytopenia, leukopenia, neutropenia, and/or anemia. Evidence of hemolysis, such as elevated indirect bilirubin level, anemia, and elevated lactate dehydrogenase are particularly suggestive of babesiosis.

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 certain species of *Ixodes* ticks [7, 8]. 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 North America, Lyme disease is found predominantly in 3 regions: the northeastern states from Virginia to eastern Canada (including Ontario, Quebec, and the eastern maritime provinces); the upper Midwest, particularly Wisconsin and Minnesota; and in northern California.

Lyme disease is a complex infection, and clinical disease can manifest as early as days and as late as many months following an infectious tick bite. Presentations include a skin lesion at the site of the tick bite and disseminated disease resulting in skin lesions distant from the tick-bite site, neuropathy, meningitis, cardiac conduction abnormalities, and/or arthritis. Interpretation of diagnostic tests for Lyme disease presents certain challenges due to the dynamics of the serologic response following infection. Finally, treatment options, including the drug, route, and duration of treatment may 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 North America. In contrast to the 2006 Infectious Diseases Society of America (IDSA) guideline, this guideline only addresses anaplasmosis and babesiosis in the context of a coinfection. Anaplasmosis is now addressed in the rickettsial disease guidelines developed by the Centers for Disease Control and Prevention (CDC) [9], and babesiosis recommendations can be found in a separate 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 Eurasian strains of *B. burgdorferi* sensu lato can cause clinical signs not associated with North American strains, this guideline also includes recommendations for evaluation and treatment of patients who present with borrelia lymphocytoma and acrodermatitis chronica atrophicans after travel to endemic areas.

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 healthcare 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 [10]. The "IDSA Handbook on Clinical Practice Guideline Development" provides more detailed information on the processes followed throughout the development of this guideline [11].

Guideline Authorship

This guideline is preceded by guidelines by the IDSA [12] and American Academy of Neurology (AAN) [13]. This guideline is a collaborative effort by IDSA, AAN, 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.

Guideline Panel Composition

Each of the 3 sponsoring organizations elected a cochair to lead the guideline panel (P.M.L. representing IDSA, J.A.R. representing AAN, and L.K.B. representing ACR) with a fourth cochair selected for his expertise in guideline methodology (Y.F.Y. representing the US 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-SOEM), American College of Physicians (ACP), Association of Medical Microbiology and Infectious Disease (AMMI) Canada, 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 3 patient representatives and 1 healthcare consumer representative. At the request of the patient representatives, we have not disclosed their names to maintain their confidentiality. 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.R.B., M.C.O., and E.E.V) performed the systematic reviews of the literature, identified and summarized the scientific evidence using questions in the "PICO" format (Patient/Population[P]; Intervention/Indicator[I]; Comparator/Control[C]; Outcome[O]).

Disclosure and Management of Potential Conflict of Interest (COI)

The Lyme conflict of interest (COI) review group consisting of 2 representatives from IDSA, AAN, and ACR were responsible for reviewing, evaluating, and approving all disclosures. All members of the expert panel complied with the consensus IDSA/AAN/ACR 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 (ie, monetary amount) and the relevance of the relationship (ie, 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 Tables 1 and 2. In addition, the IDSA/AAN/ACR adhered to Section 7 of the Council for Medical Specialty Societies' "Code for Interactions with Companies" [14]. The COI review group ensured that the majority of the panel and each cochair was without potential relevant (related to the topic) conflicts (see the Notes section). Each of the cochairs and all members of the technical team were determined to be unconflicted. See the notes section for disclosures reported to IDSA/AAN/ACR.

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.
2. Serving as an officer, board of directors' member or employee of any device, insurance, pharmaceutical or diagnostic product or commercial entity with a product or device related to the topic under consideration.
3. Representation of any commercial healthcare-related entity (with a product or device related to the topic under consideration) before FDA advisory committees or in any other interactions such an entity may have with FDA.
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 postresearch regulatory issues will **NOT** be allowed.
6. Stock or equity in any commercial healthcare-related entities (excludes diversified funds) related to the topic under consideration.

Abbreviations: CME, continuing medical education; FDA, Food and Drug Administration.

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.R.B., M.C.O., and E.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 and in April 2019. All new relevant studies pertinent to this guideline were 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. Trial data or other evidence of effectiveness from non-peer-reviewed data sources, such as abstracts and conference proceedings, letters to the editor, editorials, review articles, and unpublished data were excluded a priori for lack of sufficient peer review 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 these articles for accuracy of selection criteria. Because studies may be initially included that are not pertinent, additional review 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 was 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 [15], the Newcastle-Ottawa scale (NOS) for nonrandomized studies [16] and QUADAS-2 tool for diagnostic test accuracy studies [17]. The certainty in the evidence was initially determined for

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 cochair with no relationships.
3. Presentations at national or international meetings provided that:
a. Presentations are nonpromotional 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)

Abbreviations: ATS, American Thoracic Society; CME, continuing medical education; ICAAC, Interscience Conference on Antimicrobial Agents and Chemotherapy; IDSA, Infectious Diseases Society of America.

each critical and important outcome, and then for each recommendation using the GRADE approach for rating the confidence in the evidence [1, 2] (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, data extraction and evidence profiles tables, and additional data, such as meta-analysis results when appropriate, can be found in the 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 compared the use of an antibiotic regimen to no antibiotics, if the beneficial effects of the antibiotic regimen were uncertain, undesirable outcomes would usually be ranked higher in importance than if benefits were certain. That is, undesirable outcomes would be 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 2 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, availability, patient preferences, and costs.

Development of Clinical Recommendations

All recommendations were labeled as either "strong" or "weak" according to the GRADE approach [2] (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 [18], 2 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 [19]. A good practice statement represents a message perceived by the guideline panel as necessary to healthcare practice, that 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. "Knowledge gaps" were noted where there remained particularly important research needs of relevance to clinical recommendations.

The entire panel met for a 2-day face-to-face meeting in Arlington, Virginia, 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 guideline and approved the recommendations.

Revision Process

Public comment allows for key stakeholders to review and identify gaps in a 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 the new Lyme disease guidelines. In June 2019, the panel opened a second 75-day public comment period requesting feedback on the full guideline. The panel reviewed the feedback from the public comment phase and updated the guideline as needed.

Feedback was also obtained from external peer reviews. The guideline was reviewed and approved 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 the 3 organizations' respective Board of Directors. AAFP, AAMI-Canada, CNS, PIDS, ESA, and ESCMID have reviewed provided endorsement of the guideline.

Revision for Currency Schedule

Approximately every 2 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 (serology) testing is highly sensitive in patients with common extracutaneous manifestations that develop weeks to months after initial infection [20, 21]. Immunoglobulin G (IgG) seronegativity in an untreated patient with months to years of symptoms essentially rules out the diagnosis of Lyme disease, barring laboratory error or a rare humoral immunodeficiency state. Serologic testing is also highly specific when performed and interpreted according to current guidelines [21, 22]. Serum antibody tests should be performed using clinically validated assays in a conventional 2-tiered testing protocol, in which an enzyme immunoassay (EIA) or indirect fluorescent antibody test (IFA) is followed by immunoglobulin M (IgM) and IgG immunoblots, or in a modified 2-tiered testing protocol, in which 2 different EIAs are performed sequentially or concurrently without the use of immunoblots [23–27]. Serologic tests are intended for use in 2-tiered testing protocols, rather than as stand-alone assays, as this improves specificity [25]. 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 [21, 28, 29]. This is often the case in patients with erythema migrans, an early manifestation of Lyme disease, who are tested <2 weeks after the development of the skin lesion [21, 28, 29].

In a seropositive patient, it can be difficult to determine whether antibody reactivity is due to past infection versus active/current infection. In part, this is because both IgM and IgG *B. burgdorferi*-specific antibody responses can persist for years or even decades after the infection has been eradicated [8, 30, 31]. Furthermore, patients can be infected multiple times [32], especially if the initial infection is promptly 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. Some individuals with no prior exposure to *B. burgdorferi* may have positive serologic tests, sometimes due to cross-reactive antibodies to other microbes or due to autoimmune disease. Because of this potential for false positive results, clinicians should be selective when ordering tests in patients with a low probability of Lyme disease.

To address these limitations, numerous nonserologic methods have been proposed or developed, including nucleic acid amplification tests, culture methods, and antigen detection assays, among others. At present, few nonserologic testing methods are useful or practical for clinical diagnosis, and those that are—primarily nucleic acid amplification tests—are mostly beneficial as adjunctive tests in select clinical scenarios when 2-tiered serologic testing is positive. This document provides guidance about when to consider ordering a nonserologic test, such as a polymerase chain reaction (PCR) assay, but providers may be faced with many options when choosing, for example, a PCR test. 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. Assessing the validity of a particular nonserologic test for Lyme disease is especially challenging because none has yet been cleared or approved by the US Food and Drug Administration (FDA). Before requesting a non-FDA-cleared test for diagnostic purposes, providers are strongly encouraged to (1) verify that the diagnostic laboratory offering the test is certified under Clinical Laboratory Improvement Amendments (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 CDC may serve as a resource for this assessment [33]. Some commercially available laboratory testing methods, including nonstandard serology interpretation, urine antigen, DNA testing, the use of a lymphocyte transformation test [34], or quantitative CD57 lymphocyte assay [35] should be avoided for clinical use due to lack of systematic, independent, reproducible validation studies [36].

Treatment of Lyme Disease

Lyme disease is treated with antimicrobials with activity against *B. burgdorferi* (see Tables 3 and 4). The goals of treatment are the eventual resolution of signs and symptoms of infection, with prevention of relapsed active infection or new complications of infection. Patients with erythema migrans are treated with 7–14 days of an appropriate antibiotic depending on which drug is prescribed; other clinical manifestations are typically treated with 14–28 days of an appropriate antibiotic with duration of treatment based on which clinical manifestation is being treated.

B. burgdorferi is susceptible to antimicrobials from several classes. The antibiotics most commonly used to treat *B. burgdorferi* infection in North America include doxycycline, amoxicillin, cefuroxime, ceftriaxone, and azithromycin. Under most circumstances, oral therapy is effective and preferred over intravenous (IV) therapy due to equivalent efficacies, better tolerability, and lower cost. However, indications for IV therapy, such as treatment of a hospitalized patient, are discussed in this guideline.

The choice of antibiotic depends on a number of factors that 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

Table 3. Drug Doses

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

Regardless of the treatment regimen, complete response to treatment may be delayed beyond the treatment duration. Relapse may occur with any of these regimens; patients with objective signs of relapse may need a second course of treatment.

[a]Doses of some beta lactam antibiotics (amoxicillin, penicillin, cefuroxime, and cefotaxime) may require adjusted dosing for patients with impaired renal function.

[b]There is increasing favorable information on the safety of short courses of doxycycline in young children, which should impact the risk to benefit ratio of using this antibiotic in patients with various manifestations of Lyme disease; see the General Principles and the individual treatment sections of this guideline for further discussion.

[c]The oral suspension of cefuroxime is currently not available in the USA.

[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.

photosensitivity skin reactions associated with doxycycline); likelihood of coinfection with *Anaplasma phagocytophilum* or *Ehrlichia muris eauclairensis* (formerly known as *Ehrlichia muris*-like agent), which, if suspected, would necessitate the use of doxycycline [9]; whether there is consideration of cellulitis versus erythema migrans in the differential diagnosis; and cost. Macrolide antibiotics, such as erythromycin and azithromycin, may have lower efficacy than other antibiotic classes and are generally considered second-line treatment options for Lyme disease in North America.

Doxycycline has traditionally been avoided in children <8 years of age, in pregnancy, and in breastfeeding women because of concern for staining of permanent teeth. This is primarily based on experience with older tetracyclines, not with

Table 4. Treatment of Specific Manifestations of Lyme Disease

Disease Manifestation	Route	Medication	Duration, days (range)[a]
Erythema migrans[b]	Oral	Doxycycline	10
		Amoxicillin or cefuroxime axetil	14
		Azithromycin[c]	7 (range: 5–10)
Meningitis or radiculopathy	Oral	Doxycycline	14–21
	IV[d]	Ceftriaxone	14–21
Cranial nerve palsy	Oral	Doxycycline	14–21
Carditis	Oral[e]	Doxycycline, amoxicillin, or cefuroxime axetil	14–21
	IV[e]	Ceftriaxone	14–21
Arthritis			
Initial treatment	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	28
Recurrent or refractory arthritis	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	28
	IV	Ceftriaxone	14[f]
Acrodermatitis chronica atrophicans	Oral	Doxycycline, amoxicillin, Or cefuroxime axetil	21–28
Borrelial lymphocytoma	Oral	Doxycycline, amoxicillin, or cefuroxime axetil	14

Abbreviation: IV, intravenous.

[a]Ranges are given where different durations have been studied, and the optimal duration remains uncertain.

[b]This recommendation applies both to solitary and multiple erythema migrans.

[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 IV agent is ceftriaxone. Cefotaxime and penicillin G are alternatives.

[e]Initial IV 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 IV therapy can be extended to 28 days if inflammation is not resolving.

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, but more data on safety would be desirable [37–41]. For some Lyme disease treatment decisions, most notably the treatment of Lyme meningitis, doxycycline is the only oral option that has been well studied. This drug was found to be effective in clinical trials, and the alternative of IV therapy has additional risks. For patients with a potentially severe beta-lactam allergy, the remaining uncertainties about doxycycline may be preferable to the dangers of rechallenge with a beta-lactam antibiotic or antibiotic desensitization. The safety of doxycycline in pregnancy and breastfeeding requires more study [42, 43], and thus the decision 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 morphologic variants of *B. burgdorferi* [44] (aka "cyst" forms), to specifically target intracellular bacteria, or to eradicate fastidious "persister" cells [45].

A minority of patients treated for early Lyme disease have a transient intensification of symptoms, with or without fever, during the first 24 hours of antibiotic therapy. This phenomenon, which may be similar to the Jarisch-Herxheimer reaction during initial treatment of syphilis, is likely an inflammatory response to a bacterial antigen load released after the initial dose of antibiotics. In patients treated for Lyme disease, this reaction is usually mild, self-limited, and does not recur later in therapy. Symptoms that arise later in the course of treatment should not be classified as Jarisch-Herxheimer-like reactions and do not signify microbial burden or have prognostic value.

Lyme disease has been successfully treated using standard treatment regimens in many different patient populations, including pregnant women, children, individuals with comorbidities, and immunocompromised patients. To date, Lyme disease in pregnancy has not been found to result in congenital infection or a syndrome of congenital abnormalities, and no additional treatment or monitoring of the mother or infant is recommended beyond the standard of care. Patients with compromised immune systems have been successfully treated for Lyme disease using regimens studied in healthy hosts [46–52]. Apart from antibiotic choice, which may need to be individualized based on allergy, intolerance, or contraindications, treatment recommendations are generally applicable to different patient populations.

Tick Bites Prevention and Prophylaxis of Lyme Disease

A human Lyme disease vaccine was briefly available in the United States 2 decades ago. Citing falling sales, the manufacturer discontinued the vaccine 3 years after the FDA approved it in 1998 [53]. In the intervening years, much more has been learned about the interactions among the Lyme disease bacterium, host immunity, and tick immunity. Such knowledge is providing opportunities to explore additional immunization strategies to prevent transmission, including anti-tick vaccines, which may result in the prevention of multiple tick-borne diseases [54]. In the absence of vaccines, the risk of Lyme disease and other tick-borne diseases can be reduced by preventing tick exposure. Therefore, knowing which tick species and life stages are vectors, and when and where they are most likely to be active, can help people avoid ticks in the first place or take proper precautions to prevent bites when in risky habitats. Additionally, prevention of tick-borne diseases involves an understanding of personal protective measures and repellents (Table 5), tick removal, the indications for antibiotic prophylaxis following a tick bite (Table 6), as well as anticipatory guidance about the signs and symptoms of a tick-borne infection. Healthcare professionals can play a very important role by increasing awareness and educating patients about ticks, tick-borne pathogens, and measures to reduce exposure, thereby increasing their confidence and likelihood to practice precautionary behaviors [55].

In North America, there are several human-biting tick species, but the blacklegged (deer) tick (*Ixodes scapularis*) and western blacklegged tick (*I. pacificus*) are the vectors for the agents of Lyme disease, *B. burgdorferi* sensu stricto (hereafter referred to as *B. burgdorferi*), and less commonly, *B. mayonii* [56], to humans [57] (Figure 2). *I. scapularis* is responsible for the overwhelming majority of *B. burgdorferi* transmission in North America [57], and therefore much of the description of factors affecting Lyme disease risk summarized below is derived from research on *I. scapularis*. Many of the findings apply to *I. pacificus*, which vectors Lyme disease in the Pacific Northwest, particularly in Northern California and Oregon, but clinicians in the western United States should refer to state health agency websites for more specific information and guidance.

For both *I. scapularis* and *I. pacificus* there are 3 postegg host-seeking (also known as questing) life stages: the larva, nymph, and adult. Importantly for Lyme disease risk assessment, not all life stages can transmit infection to people. Larvae hatch free of *B. burgdorferi* infection and therefore are not considered vectors of that pathogen [58], but if they acquire *B. burgdorferi* while

Table 5. Personal Prevention Measures

Before venturing outside	During and/or after exposure to tick habitat[b]
Personal Prevention Measures[a]	• Conduct a thorough tick check of extremities, torso, and areas where ticks may be visually obscured (eg, axilla, nape of neck, hairline, in and around ears, umbilicus, groin, popliteal fossa)
• Avoid risky habitats	• Bathe or shower within 2 hours
• Wear light-colored clothing	• Dry clothes on high heat for at least 10 minutes; if not possible, wash clothes in hot water.
• Wear long sleeves and pants	
• Tuck pants into socks or footwear	
• Wear permethrin-treated clothing	
Use an EPA-approved repellent or insecticide as per manufacturer's instructions	**If an attached tick is detected**
• DEET	• Remove properly (see Figure 5) and clean bite area https://www.cdc.gov/lyme/removal/index.html
• Picaridin	• Tip: store tick (eg, in sealed container / plastic bag; wrapped in clear tape; or taped to a piece of paper). Label with date and likely geographic location of exposure.
• IR3535	• See clinician and show tick if concerned that it is an *Ixodes* spp. and has fed at least 36 hours (Figures 2 and 6 and Table 3).
• Oil of lemon eucalyptus (OLE)	• Monitor health for symptoms of Lyme disease and other tick-borne diseases
• p-methane-3,8-diol (PMD)	
• 2-undecanone	
• Permethrin (for application to clothing and gear only)	

Abbreviations: DEET, N,N-Diethyl-meta-toluamide; EPA, Environmental Protection Agency.

[a]Tip: Have handy—fine-tipped tweezers, tick storage container, and hand sanitizer.

[b]Continue to conduct a tick check whenever possible to detect and remove feeding ticks as soon as possible.

feeding on infected reservoir hosts, such as white-footed mice (*Peromyscus leucopus*) in the eastern United States, they can then transmit it as nymphs and adults. Although both nymphs and adults can vector *B. burgdorferi*, nymphs are the main Lyme disease vectors due to their smaller size and cryptic coloration (ie, lower detection probability), greater abundance, and their seasonality that coincides with higher levels of human outdoor activity [57]. Adults are less important as vectors for 2 main reasons. First, adult male *Ixodes* spp. ticks do not attach or feed long enough to infect people [59]. Second, adult females, which are reddish and larger than nymphs, are more quickly detected and removed before they transmit the infection. Thus, the nymphal questing period poses the greatest risk. Nymphs can be active from spring through fall, but their activity peaks in late spring and summer, when most cases of Lyme disease occur [56, 57] (Figure 3). Adult ticks are primarily active in fall and spring but also in winter, when temperatures exceed 4° C [60]. Risk at these times of the year is much lower but appears to be more significant for children and older adults, who may not as readily detect and remove ticks in time to prevent transmission [61, 62].

As *I. scapularis* vectors >95% of cases of Lyme disease in North America [57], most cases occur within its geographical range, which encompasses much of the eastern United States. The distribution of Lyme disease risk, however, is not uniform and corresponds closely to the distribution of *B. burgdorferi*-infected, questing *I. scapularis* nymphs [64]. Fourteen states in the northeastern, mid-Atlantic, and north-central United States, where infected questing nymphs are abundant, consistently

Table 6. Management of a suspected *Ixodes* tick bite in the USA. [Refer to guideline recommendation number in brackets]

Do	Do Not
1. Remove tick with clean fine-tipped tweezers (or other comparable device) [I. B] (see Figure 5)	1. Do not use other nonmechanical methods for tick removal.
2. Identify tick [II. A]. Send to a laboratory, refer to an online resource, or see Figure 2	2. Do not test tick for pathogens (eg, send for PCR).
3. Determine if tick meets high-risk criteria [III] a) identified as *Ixodes* vector species b) bite occurred in a highly endemic area (see Figure 4 and consult state health data) c) attached for ≥36 hours (see Figure 6)	3. Do not initiate prophylaxis in any other scenario.
Consider initiating prophylaxis if a, b, and c are met, AND it is within 72 hours of tick removal [IV]. See dosing below[a].	

Abbreviation: PCR, polymerase chain reaction.

[a] Doxycycline is given as a single oral dose, 200 mg for adults and 4.4 mg/kg (up to a maximum dose of 200 mg) for children.

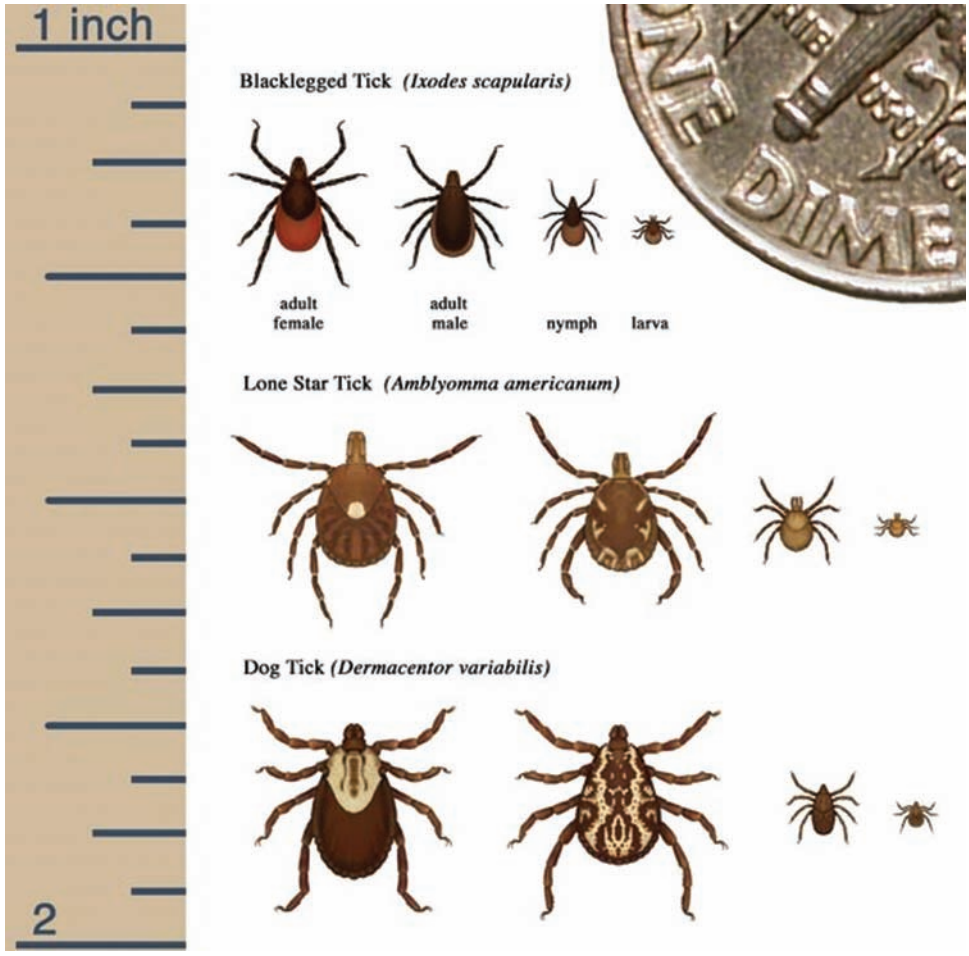

Figure 2. Dorsal view of the unfed blacklegged tick (*Ixodes scapularis*) as well as 2 other common human-biting tick. Western blacklegged tick (*I. pacificus*) looks very similar to *I. scapularis*. Four life stages and their relative sizes are shown. Note how the larva has 6 legs, whereas the other stages have 8 legs. Note how the adult female has a reddish abdomen when flat, whereas none of the other life stages do. Note how the black shield on the back of the ticks (= scutum) covers the entire back of the adult male, whereas it only extends about half-way down the back of the other stages. Both nymphs and adult *Ixodes* females can transmit infection. Because the nymphs are very small (the size of a poppy seed), they usually escape detection and therefore are responsible for the majority of cases of Lyme disease. Because the adult females are larger (the size of a sesame seed), and because they have the reddish abdomen, people often detect them before they can attach or before they can feed long enough to transmit *Borrelia burgdorferi*. Neither larval ticks nor adult males can transmit *B. burgdorferi*. Source: CDC.

account for more than 95% of all cases of Lyme disease reported to the CDC [56] (see Figure 4 and https://www.cdc.gov/lyme/datasurveillance/maps-recent.html for the most recent data). In more southern states, however, where *I. scapularis* is widely established [65], the risk of exposure to *B. burgdorferi*-infected ticks is much lower [64]. This difference in risk is due in part

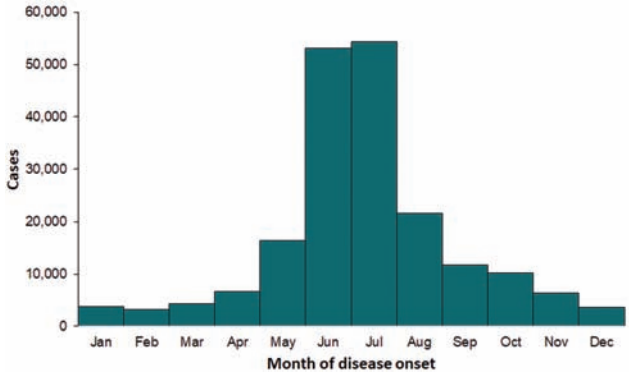

Figure 3. Lyme disease. Confirmed cases by month of disease onset, United States, 2001–2017 [63].

to negligible or extremely low prevalence of infection in both nymphs and adult *I. scapularis* [64, 66], as well as the rare tendency of southern nymphal blacklegged ticks to quest above the leaf litter and feed on reservoir hosts, in contrast to their northern counterparts [67–69]. Reports of nymphal tick bites in this region are very rare, again in contrast to reports in northern regions [70].

Over the last 3 decades, the geographic risk of exposure has expanded as northern *I. scapularis* populations have spread into new areas [65] followed by concomitant increases in tick-borne disease both in the northern [71, 72] and southern [73, 74] United States and Canada [75]. Multiple factors most likely are responsible for the ongoing emergence of *I. scapularis* and Lyme disease. Examples include changes in landscape and land use, wildlife host populations, and climate that increase the habitat and survival of tick populations, as well as increasing overlap between human and tick activity. 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). *I. scapularis* can be found in urban, suburban, and rural landscapes in a variety of habitats, although they are most abundant in or near [76] wooded areas, where wildlife hosts are ample and a sufficient layer of leaf litter reduces desiccation risk and promotes their survival [77]. The public can take several measures to minimize the environmental risk of Lyme disease, that is, the abundance of infected ticks in their yard. Options and further references can be found on the CDC website (https://www.cdc.gov/lyme/prev/index.html).

I. WHICH MEASURES SHOULD BE USED TO PREVENT TICK BITES AND TICK-BORNE INFECTIONS?

(A) Personal Protective Measures

Recommendation:

1. Individuals at risk of exposure should implement personal protective measures 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 (Table 5). 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 [57, 78–80]. Wearing light-colored clothing

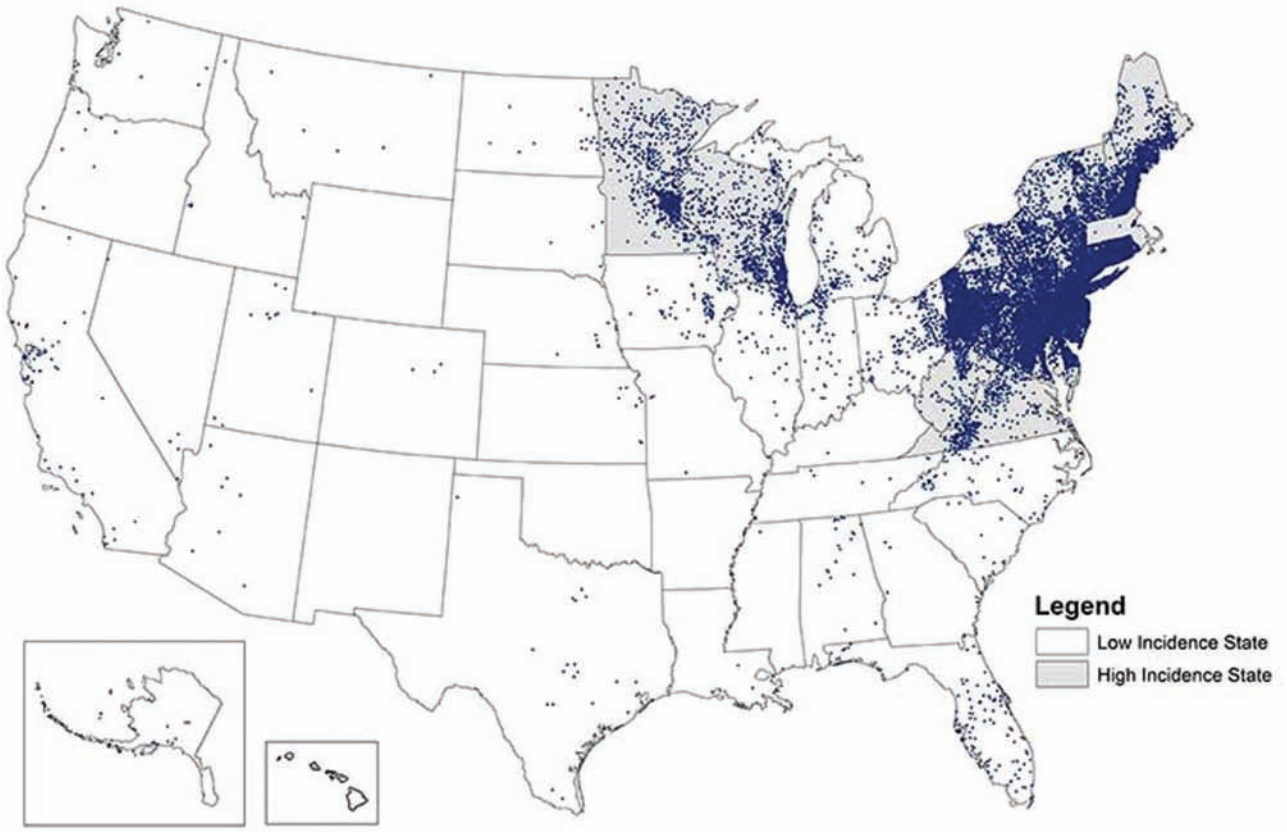

Figure 4. Reported cases of Lyme disease, United States, 2018. Incidence of confirmed Lyme disease cases (2018), by county of residence in the United States and classification of states as high, neighboring, or low Lyme disease incidence states. For the most current map, please see: https://www.cdc.gov/lyme/datasurveillance/maps-recent.html [63].

with long sleeves and long pants can make it easier to see ticks crawling on clothing before they can attach to skin. Because nymphal *I. scapularis* quest near the ground, tucking pants into socks can reduce the chances of ticks attaching to skin. Tucking pants into sock similarly may reduce tick exposure. Because *I. scapularis* may crawl on human hosts for up to several hours before attaching, a thorough tick check after being outdoors helps to find ticks before they attach. Bathing or showering within 2 hours of outdoor activity can significantly reduce the risk of Lyme disease [81]. Nymphal ticks most frequently are found attached to the legs, arms, and back [62, 76], and bathing provides a good opportunity for a thorough tick check especially in areas where visual detection of ticks may be obscured such as the axilla, nape of neck, in and around ears, umbilicus, groin, and popliteal fossa. Bathing may also wash off unattached ticks. After outdoor activities, placing clothes directly in a dryer on high heat for at least 10 minutes is highly effective for killing *I. scapularis*, though up to 60 minutes may be required for other tick species [82, 83]. Washing clothes in hot, but not cold or warm water, will also kill *I. scapularis* [82]. Because companion animals (eg, dogs and cats) that spend time outdoors may bring unattached ticks into the home, they [76] should also be checked regularly for ticks, even if they are treated with tick control products, to prevent subsequent tick attachment to humans [84]. Importantly, although there is a positive association between companion animal ownership and tick exposure, there is no direct evidence that companion animal ownership increases the risk of falling ill with a tick-borne disease.

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

Knowledge Gaps. Properly designed studies performed with human subjects under realistic conditions are required to test the efficacy of personal protection measures. Similarly, research is needed to inform how to motivate the adoption and continued use of best practice personal protection measures.

(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 (OLE), p-methane-3,8-diol (PMD), 2-undecanone, 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 (OLE), p-methane-3,8-diol (PMD, the synthetic active ingredient in oil of lemon eucalyptus), 2-undecanone, and permethrin reduced the number of ticks detected crawling on or attached to subjects compared with controls [85–90] (Table 5). Other commercially available products, including botanical agents and essential oils (eg, essential oils of rosemary, cinnamon leaf, lemongrass, geraniol [91], nootkatone, and carvacrol [92]) cannot be recommended due to insufficient evidence.

DEET, picaridin, IR3535, OLE, PMD, and 2-undecanone can be applied directly to skin and clothing. Different concentrations and preparations affect their efficacy and duration of activity. In general, products with higher concentrations provide greater and/or longer periods of efficacy compared with lower concentrations [85–90], although products containing >50% DEET [93] do not 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 pretreated, permethrin-impregnated material provide highly effective protection against tick bites [88, 94–96] and are more effective compared with clothes treated with DEET [88, 94].

To improve efficacy and safety, repellents should always be applied to targeted areas of the body and/or clothes according to the manufacturer's instructions and Environmental Protection Agency (EPA) label. Repellents should only be applied to exposed skin or clothing and should not be sprayed under clothing. Adults should supervise the application of repellents on children. The EPA has approved DEET for use on children with no age restriction. Because of a lack of safety data, however, the American Academy of Pediatrics (AAP) and the CDC only recommend DEET for infants at least 2 months of age. The AAP, CDC, and EPA do not recommend OLE and PMD for children <3 years of age. To maintain efficacy, repellents may need to be reapplied after swimming, washing, or heavy perspiration. The use of products that combine sunscreen and DEET is discouraged because frequent application of the sunscreen may exceed the recommended exposure to the repellent. Furthermore, sunscreen may increase the absorption of DEET through the skin [97]. Consequently, the FDA recommends that sunscreen be applied before DEET.

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 [98–106]. Some reported cases of encephalopathy following DEET application were likely due to improper application, an excessive dose, or unintentional ingestion [98, 99, 102]. 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 [99, 100].

Unlike the previous products, permethrin (0.5%) kills ticks on contact and must be applied to clothing and gear (eg, boots) in advance and allowed to dry prior to use. Field studies indicate that clothes sprayed with permethrin or made with pretreated, permethrin-impregnated material provide highly

effective protection against tick bites [88, 94–96] and are more effective compared with clothes treated with DEET [88, 94].

For people with frequent occupational or recreational exposure to tick habitats, a feasible option would be to wear permethrin-treated clothing and to apply a repellent to exposed skin, if additional protection were desired. For those who prefer an alternative to conventional synthetic repellents, IR3535, OLE, PMD, 2-undecanone are all considered by the EPA as biopesticides (derived from natural materials). For more information and to decide which repellent to recommend, there are resources at the websites of the EPA, CDC, and many state agencies.

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

Knowledge Gaps. Properly designed studies performed with human subjects under natural conditions are required to test the efficacy (ideally, the prevention of disease) and safety of additional options for repellents. For example, a small field study [92] indicated that clothes sprayed with natural-product based repellents (nootkatone, carvacrol, geraniol) can effectively repel ticks, but before these products can be recommended, more extensive studies are needed to confirm these results. Further studies to address the adverse effects of repellents are needed. Nonrepellent- and noninsecticide-based arthropod bite-resistant textiles are currently commercially available; these and other textiles developed in the future should be tested for effectiveness against ticks as a nonchemical-based option for prevention of tick bites.

(C) Removal of Attached Ticks

Recommendations:

1. We recommend promptly removing attached ticks by mechanical means using a clean fine-tipped 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 other heat device) 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* that occurs after 36–48 hours of attachment. Thus, performing tick checks after exposure and promptly removing any attached *Ixodes* spp. ticks is a potentially effective means to prevent Lyme disease. There are many devices available to help extract ticks, and proper removal requires grasping and pulling the mouthparts at the closest point of attachment to the skin (see Figure 5) [107–110]. The probability of transmission, however, will be reduced even if the tick inadvertently is crushed or squeezed during removal [109]. If a tick is partially removed, but detached mouthparts remain and cannot easily be removed from the skin, they should be left alone and permitted to fall out. Nonmechanical means of tick removal, such as applying chemicals, petroleum products, or heat may cause the tick to regurgitate and potentially increase the risk of pathogen transmission.

In animal laboratory experiments, the probability of *B. burgdorferi* transmission increases the longer the tick has been attached and feeding. In 4 studies in which laboratory animals each were exposed to a single infected *I. scapularis* nymph, no transmission occurred within 24 hours, and the majority of animals became infected ≥48 hours of attachment [109, 112–115]. A mathematical model [114] applied to the combined data from two experiments [113, 114] further estimated that infection did not occur before 36–40 hours of attachment, and that 50% of infected nymphs transmitted *B. burgdorferi* by 68 hours of attachment. The transmission of *B. mayonii* to laboratory animals using single infected nymphs occurred after 48 hours of attachment [112, 116].

Early studies had documented rare transmission of *B. burgdorferi* <24 hours and within 24–37 hours of tick attachment [115, 117, 118]. In these studies, however, multiple infected *I. scapularis* nymphs were simultaneously placed on laboratory animals, a scenario that is relevant for enzootic transmission to

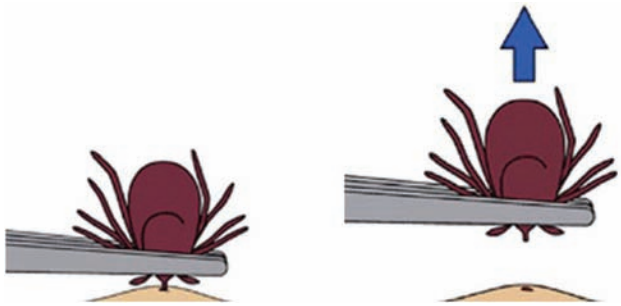

Figure 5. Proper tick removal [111]. Proper removal requires grasping and pulling the mouthparts at the closest point of attachment to the skin.

animals but less so for transmission to humans [112]. Even in these studies, however, infection within the first 24 hours of tick attachment is not guaranteed [112]. Transmission to mice exposed to multiple infected *I. pacificus* nymphs did not occur <24 hours of feeding but was detected by 48 hours of feeding [119]. Similarly, when multiple infected adult female *I. scapularis* were fed simultaneously on animals, no transmission was detected at 24 or 36 hours of attachment but only at 48 hours [120].

For prevention of tick-borne diseases, it is important to remember that other pathogens vectored by *Ixodes* spp. ticks may require less attachment time to infect a host. For animals exposed to a single infected tick, Powassan virus may be transmitted within 15 minutes of attachment [121] and *Anaplasma phagocytophilum* [113] and *B. miyamotoi* [122] within 24 hours. For *Babesia microti*, the only study that used single infected ticks did not measure transmission at time points prior to 54 hours, by which time 72% of animals were infected [123]. Although a study where animals were exposed to multiple infected ticks detected transmission of *B. microti* by 36 hours, transmission primarily occurred after 48 hours of attachment [124].

Observations from 2 European epidemiological studies in which tick engorgement levels were measured suggest that transmission of *B. burgdorferi* sensu lato may occur within 24 hours of attachment of *I. ricinis* ticks [125, 126]. It is unclear whether differences in the tick or *Borrelia* species may be responsible for the faster transmission rate. Travel history therefore may further inform anticipatory guidance.

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.

II. WHICH DIAGNOSTIC TESTS SHOULD BE USED FOLLOWING A TICK BITE?

(A) Diagnostic Tick Testing

Recommendations:

1. We recommend submitting the removed tick for species identification *(good practice statement).*
2. We recommend against testing a removed *Ixodes* tick for *B. burgdorferi (strong recommendation, moderate-quality evidence).* **Comment:** The presence or absence of *B. burgdorferi* in an *Ixodes* tick removed from a person does not reliably predict the likelihood of clinical infection.

Summary of The Evidence. Knowing tick characteristics (ie, species, life stage, and an assessment of the degree of blood engorgement) is helpful for anticipatory guidance and in determining if antibiotic prophylaxis to prevent Lyme disease is appropriate [127]. Tick identification is available in most commercial laboratories and at some local health departments. Studies from the United States and Europe have shown that detecting *B. burgdorferi* sensu lato in *Ixodes* spp. ticks, however, poorly predicts either subsequent disease (0–12.4%) [126, 128–133] or asymptomatic seroconversion (0–4.7%) [126, 129, 130, 132, 134]. This is likely due to a variety of factors that influence the likelihood of transmission and the observation that most *Ixodes* spp. ticks discovered by patients have been attached for <48 hours [61, 62, 135].

Rationale for Recommendation. Because different tick species transmit different pathogens, tick identification by a qualified expert or laboratory would inform patient counseling about early signs of Lyme disease and other tick-borne diseases. Patients should be given anticipatory guidance so that a prompt diagnosis of Lyme disease (as well as other relevant tick-borne infections) can be made should symptoms develop. In contrast, testing ticks for *B. burgdorferi* may lead to unnecessary antibiotic prescriptions in patients who would not go on to develop Lyme disease. Even in areas that are highly endemic for Lyme disease, where >20% of nymphal ticks and >50% of adult ticks are infected with *B. burgdorferi*, mathematical models estimate that individuals presenting with an *Ixodes* spp. tick bite have a low probability of developing Lyme disease (2.5–4.6% [113, 114];), even if the tick tests positive.

Knowledge Gaps. Education about tick identification and estimates of engorgement levels would help treatment decisions and anticipatory guidance, especially as different tick species transmit different pathogens. Development of technical aides (eg, smartphone applications) to provide image-based identification services may further facilitate timely and accurate tick identification and even estimates of feeding duration. Such information may also help physicians learn about the local tick species. Studies are 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* spp. tick bite *(strong recommendation, moderate-quality evidence).*

Summary of The Evidence. Following the removal of an *Ixodes* spp. tick, asymptomatic patients would 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 [136] and is now even higher, even doubled, in some Lyme disease endemic regions [137, 138]. Although follow-up testing

4–6 weeks after the tick bite could detect an asymptomatic seroconversion, we recommend against testing as there is insufficient evidence that patients with asymptomatic seropositivity should receive antibiotic therapy.

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 are untreated patients with erythema migrans [139–141]. Moreover, a positive serologic test for Lyme disease near the time of a tick bite most likely represents past exposure or a false positive, as a newly acquired infection would not yet have prompted antibody generation.

Knowledge Gaps. Longitudinal studies are needed to better understand the long-term outcomes of tick bites in seropositive patients who are asymptomatic.

III. WHO SHOULD RECEIVE ANTIBIOTIC PROPHYLAXIS TO PREVENT LYME DISEASE FOLLOWING PRESENTATION WITH A TICK BITE?

Recommendation:

1. We recommend that prophylactic antibiotic therapy be 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 risk or low risk *(strong recommendation, high-quality evidence).* **Comment**: If a tick bite cannot be classified with a high level of certainty as a high-risk bite, a wait-and-watch approach is recommended. A tick bite is considered to be high-risk only if it meets the following 3 criteria: the tick bite was from (a) an identified *Ixodes spp.* vector species, (b) it occurred in a highly endemic area, and (c) the tick was attached for ≥36 hours.

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 *Ixodes* spp. ticks in the region of exposure [142]. In highly endemic areas of the northeastern, the middle Atlantic, and the north-central United States, nymphal *I. scapularis* infection prevalence exceeds 20% [64, 66, 143]. Using reported Lyme disease incidence data, the CDC classifies states as i) high incidence, ii) neighboring high incidence states (and thus with presumed elevated risk), and iii) low incidence [56] (for the most recent maps and data, see: https://www.cdc.gov/lyme/datasurveillance/maps-recent.html). As a caveat, within a low-incidence state, some areas can be highly endemic for *B. burgdorferi* [64, 143] and Lyme disease [72, 74]; conversely, within a high incidence state, there are areas with lower levels of infection prevalence [143]. Similarly, because the infection prevalence among *I. pacificus* ticks often is <20% [66, 144], their bites generally are not considered high-risk, but some areas with >20% nymphal infection prevalence exist [144, 145]. To determine whether an *Ixodes* spp. tick bite comes from a highly endemic area, clinicians should consult state health agency Lyme disease risk maps depicting tick infection prevalence, if available.

As discussed earlier, the duration of tick attachment (see Figure 6) is among the most important predictors of subsequent Lyme disease. Unfed (ie, flat) and recently attached 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 as the majority of transmission occurs after 36–48 hours of attachment [109, 113–115, 117]. Clinical studies [133, 146] 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 [133]. A meta-analysis of 4 studies [147] 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 a brief duration of tick attachment (ie, <36 hours) or exposure in regions with low Lyme disease incidence, the absolute risk of Lyme disease will be decreased, and therefore the benefit of prophylactic antibiotics will be decreased 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 an *Ixodes* spp. vector species or are *Ixodes* spp. but do not meet high-risk criteria, the risk of adverse reactions from antibiotic exposure may not be matched by a likely benefit. 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 local *Ixodes* spp.-borne infections. First, prophylaxis with doxycycline does not guarantee infection avoidance. For instance, data from a laboratory animal study [149] suggest that mitigation of transmission by oral doxycycline is most successful when taken soon after tick removal. Thus, patients should be advised to seek medical attention if they

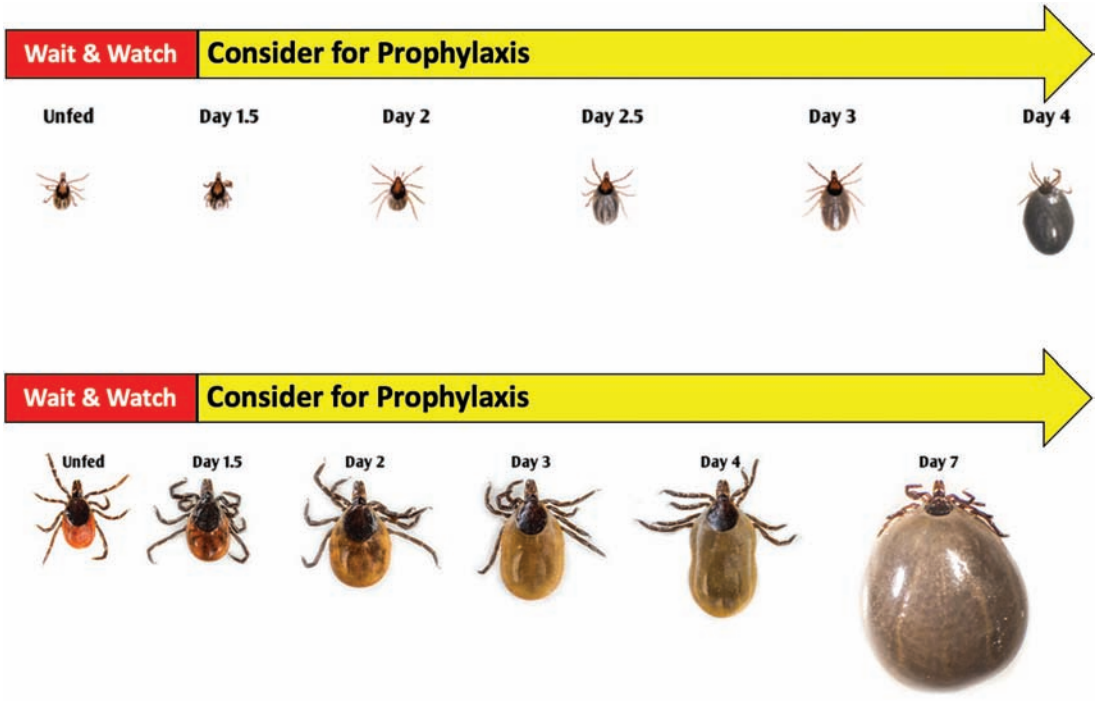

Figure 6. Relative sizes of engorging nymphal and adult female *Ixodes scapularis* (blacklegged = deer tick) as a function of time spent feeding (= attachment time). Transmission of *Borrelia burgdorferi* requires 36–48 hours of feeding [101], and therefore antibiotic prophylaxis is recommended only if the tick has been attached for at least 36 hours, or 1.5 days [148]. By itself, duration of feeding is insufficient for recommending antibiotic prophylaxis; see Figure 7 for the complete list of criteria needed to determine whether a tick bite is a high risk tick bite. *A*,Nymphs (Feeding time: Unfed = 0 hrs; Day 1.5 = 36 hrs; Day 2 = 48 hrs; Day 2.5 = 60 hrs; Day 3 = 72 hrs; Day 4 = 96 hrs). *B*, Adult females over the same time period. Unfed nymph and adult female are the sizes of poppy and sesame seeds, respectively. Not actual size. (Source: https://tickencounter.org/tick_identification/tick_growth_comparison, accessed 11/22/19.)

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. Second, *I. scapularis* ticks may transmit pathogens causing other diseases, including anaplasmosis, babesiosis, and ehrlichiosis, for which systematic data supporting postexposure antibiotic prophylaxis currently do not exist.

Knowledge Gaps. A limitation of this recommendation is the reliable and timely determination of a tick bite as a high-risk tick bite. Accurate identification of a tick species may be challenging, especially as the tick feeds. The determination of the timing of the bite by history is often unreliable [62, 133]. An examination of the scutal index (a measure of engorgement used to estimate the duration of attachment) of *Ixodes* spp. ticks attached to patients in a highly endemic region over 17 years found that >40% did not meet the high-risk criteria [127]. Prescription of an antibiotic would not be indicated for these bites. Thus, research is needed to develop methods to deliver reliable and timely information about the tick bite to the clinician, including the feasibility of training laboratory personnel in the measurement of the scutal index and the development and testing of point-of-care technical aides for tick identification and measurement of engorgement levels. The ability to accurately identify tick species and engorgement level will likely become even more significant in the future as blacklegged tick populations expand, and as the geographic distributions of blacklegged and other tick species increasingly overlap.

Infection prevalence, as well as strain diversity, of *B. burgdorferi* among *I. scapularis* ticks can be locally and regionally variable [64, 66, 143, 150, 151]. 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 [56, 64, 65]. Through their Tick Surveillance Program, the CDC provides guidance and support to public health agencies for conducting active surveillance for *Ixodes* spp. tick and associated pathogens to provide accurate and current data for healthcare providers on the local risk of Lyme and other diseases [152]. Resources are needed, however, for such surveillance to be conducted on a regular and spatially relevant basis. Clinical studies to evaluate the utility of chemoprophylaxis to prevent other *I. scapularis*-borne pathogens 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* spp. bites in all age groups, 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:** Doxycycline is given as a single oral dose, 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, are included for review (see Evidence Profile Tables IV) [147]. Most of the included trials recruited both adults and children; 1 trial recruited only children [153]. Two potential dosing alternatives have been studied in this setting: a single dose of doxycycline (200 mg × 1 dose) [146] and 10-day course of other antibiotics (tetracycline [1000 mg/day] [153], penicillin [1000 mg/day] [129], and amoxicillin [750 mg/day]) [132]. 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 [RR]: 0.27, 95% confidence interval [CI] (.10, .75); absolute risk: 22 fewer per 1000, 95% CI (7 to 27 fewer per 1000)). 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. The doxycycline single-dose regimen is preferred due to its efficacy, ease of use, and a relatively low risk of side effects (see Introduction to Treatment for a more detailed discussion). Single doses of other 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 may have been due to insufficient enrollment of subjects in these studies. There is currently insufficient evidence to recommend topical antibiotics to prevent Lyme disease [154, 155]. Despite the paucity of pediatric data, it is prudent to extrapolate the use of single-dose prophylaxis to children because the risk of adverse effects likely would be the same as in persons older than 12 years of age. The caveat that there is no study of the efficacy of doxycycline under age 12 years should be provided to the parent, so they understand that monitoring for symptoms and signs is still important.

Knowledge Gaps. 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 necessary to assess whether topical antibiotics can prevent Lyme disease.

Early 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 [12, 156–158] (see Figure 7). Erythema migrans occurs at the site of inoculation of *B. burgdorferi* into the skin by the bite of an infected *Ixodes* tick. Patients with erythema migrans may have concomitant constitutional symptoms (~65% in the US and ~37% in Europe), such as fatigue, arthralgias, myalgias, and headache [12, 156–158]. After deposition into the skin, the spirochetal bacteria may disseminate in untreated patients to other anatomic sites leading to regional lymphadenopathy, additional erythema migrans skin lesions, certain neurologic and cardiac manifestations, and/or arthritis [156, 158].

V. WHAT IS THE PREFERRED DIAGNOSTIC TESTING STRATEGY FOR ERYTHEMA MIGRANS?

Recommendations:

1. In patients with potential tick exposure in a Lyme disease endemic area who have 1 or more skin lesions compatible with erythema migrans, we recommend clinical diagnosis rather than laboratory testing *(strong recommendation, moderate-quality evidence).*
2. In patients with 1 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 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.

Figure 7. Early Lyme rash.

Summary of The Evidence. Most patients with a single erythema migrans skin lesion are seronegative at the time of initial presentation. Among untreated patients with microbiologically confirmed, solitary erythema migrans lesions, as few as 20% are seropositive using conventional 2-tiered antibody testing (enzyme-linked immunosorbent assay [ELISA] or indirect fluorescent antibody testing, followed by immunoblotting) performed on an acute-phase serum sample collected within 1 week of noticing the lesion [29, 159, 160]. Acute-phase sensitivity is comparatively higher if the lesion has been present for a longer time period without treatment [29, 159, 161], reaching 86% in the 4th week of illness [159] or in patients presenting with multiple erythema migrans skin lesions [21, 159, 162].

In a study directly comparing antibody testing with various direct detection methods in patients with a clinical diagnosis of solitary or multiple erythema migrans skin lesions (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%) [163]. The least sensitive method was conventional 2-tiered antibody testing performed on acute-phase serum samples (40.4%). Intermediate sensitivity was demonstrated using culture of 2 mm 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 [164, 165].

Studies involving skin biopsy culture of untreated erythema migrans lesions have typically reported a diagnostic sensitivity of approximately 40–60% [163, 165–174] with some reporting lower yield [175–178] and a few reporting sensitivity exceeding 70% [179–182]. 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 [163, 165, 167, 169, 171–177]. 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 mostly in the 30–50% range in the United States [165, 175, 183–185], although substantially lower yields have been reported [186, 187]. PCR sensitivity varies according to the specific technique, and the application of multiple PCR assays to the same sample can improve sensitivity [165].

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 [188]. In such cases, if the patient will not be treated empirically with antimicrobial therapy, the most practical approach is to perform serologic testing on an acute-phase serum sample or (if initial results are negative) 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 more timely diagnosis; 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 (described below) limit their use and availability; recognition of these limitations has informed our testing recommendations.

The most potentially useful direct detection method is real-time PCR for *B. burgdorferi* performed on a skin punch biopsy of at least 2-mm diameter, taken from the margin of the skin lesion. This method offers higher sensitivity compared with other direct detection or serologic testing methods, and turnaround time can be relatively short. However, the need for a skin biopsy is a limiting factor because many primary or urgent care settings may not offer this procedure, requiring referral to a dermatologist. Furthermore, real-time PCR for *B. burgdorferi* is not standardized and is typically available only at large reference laboratories, in part because currently there are no FDA-cleared molecular assays. Shipping samples to a reference laboratory increases turnaround time, often by several days.

Culture of skin biopsy samples or high-volume plasma samples may approach the sensitivity of skin PCR, but *B. burgdorferi* culture is rarely available, even at large referral centers. In addition, cultures require long incubation periods, sometimes exceeding 8 weeks. The use of *B. burgdorferi* PCR directly on blood samples is substantially less sensitive compared with PCR performed on skin lesion samples.

VI. WHAT ARE THE PREFERRED ANTIBIOTIC REGIMENS FOR THE TREATMENT OF ERYTHEMA MIGRANS?

Recommendation:

1. For patients with erythema migrans, we recommend using oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil *(strong recommendation, moderate-quality evidence).* **Comment:** For patients unable to take both doxycycline and beta-lactam antibiotics, the preferred second-line agent is azithromycin.

Summary of Evidence. Evidence for this recommendation is based on both US and European studies, because the *Borrelia* species involved in both locations are similarly susceptible to antimicrobials in in vitro studies [189, 190]. Although erythema migrans 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

(eg, Lyme arthritis) [140, 191, 192]. Based on clinical trial data and on in vitro susceptibility testing data, the 3 widely used oral antibiotics in North America, doxycycline, amoxicillin, or cefuroxime axetil, appear to have similar efficacy for the treatment of patients with erythema migrans (see Evidence Profile Tables VI) [193–202]. Clinical experience and clinical trial data in Europe exclusively suggest comparable clinical efficacy of penicillin VK compared with amoxicillin or doxycycline, although more clarity on the optimal dosage would be desirable [193].

Azithromycin has been found to be effective clinically and of comparable efficacy to comparators for patients with erythema migrans in all clinical trials conducted to date except for 1 (see Evidence Profile Tables VI) [3, 194, 203–209]. The explanation for the worse outcomes reported in 1 trial comparing azithromycin with amoxicillin conducted in the United States is unclear [3]. This trial was a randomized, double-blind study, and no similar study on the efficacy of azithromycin for erythema migrans has been conducted subsequently in the United States. Methodologic issues may explain the differences in results, particularly because 14% of the enrolled subjects may have had the southern tick-associated rash illness (STARI) rather than Lyme disease [210]. 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 [3]. Because of results from that study, however, azithromycin is often considered to be a second-line agent in North America to be used for patients who cannot safely take beta-lactam or tetracycline antibiotics [156, 158].

For patients with suspicion of early Lyme disease presenting as an acute febrile illness without an erythema migrans skin lesion, the same antibiotic regimens as used for patients with erythema migrans should be effective, but there is a lack of systematic studies to support this opinion.

Rationale for Recommendation. Given the comparable efficacy of doxycycline, amoxicillin, and cefuroxime axetil, factors [200] other than efficacy should be considered in the selection of which oral antibiotic to prescribe for the treatment of patients in North America with erythema migrans (see Table 5). Although the AAP recommends doxycycline, amoxicillin, or cefuroxime axetil for the treatment of erythema migrans in children of any age, some clinicians would reserve doxycycline for young children who are unable to tolerate beta-lactam antibiotics given the limited evidence basis for its safety [211, 212]. The decision to use doxycycline to treat erythema migrans in young children, pregnant women [42, 43] and breastfeeding women who wish to continue breastfeeding and have no contraindication to beta-lactam antibiotics should be individualized and made with careful deliberation (also see also the Treatment of Lyme Disease discussion in the General Principle section above).

Knowledge Gaps. Additional studies conducted in the United States on the efficacy of penicillin VK, azithromycin, and clarithromycin [213, 214] for treating patients with erythema migrans, and studies comparing twice daily with 3 times daily dosing of amoxicillin are warranted. Additional studies should be performed to better define the optimal dose of penicillin VK. Studies on how to properly diagnose and treat patients with early Lyme disease presenting as an acute febrile illness without erythema migrans should be performed. 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 ERYTHEMA MIGRANS BE TREATED?

Recommendation:

1. We recommend that patients with erythema migrans be treated with either a 10-day course of doxycycline or a 14-day course of amoxicillin or cefuroxime axetil rather than longer treatment courses *(strong recommendation, moderate-quality evidence).* **Comment:** If azithromycin is used, the indicated duration is 5–10 days, with a 7-day course preferred in the United States, as this duration of therapy was used in the largest clinical trial performed in the United States [3].

Summary of Evidence. Different durations of antibiotic therapy with doxycycline or beta-lactam antibiotics have been evaluated in the treatment of patients with erythema migrans ranging from a 5-day course of therapy to 21 days (See Evidence Profile Tables VII) [3, 46, 47, 156, 157, 191, 193–199, 202–209, 214–229]. Duration of treatment with azithromycin in clinical studies has varied from 5 to 10 days [3, 203–209]. Typically, the 5-day regimens have included 6 doses, with 2 doses taken on day 1. No difference in outcomes has been associated with the 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 erythema migrans showed equivalent efficacy of 10 days compared with 20 days of doxycycline therapy [222]. Another prospective study showed similar efficacy of 10 days compared with 15 days of doxycycline for patients with erythema migrans [221]. The shorter course of azithromycin therapy is indicated because the drug has a prolonged tissue half-life.

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

VIII. SHOULD PATIENTS WITH THE SOUTHERN TICK-ASSOCIATED RASH ILLNESS (STARI) BE TREATED WITH ANTIBIOTICS?

Recommendation:

1. In patients who develop an erythema migrans-like skin lesion following the bite of the lone star tick (*Amblyomma*

americanum), an illness referred to as 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 [4]. Distinguishing single erythema migrans due to Lyme disease from STARI may not be possible clinically unless the responsible tick has been identified [5]. When STARI cannot be distinguished from Lyme disease-associated erythema migrans in areas endemic for both conditions, antibiotic therapy directed toward 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* [230–234]. To date, no infectious agent has been identified in STARI patients [210, 235–239], except in 1 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 [240]. Recent data suggest that STARI and Lyme disease-associated erythema migrans produce different host metabolic biosignatures [241]. There are no known extracutaneous sequelae associated with STARI, though few untreated patient case histories have been reported [242]. 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 nonendemic and there are abundant lone star ticks, physicians and patients may choose observation rather than antibiotic treatment for erythema migrans [4, 242]. 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 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.

Knowledge Gaps. 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) in 2 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, Lyme neuroborreliosis can be divided into early and late manifestations. Early Lyme neuroborreliosis includes meningitis, cranial neuritis, radiculoneuritis, and more rarely encephalomyelitis, typically has an onset over hours to days, and occurs in the first few months of infection. Later in infection, Lyme neuroborreliosis may similarly involve the PNS or CNS but have a more indolent evolution. Pathophysiologically, there is probably little difference between early and late Lyme neuroborreliosis.

IX. WHAT IS THE PREFERRED DIAGNOSTIC TESTING STRATEGY FOR LYME NEUROBORRELIOSIS?

Recommendations:

1. When assessing patients for possible Lyme neuroborreliosis involving either the PNS or CNS, we recommend serum antibody testing rather than PCR or culture of either CSF or serum *(strong recommendation, moderate-quality 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 routine PCR or culture of CSF or serum *(strong recommendation, moderate-quality evidence).*

Summary of The Evidence. Several studies have demonstrated that most patients with early Lyme neuroborreliosis are seropositive by conventional 2-tiered testing at the time of initial clinical presentation [21, 162, 243–245]. 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 [245]. 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 2-tiered testing protocols (see Diagnostic Testing discussion in the General Principles section) [246–249]. 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 [6, 250, 251]. Notably, active CNS (but not necessarily PNS) Lyme neuroborreliosis is usually accompanied by a CSF lymphocytic/monocytic pleocytosis, supporting a diagnosis of active CNS infection. Diagnostic sensitivity of the antibody index in US patients with Lyme meningitis exceeded 85% in 2 small studies [252, 253], 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% [254–256]. European studies suggest that in rare patients, the CSF:serum index may be positive before peripheral blood serology is positive. 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 indicated outside the research setting to evaluate for intrathecal antibody production [147, 257].

Direct detection of *B. burgdorferi* in CSF, by PCR or culture, is usually not possible in patients with Lyme neuroborreliosis. A meta-analysis including both US 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 [258]. In a study of US patients with Lyme meningitis, PCR sensitivity was only 5% [259]. As with CSF PCR, the sensitivity of CSF culture is poor [260, 261].

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 [260, 262, 263]. CXCL13, a chemokine, has been proposed as a biomarker for Lyme neuroborreliosis. Elevated levels of CSF CXCL13 correlate well with intrathecal *B. burgdorferi*-specific antibody responses in patients with acute Lyme meningitis [264–268]. However, CSF CXCL13 concentrations may be elevated in numerous other infectious, inflammatory, and neoplastic conditions [265–274]. Studies to date have used different threshold concentrations to define significantly elevated CSF CXCL13 levels. As standardized upper limits and interpretive criteria remain to be definitively determined, clinical performance characteristics are unclear. Notably, CSF CXCL13 concentration can fall rapidly with effective treatment; although 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 and may rarely be elevated in early disease before peripheral blood serology is positive. A normal antibody index value, however, does not exclude the diagnosis. Measurement of CXCL13 has not been sufficiently studied or standardized to recommend at present.

Knowledge Gaps. Adequately powered studies of US patients are needed to determine the performance characteristics of CSF:serum antibody index determinations and to standardize this testing, particularly because different methodologies use different thresholds to define positive and negative. Additional research is needed to determine the diagnostic value of CSF CXCL13 and, if useful, to determine an appropriate threshold above which values are considered informative for clinical diagnostic purposes.

CSF Examination in the Management of Patients Suspected of Lyme Neuroborreliosis

The recommended treatment for neuroborreliosis may be the same whether meningitis is present or not, so the decision to perform a CSF examination must be individualized. CSF examination in patients with suspected neuroborreliosis can serve 4 purposes. First, if meningitis is suspected, it permits the exclusion of bacterial, viral, or other etiologies, besides Lyme neuroborreliosis. Second, if a CSF pleocytosis (typically lymphocytic or monocytic) [274] is evident, it provides a metric for treatment efficacy. Because 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. Third, it permits a more definitive diagnosis of CNS neuroborreliosis (although CSF may be normal if neuroborreliosis is limited to the PNS), particularly when there is parenchymal brain or spinal fluid inflammation and if intrathecal antibody production is present. Fourth, because Lyme disease, particularly in children, can be associated with a pseudotumor-like picture [275], even in the absence of other signs or symptoms of meningitis, it permits assessment for raised intracranial pressure (ICP).

X. FOR WHICH NEUROLOGICAL PRESENTATIONS SHOULD PATIENTS BE TESTED FOR LYME DISEASE?

Recommendations:

1. In patients presenting with 1 or more of the following acute disorders: meningitis, painful radiculoneuritis, mononeuropathy multiplex including confluent mononeuropathy multiplex,

acute cranial neuropathies (particularly VII, VIII, less commonly III, V, VI, and others), or in patients with evidence of spinal cord (or rarely brain) inflammation, the former particularly in association with painful radiculitis involving related spinal cord segments, 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 suggest 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 facial (VIIth) cranial nerve is the most common, involvement of the nerves to the extraocular muscles, the trigeminal (Vth) nerve and occasionally the acousticovestibular (VIIIth) nerve [276] occur as well.

The few systematic studies that have been performed have failed to identify consistent associations between Lyme disease and amyotrophic lateral sclerosis [277–279], multiple sclerosis [280, 281], Alzheimer's disease [282], or Parkinson's disease [277–279]. Seizures appear to be quite uncommon in Lyme neuroborreliosis. Although some early studies in hyperendemic regions supported an association between ALS and serologic evidence of exposure to *B. burgdorferi* [283–285], subsequent studies have not confirmed this observation [286, 287].

Radiographic white matter changes have been described in numerous case series. The largest systematic study of brain imaging in patients with confirmed Lyme neuroborreliosis found rare patients with contrast enhancing parenchymal abnormalities, but nonspecific white matter abnormalities were no more common than in controls [288].

Rationale for Recommendation. These recommendations place a high value on avoiding false positive Lyme disease test results, which can delay appropriate medical evaluation 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—that is, without a history of tick bite, erythema migrans, or other more typical manifestations, would result in far more false positive than true positive results [289].

On the other hand, the a priori likelihood of Lyme (vs enteroviral) meningitis can be enhanced, particularly in children, by consideration of several clinical features. Lyme meningitis is measurably more likely with the co-occurrence of facial nerve palsy, symptoms of longer duration (>7 days), and mononuclear cell predominant CSF pleocytosis [290–292].

Lyme disease can very rarely cause focal inflammation in the brain or spinal cord (ie, 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 nonspecific T2 white matter hyperintensities are not generally useful to diagnose Lyme neuroborreliosis. Misattribution of these to Lyme disease could lead to overuse of antibiotics with underemphasis on treatable vascular risk factors.

Knowledge Gaps. 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.

XI. SHOULD ADULT PATIENTS WITH PSYCHIATRIC ILLNESSES BE TESTED FOR LYME DISEASE?

Recommendation:

1. In patients with psychiatric illness, we recommend against routine 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 [293–296]. There is no controlled prospective evidence that treatment for Lyme disease is effective for any specific psychiatric disease. Although 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. Although 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.

XII. 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, pediatric autoimmune and neuropsychiatric disorders associated with streptococcal infections [PANDAS], learning disabilities, or psychiatric disorders), and 2 studies have shown no association between Lyme disease and autism spectrum disorders [188, 297, 298]. 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 pretest probability (prevalence) of Lyme disease in this population, testing all such children in the absence of more specific signs of Lyme disease 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.

XIII. 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 IV ceftriaxone, cefotaxime, penicillin G, 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 such as side effect profile, ease of administration, ability to tolerate oral medication, concerns about compliance unrelated to effectiveness. Treatment route may be changed from IV to oral during treatment. The preferred antibiotic duration is 14–21 days.

Summary of The Evidence. Treatment of Lyme disease-associated meningitis is effective using IV cefotaxime or ceftriaxone, meningeal dose IV penicillin, or oral doxycycline, with no statistically significant differences in either response rate or relative risk of adverse effects (see Evidence Profile Tables XIII). In 2 studies, 14-day courses of oral doxycycline (200 mg/day), IV penicillin, and IV ceftriaxone were equally effective [299, 300]. Although adverse effects were more frequent with IV treatment, relative risk (RR) confidence intervals (CIs) were broad (RR IV vs PO 1.29 [95% CI .83–2.01]). In most studies, 14-day courses of treatment have proven highly efficacious. Although some studies have used 21 days, none directly compare the efficacy of 14 versus 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 Lyme neuroborreliosis patients with 100 days of oral amoxicillin [301] following 3 weeks of IV ceftriaxone did not improve response (RR with vs without 100 days 1.06 [95% CI .89–1.25]) but significantly increased the incidence of adverse effects (RR 3.70 [95% CI 1.29–10.61]).

Studies comparing the efficacy of oral and IV 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, B. garinii* and more recently *B. bavariensis*) differ from *B. burgdorferi* sensu stricto, the strain responsible for Lyme disease in the United States, antimicrobial sensitivities are generally identical, and antibiotic pharmacokinetics should not differ. Other than small case series [302] and unpublished observations, no high-quality studies have addressed this in US patients, potentially diminishing the generalizability 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 the risks associated with IV catheters [39], 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.

Although evidence supports the use of oral doxycycline in patients with nervous system Lyme disease, prior to confirmation of this diagnosis, patients may require an initial IV regimen that empirically covers other bacterial and viral pathogens (see guidelines for management of bacterial meningitis and encephalitis [303]). Once these alternative diagnoses are excluded, or the diagnosis of Lyme neuroborreliosis is confirmed, treatment with oral doxycycline may be considered. Although other oral antibiotics have not been assessed directly, analysis of the incidence of Lyme neuroborreliosis after treatment of patients with erythema migrans with cefuroxime axetil, amoxicillin, or azithromycin raises the possibility that these agents might be effective [200].

Knowledge Gaps. A study confirming the therapeutic equivalence of oral and IV treatment in North American adult and pediatric patients is needed.

XIV. SHOULD PATIENTS WITH LYME DISEASE-RELATED PARENCHYMAL INVOLVEMENT OF THE BRAIN OR SPINAL CORD BE TREATED WITH ORAL OR INTRAVENOUS ANTIBIOTICS?

Recommendation:

1. In patients with Lyme disease-associated parenchymal involvement of the brain or spinal cord, we recommend using IV 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, IV antibiotics with good CNS penetration are recommended. Given the rarity of this disorder, it is unlikely the question will be amenable to systematic study.

XV. 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 [6].

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 [6, 304]. Although some studies in Lyme disease-associated facial nerve palsy suggest benefit [250], others raise the possibility of harm [305]; this body of research is small and methodologically limited [250, 251, 306]. Although theoretical concerns about the potential immunosuppressive effects of corticosteroids in infections are quite understandable, no well-controlled, prospective studies address this question in Lyme neuroborreliosis. As the diagnosis of Lyme neuroborreliosis may not be obvious at the time of presentation with a facial nerve palsy and because corticosteroids are most effective in idiopathic facial nerve palsy if administered within the first 72 hours after onset, corticosteroids should be instituted immediately in patients in whom the diagnosis of Lyme disease is uncertain. When the diagnosis of Lyme disease becomes apparent, the decision to stop corticosteroids that have already been started, or to start them in a patient initially presenting with acute Lyme disease-associated facial palsy, is a matter of patient preference and clinical judgment.

Rationale for Recommendation. Corticosteroids are recommended in the absence of an established diagnosis of Lyme disease because of their benefit in idiopathic facial nerve palsy and because their effect in Lyme disease is unknown. The failure to initiate corticosteroids in timely fashion prior to obtaining results from Lyme disease testing could potentially harm patients with idiopathic facial nerve palsy.

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

Reduction of Intracranial Pressure in Patients With Lyme Disease

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. Because herniation has never been reported in Lyme neuroborreliosis, the risk in these circumstances is presumably related to other diagnoses under consideration. Lyme neuroborreliosis has been associated with raised intracranial pressure, which can

compromise vision. All but 2 of the reported cases have been in children [307, 308]. Although data in Lyme disease are only anecdotal, as in all other circumstances, raised intracranial pressure with papilledema should be treated with techniques to lower intracranial pressure to prevent visual loss, regardless of etiology.

Lyme Carditis

Lyme carditis is a manifestation of early disseminated infection with *B. burgdorferi* and typically occurs within several days to about a month (average 21 days) after the initial illness/infection, most often in the summer and fall [192, 309, 310]. Initial studies suggested that 4–10% of untreated patients developed carditis [311, 312], though more recent data indicate that this number may be significantly lower [310, 313]. Epidemiologic studies suggest that only about 40% of patients with Lyme carditis recall the characteristic erythema migrans skin lesion [310]. Peak incidence is seen in childhood and middle age [310], most typically in young adult and middle-aged men [310, 313]. It is not known if the male predominance is the result of more intense exposure or greater susceptibility [313]. Although *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 [192, 311, 314]. Atrial and ventricular arrhythmias may be seen and there may be involvement of the sinus node and distal conduction system [315–318]. *B. burgdorferi* infection may also present as pericarditis and acute myocarditis with associated ventricular dysfunction [319]. Although recovery from acute Lyme carditis with supportive care and antibiotic treatment is the norm, deaths have been reported [310]. It is unclear whether *B. burgdorferi* infection can result in chronic cardiomyopathy [320–322].

XVI. SHOULD ALL PATIENTS WITH EARLY LYME DISEASE RECEIVE AN ELECTROCARDIOGRAM (ECG) 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 and signs of cardiac involvement in Lyme disease include dyspnea, edema, palpitations, lightheadedness, chest pain, and syncope.

Summary of The Evidence. Patients with other early manifestations of Lyme disease should be asked specifically if they have experienced symptoms such as syncope, presyncope, palpitations, or dyspnea, and an ECG should be performed in those who have symptoms or signs compatible with cardiac involvement. Asymptomatic patients do not have Lyme carditis, and numerous studies have demonstrated that the incidence of nonspecific ECG changes in patients with early Lyme disease is not different from normal controls [311, 314, 323–326].

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 unnecessary referrals, hospital admissions, and anxiety in patients who are clinically unlikely to have Lyme carditis.

XVII. WHICH PATIENTS WITH LYME CARDITIS REQUIRE HOSPITALIZATION?

Recommendation:

1. In patients with or at risk for severe cardiac complications of Lyme disease including those with significant PR prolongation (PR > 300 milliseconds), other arrhythmias, or clinical manifestations of myopericarditis, we recommend hospital admission with continuous ECG monitoring *(strong recommendation, very low-quality evidence).* **Comment:** Clinical manifestations of Lyme carditis include exercise intolerance, palpitations, presyncope, syncope, pericarditic pain, evidence of pericardial effusion, elevated biomarkers (such as troponin), edema, and 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. Although 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 [192, 316, 327]. Thus, a PR interval of ≥300 milliseconds 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 [311, 323] is also an indication for admission. In the setting of AV block, electrocardiographic monitoring should be continued until there is substantial improvement in cardiac conduction.

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.

XVIII. WHAT PACING MODALITY SHOULD BE USED IF NEEDED 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 rather than 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 needed [191, 192, 323, 327, 328]. 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 [329]. The ability to reliably temporarily pace patients for the period necessary to permit recovery may be enhanced by using externalized screw-in pacing leads. Although aspirin and steroids have been used as adjuvant therapy to facilitate recovery of AV conduction in patients with Lyme carditis, there are no controlled studies to support their use. In patients for whom Lyme serologic test results are not yet available, some have used an elevated sedimentation rate or C-reactive protein as rapidly available corroborative evidence of Lyme carditis, supporting a delay in permanent pacing. However, there are also no controlled data examining this strategy.

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

XIX. WHAT ARE THE PREFERRED ANTIBIOTIC 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 14–21 days of total antibiotic therapy over longer durations of treatment *(weak recommendation, very low-quality evidence).* **Comment:** Oral antibiotic choices for Lyme carditis are 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 [223, 301], as well as observational data [330]. One randomized controlled trial [223] 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 and more dermatologic adverse events with doxycycline (see Evidence Profile Tables XIX). 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 are 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 (alternative IV antibiotics are listed in Table 3). 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.

XX. SHOULD PATIENTS BEING EVALUATED FOR ACUTE MYOCARDITIS/PERICARDITIS OR CHRONIC CARDIOMYOPATHY OF UNKNOWN CAUSE BE TESTED FOR LYME DISEASE?

Recommendations:

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 acute myocardial dysfunction or pericarditis, positive Lyme serologic testing, and a clinical scenario compatible with Lyme disease,

who have clinically improved after antibiotic therapy directed at *B. burgdorferi* [319, 322]. 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 [331, 332]. In contrast, there is some suggestion that in eastern Europe similar patients may have a higher prevalence of positive Lyme serologic tests than controls [333] and may respond to specific treatment for Lyme disease [321]. 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 (see Figure 4), 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 *B. burgdorferi* is of unlikely benefit in patients with chronic cardiomyopathy and may result in unnecessary antibiotic exposure without expectation of improvement.

Knowledge Gaps. Ideally randomized controlled trials would help define 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. However, given the rarity and overall excellent prognosis of Lyme carditis, such studies may not be feasible. It also remains unknown whether and which patients with Lyme carditis might benefit from the anti-inflammatory effects of aspirin or corticosteroid therapy. Further information is also needed about the value of nonspecific inflammatory biomarkers, such as the erythrocyte sedimentation rate and C-reactive protein, as 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

Although historically arthritis was reported to occur in 60% of patients with untreated erythema migrans [140], recognition and treatment of Lyme disease in its earliest stages may explain surveillance data over the past 15 years that document a 30% annual incidence of arthritis as a presenting manifestation. The percentage of Lyme disease patients with arthritis may be even lower because joint pain (arthralgia) is often erroneously equated with joint inflammation (arthritis).

Lyme arthritis typically presents with marked swelling of 1 or a few large joints, most often the knee, with less pain than expected based on the degree of swelling [334]. In young children, however, 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 [335]. 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, <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 disease-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 a tick bite, isolated knee involvement, and lack of fever. Absence of a history of a tick bite, however, should not preclude consideration of Lyme arthritis in patients who have potential exposure in endemic areas. Predictors for septic arthritis include a peripheral blood absolute neutrophil count >10 000, erythrocyte sedimentation rate of >40, hip involvement, and pain with short arc motion [335, 336]. 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, which distinguish septic arthritis from transient synovitis of the hip, should not be employed in distinguishing septic arthritis from Lyme arthritis [337]. When there is any doubt, joint fluid should be obtained for culture for other bacterial causes of septic arthritis.

XXI. WHAT IS THE PREFERRED DIAGNOSTIC TESTING STRATEGY FOR LYME ARTHRITIS?

Recommendations:

1. When assessing possible Lyme arthritis, we recommend serum antibody testing over PCR or culture of blood or synovial fluid/tissue *(strong recommendation, moderate-quality 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 evidence).*

Summary of The Evidence. Lyme disease 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 white blood cells (WBCs) per μL, with a mean of 128 000 cells, whereas the mean cell count in Lyme arthritis ranges from ~46 000 to 60 000 [338–340] in children. Synovial WBC counts tend to be lower in adults [160]; however, there are occasional patients with Lyme arthritis whose synovial fluid has >100 000 WBCs [339]. Both septic and Lyme arthritis synovial fluids have a neutrophil predominance [160, 338–340]. 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 2-tiered testing with Western immunoblotting, is very high—in the range of 95–100% [21, 161, 162, 243, 341]. 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 [21, 341]. 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 2-tiered testing algorithms, which make use of 2 different enzyme immunoassays either sequentially or concurrently, provide similarly high sensitivity compared with conventional 2-tiered testing with immunoblotting [20, 246, 247, 249, 342]. 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 2-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. A European study demonstrated that *Borrelia* culture of plasma in patients with Lyme arthritis had a sensitivity of 7.7% [262]. A US study including 11 patients with Lyme arthritis reported that 5 (45%) were positive using a PCR assay applied to serum samples [343].

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% to 100% [179, 341, 343–347]. 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 [348]. Another study documented 0% sensitivity using culture of synovial tissue, synovial fluid, and cartilage [349]. 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%) [345]. 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%) [350].

Antibody testing applied to synovial fluid is not a clinically validated method and may lead to misdiagnosis of Lyme arthritis [351].

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 2-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 [30], 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 because PCR may remain positive for weeks or months after antimicrobial therapy, and therefore positive results do not necessarily equate with active infection [179, 344, 347, 352]. We recommend against other direct detection methods (culture or microscopic examination of synovial tissue or fluid, or blood PCR or culture), because diagnostic accuracy is lower compared with the recommended tests. Antibody testing performed on synovial fluid samples is discouraged, as it can produce false-positive results [351].

Knowledge Gaps. 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.

XXII. 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 IV antibiotics were effective in treating Lyme arthritis when compared to placebo [353, 354]. Two studies showed the superiority of IV cephalosporins over IV penicillin in leading to improvement and resolution of arthritis [355, 356]. Subsequent studies demonstrated the efficacy of oral therapy for Lyme arthritis. A randomized controlled trial (RCT) [357] 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 Lyme neuroborreliosis was noted between groups. Note that the dosing regimen for doxycycline differs from that studied for Lyme 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 XXII). 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 above in the Treatment of Lyme Disease section of the General Principles. 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 [357]. 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.

Knowledge Gaps. 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 nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intraarticular steroids are lacking. Such studies should assess the rate of arthritis resolution as well as recurrence of arthritis or other manifestations of Lyme disease.

XXIII. 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 exclusion of other causes of joint swelling than Lyme arthritis, medication adherence, 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 [357]. 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 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 [355, 356]. The rate of resolution with 14- and 28-day courses of IV ceftriaxone overlap, however, as do adverse event and discontinuation rates [358]. 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 [357, 359, 360]. 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 [179] *B. burgdorferi* spirochetes were moribund or dead in joint fluid even before antibiotic treatment, yet spirochetal DNA 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 [361], and an ultrasound study revealed hamstring tenosynovitis in Lyme arthritis patients [362]. It is possible that spirochetes might be present in joint tissues, such as tendons, without viable spirochetes being found in joint fluid. Slow resolution of arthritis may be due in part to spirochete DNA or other remnants of the pathogen that remain within the joint [363].

Rationale for Recommendations. Resolution rates of Lyme arthritis with ceftriaxone tend to be higher than with oral therapy or IV penicillin, and therefore ceftriaxone is suggested 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.

Knowledge Gaps. 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 postinfectious-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 noninfectious forms of inflammatory arthritis.

XXIV. HOW SHOULD POST-ANTIBIOTIC (PREVIOUSLY TERMED ANTIBIOTIC-REFRACTORY) LYME ARTHRITIS BE TREATED?

Recommendation:

1. In patients who have failed 1 course of oral antibiotics and 1 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, intraarticular 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 if that treatment has included 1 course of IV therapy.

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 [359]. This form of persistent joint inflammation was previously called "antibiotic-refractory" Lyme arthritis and is now referred to as "postantibiotic Lyme arthritis" to avoid confusion with antibiotic resistance. A variety of approaches has been used to treat patients who develop postantibiotic 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 [364], 20 patients with postantibiotic 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 [359], 62 patients who developed postantibiotic 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 disease-modifying antirheumatic drugs (DMARDs) alone or synovectomy followed by DMARDs. Overall, only 3.2% (2 of 62) of the postantibiotic Lyme arthritis patients experienced total

treatment failure. A similar rate of arthritis resolution was seen in a prospective cohort study [364] of 20 patients with postantibiotic 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 [365]. 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 a tumor necrosis factor (TNF) inhibitor, and they had marked improvement within months.

In an earlier 10- to 20-year follow-up study [366], 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 = .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 [365]. 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) [367]. These children usually achieved remission with NSAIDs or intraarticular corticosteroids. However, 3 children were treated with methotrexate and hydroxychloroquine or sulfasalazine. All were in complete remission at follow-up 1 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 [368]. Of these 112 children, 18 received intraarticular steroids with or without a second round of antibiotics; 17% of the children receiving intraarticular steroids developed postantibiotic Lyme arthritis, compared to 44% receiving a second course of antibiotics alone (P = .04). Recovery times were shorter in the steroid treated group [368].

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 postantibiotic 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 1 course of oral and 1 course of IV antibiotics. Some patients may respond to NSAIDs alone or in combination with intraarticular steroids; DMARDs (including hydroxychloroquine, methotrexate, and TNF inhibitors) can be considered [359, 366, 367]. 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 [362]. Consultation with a rheumatologist or other trained specialists is suggested to ensure that there is no other potential explanation for joint swelling or synovial proliferation (eg, underlying osteoarthritis) and that other nonpharmacologic modalities are used such as physical therapy to improve outcomes, especially if atrophy of the quadriceps has developed.

Knowledge Gaps. 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 postantibiotic persistent synovitis.

Prolonged Symptoms Following Treatment of Lyme Disease

The prevalence of persistent symptoms following standard treatment of Lyme disease is unclear; estimates vary depending 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 nonspecific subjective symptoms in 10–20% or more 1 year after treatment [369, 370]. Although these symptoms appear to subside over time [371–373], they can be quite disabling. Importantly, prospective controlled trials, in which healthy controls have been followed for months to years alongside patients who have been treated for Lyme disease, have found that the frequency of this symptom complex is the same in controls as in treated Lyme disease patients [195, 217, 374–376], raising the possibility that this phenomenon, in whole or in part, may represent anchoring to a recent diagnosis of Lyme disease.

XXV. SHOULD PATIENTS WITH PERSISTENT SYMPTOMS FOLLOWING STANDARD TREATMENT OF LYME DISEASE RECEIVE ADDITIONAL ANTIBIOTICS?

Recommendation:

1. For patients who have persistent or recurring nonspecific symptoms such as fatigue, pain, or cognitive impairment following recommended treatment for 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 for months after standard treatment for documented Lyme disease.

In the largest trial 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, were randomized 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 [377, 378]. At 30, 60, and 180 days there was no difference between the treatment and placebo arms as assessed by symptom severity and neurocognitive measures. In a second trial 54 subjects were randomized to 28 days of IV ceftriaxone versus IV placebo, assessing a variety of outcome measures including fatigue, pain, and cognitive function [379]. 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 [380]. A third trial evaluated a longer duration of therapy, comparing the outcome of IV ceftriaxone (23 subjects) to IV placebo (14 subjects), given for 10 weeks [381]. A cognitive index score at week 24 did not differ between treatment and placebo 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 second study. In the second and third of these studies, fatigue improved over baseline among placebo-treated patients (9.1% and 14.5%, respectively). Finally, in a more recent trial 281 patients (89% of whom had previously received antibiotic treatment for the diagnosis of Lyme disease) were randomized to receive 14 days of IV ceftriaxone, followed by 12 weeks of either doxycycline, clarithromycin plus hydroxychloroquine, or placebo [382]. 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 both antibiotics and to IV catheters. One serious antibiotic allergic reaction occurred in each of 2 studies. Additional adverse events in two of the studies (totaling <100 subjects) included 6 IV catheter complications and 1 instance of ceftriaxone-associated gallbladder pseudolithiasis requiring cholecystectomy. Diarrhea occurred in 43% of patients receiving ceftriaxone in 1 study. Despite these examples of harm from prolonged antibiotics, many patients continue to receive prolonged IV antibiotic therapy for symptoms following initial Lyme disease treatment—a practice that has been associated with documented deaths [383, 384].

Thus, the evidence does not support the hypothesis that persistent symptoms should be interpreted as clinical infection, or that antibiotic retreatment is safe and effective. Studies conducted in animal models have raised hypotheses of microbiologic persistence. However, these studies are methodologically highly heterogeneous and have limited generalizability to natural human infection [380]. 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 compared to 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. 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 1 systematic study, more than half of patients previously given this diagnosis actually had other specific disorders including rheumatoid arthritis or osteoarthritis, amyotrophic lateral sclerosis, myasthenia gravis, or depression [385]. Regardless of their underlying diagnosis, many patients who receive the diagnoses of chronic Lyme disease are ill, highly symptomatic, and may be quite disabled by their underlying illnesses and symptoms. When evaluating such patients, clinicians should conduct 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 toward 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 high-quality studies have addressed this question. However, 2 considerations are relevant. First, by definition, these patients often have no compelling clinical or laboratory support for the diagnosis of ongoing or antecedent Lyme disease. Second, the above studies (section XXVII) of persistent symptomatology after treatment of verified Lyme disease have found that prolonged antimicrobial therapy is not helpful and may cause harm. From this, one can infer that prolonged antibiotic treatment is unlikely to benefit individuals who lack a verifiable history of Lyme disease while exposing them to significant risk.

Knowledge Gaps. 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 United States for these conditions will most often have acquired their infection in Europe or in Lyme disease-endemic areas of Central or East Asia. Borrelial lymphocytoma is an inflammatory skin lesion, usually a bluish-purplish nodule, papule, or plaque, which occurs weeks to months after initial infection. Acrodermatitis chronica atrophicans is an atrophic dermatitis affecting extensor surfaces, especially of the hands, and may present months to years after initial infection.

XXVI. 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 are 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 indicated both for resolution of lymphocytoma and to prevent further dissemination of infection to other tissues.

Knowledge Gaps. Comparative clinical studies would be needed to determine the optimal duration of therapy.

XXVII. 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 21–28 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 [386, 387].

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

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

Lyme Disease Coinfections

Ixodes ticks that transmit *B. burgdorferi* also harbor 6 other infectious organisms capable of causing human infection in North America [138, 143, 330, 388–395]. The 2 most commonly identified co-infecting pathogens are the rickettsial bacterium *Anaplasma phagocytophilum* and the protozoan parasite *Babesia microti* [7, 137, 393, 396–399].

The frequency of coinfection in studies varies depending on location, case definition, enrollment criteria, and laboratory detection methods [137, 143, 390, 391, 393, 398–403]. For *A. phagocytophilum*, the agent of human

granulocytic anaplasmosis (HGA), for patients presenting with *B. burgdorferi* infection, the rate of HGA coinfection varies between 2.0% and 11.7% in reported studies [390, 391, 393, 398, 401, 403]. Data have been mixed as to whether Lyme disease and HGA coinfection presents as a more severe illness than early Lyme disease alone [393, 398, 401, 403]. Epidemiologic studies in areas where *B. burgdorferi* and *Babesia microti* are endemic suggest that about 2–10% (range 2%-40%) of early Lyme disease patients experience babesiosis coinfection [137, 393, 399, 401, 402, 404]. Coexisting babesiosis may increase the severity seen with early Lyme disease [137, 391, 397, 401]. Lyme disease appears to have little impact on the clinical manifestations of babesia infection [137, 401].

Other pathogens potentially cotransmitted 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* co-infections with these agents is not well established, they appear to be less frequent than those caused by *A. phagocytophilum* and *B. microti* [138, 391, 394, 395, 405–407]. Prompt evaluation for coinfection should be considered wherever Lyme disease is transmitted if 1 or more coinfecting 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* [148, 391, 408]. Although *I. scapularis* may take blood meals from animals infected with *Bartonella* species, transmission from ticks to humans has not been identified [148, 391, 408–410].

Clinicians seeking detailed information about the diagnosis and management of the 2 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 Guideline on diagnosis and management of babesiosis, which recommends peripheral blood smear examination or PCR for timely diagnosis. The preferred treatment regimen for babesiosis requires combination therapy with either atovaquone in combination with azithromycin or clindamycin in combination with quinine. Severe babesiosis may require red blood cell exchange transfusion. Guidance regarding HGA may be found in the 2016 report from the CDC [9] that recommends diagnostic testing through DNA amplification assays, although 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. Preferred treatment for HGA is doxycycline.

XXVIII. 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 a high-grade fever or characteristic laboratory abnormalities, clinicians should assess for possible coinfection with *Anaplasma phagocytophilum* and/or *B. 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 >1 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 found in both anaplasmosis and babesiosis include thrombocytopenia, leukopenia, neutropenia, and/or anemia. Evidence of hemolysis, such as elevated indirect bilirubin level, anemia, and elevated lactate dehydrogenase are particularly suggestive of babesiosis.

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 coinfection: thrombocytopenia, leukopenia, neutropenia, anemia, and elevated indirect bilirubin levels [9, 156, 398, 401, 411–413].

Rationale for Recommendation. In North America, there are 6 different pathogens besides *B. burgdorferi* that are transmitted by *I. scapularis* ticks [156]. Three of them, *A. phagocytophilum, Babesia microti,* and *Ehrlichia muris eauclairensis* (the latter is only endemic to the Midwest region of the US [391]) need special treatment considerations in patients presenting with erythema migrans. Beta-lactam antibiotics are ineffective for *A. phagocytophilum*, *Ehrlichia muris eauclairensis*, and *B. microti* infections [9, 156, 391]. Doxycycline is highly effective against both *A. phagocytophilum* and *Ehrlichia muris eauclairensis* [9, 391] and is the treatment of choice for these infections. *B. microti* infections will require specific antimicrobial treatment [*Babesia* in press] [156, 414]. Other potential coinfections 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 treatment is mainly supportive.

Knowledge Gaps. Additional studies are needed to determine the frequency of *I. scapularis*-transmitted coinfections in different geographic areas of the United States, as well as to track range expansion of coinfecting pathogens. Further investigations are needed to study the cost-effectiveness of multiplex

laboratory assays for the simultaneous diagnosis of multiple coinfections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors listed in the byline of this article contributed to the joint guideline in the following ways to meet authorship criteria.

1a. Substantial contributions to study conception and design: Maria E. Aguero-Rosenfeld, Paul G. Auwaerter, Kelly Baldwin, Raveendhara R. Bannuru, Kiran K. Belani, Linda K. Bockenstedt, William R. Bowie, John A. Branda, David B. Clifford, Francis J. DiMario Jr., Yngve T. Falck-Ytter, John J. Halperin, Peter J. Krause, Paul M. Lantos, Valery Lavergne, Matthew H. Liang, H. Cody Meissner, Lise E. Nigrovic, James (Jay) J. Nocton, Mikala C. Osani, Amy A. Pruitt, Jeffrey Rumbaugh, Jane Rips, Lynda E. Rosenfeld, Margot L. Savoy, Sunil K. Sood, Allen C. Steere, Franc Strle, Robert Sundel, Jean Tsao, Elizaveta E. Vaysbrot, Gary P. Wormser, Lawrence S. Zemel.

1b. Substantial contributions to acquisition of data: Maria E. Aguero-Rosenfeld, Paul G. Auwaerter, Kelly Baldwin, Raveendhara R. Bannuru, Kiran K. Belani, Linda K. Bockenstedt, William R. Bowie, John A. Branda, David B. Clifford, Francis J. DiMario Jr., Yngve T. Falck-Ytter, John J. Halperin, Peter J. Krause, Paul M. Lantos, Valery Lavergne, Matthew H. Liang, H. Cody Meissner, Lise E. Nigrovic, James (Jay) J. Nocton, Mikala C. Osani, Amy A. Pruitt , Jeffrey Rumbaugh, Lynda E. Rosenfeld, Margot L. Savoy, Sunil K. Sood, Allen C. Steere, Franc Strle, Robert Sundel, Jean Tsao, Elizaveta E. Vaysbrot, Gary P. Wormser, Lawrence S. Zemel.

1c. Substantial contributions to analysis and interpretation of data: Maria E. Aguero-Rosenfeld, Paul G. Auwaerter, Kelly Baldwin, Raveendhara R. Bannuru, Kiran K. Belani, Linda K. Bockenstedt, William R. Bowie, John A. Branda, David B. Clifford, Francis J. DiMario Jr., Yngve T. Falck-Ytter, John J. Halperin, Peter J. Krause, Paul M. Lantos, Valery Lavergne, Matthew H. Liang, H. Cody Meissner, Lise E. Nigrovic, James (Jay) J. Nocton, Mikala C. Osani, Amy A. Pruitt , Jeffrey Rumbaugh, Jane Rips, Lynda E. Rosenfeld, Margot L. Savoy, Sunil K. Sood, Allen C. Steere, Franc Strle, Robert Sundel, Jean Tsao, Elizaveta E. Vaysbrot, Gary P. Wormser, Lawrence S. Zemel.

2. Drafting the article or revising it critically for important intellectual content: Maria E. Aguero-Rosenfeld, Paul G. Auwaerter, Kelly Baldwin, Raveendhara R. Bannuru, Kiran K. Belani, Linda K. Bockenstedt, William R. Bowie, John A. Branda, David B. Clifford, Francis J. DiMario Jr., Yngve T. Falck-Ytter, John J. Halperin, Peter J. Krause, Paul M. Lantos, Valery Lavergne, Matthew H. Liang, H. Cody Meissner, Lise E. Nigrovic, James (Jay) J. Nocton, Mikala C. Osani, Amy A. Pruitt, Jeffrey Rumbaugh, Jane Rips, Lynda E. Rosenfeld, Margot L. Savoy, Sunil K. Sood, Allen C. Steere, Franc Strle, Robert Sundel, Jean Tsao, Elizaveta E. Vaysbrot, Gary P. Wormser, Lawrence S. Zemel.

3. Final approval of the version of the article to be published: Maria E. Aguero-Rosenfeld, Paul G. Auwaerter, Kelly Baldwin, Raveendhara R. Bannuru, Kiran K. Belani, Linda K. Bockenstedt, William R. Bowie, John A. Branda, David B. Clifford, Francis J. DiMario Jr., Yngve T. Falck-Ytter, John J. Halperin, Peter J. Krause, Paul M. Lantos, Valery Lavergne, Matthew H. Liang, H. Cody Meissner, Lise E. Nigrovic, James (Jay) J. Nocton, Mikala C. Osani, Amy A. Pruitt , Jeffrey Rumbaugh, Jane Rips, Lynda E. Rosenfeld, Margot L. Savoy, Sunil K. Sood, Allen C. Steere, Franc Strle, Robert Sundel, Jean Tsao, Elizaveta E. Vaysbrot, Gary P. Wormser, Lawrence S. Zemel.

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B. receives research funding from the Lyme Disease Biobank Foundation and Zeus Scientific; serves as a scientific advisor and consultant to DiaSorin, Inc.; has served as a scientific advisor and consultant for T2 Biosystems; has served on the scientific advisory board of Roche Diagnostics and AdvanDx; has received research funding from Karius, Inc., Alere, Inc., T2 Biosystems, BioMérieux, TBS Technologies, Immunetics, Inc., DiaSorin, Inc., Kephera Diagnostics, Inc., and the Bay Area Lyme Foundation; has participated in unfunded research collaborations with Karius Inc. and Kephera Diagnostics; was a member of the editorial board of the *Journal of Clinical Microbiology*; was a co-inventor on an application for a patent to protect intellectual property; and his spouse is an employee of Informed DNA. D. B. C. receives research funding from the NIH, and the Alzheimer's Association; serves as scientific consultant to Inhibikase and Excision BioTherapeutics; serves on Data and Safety Monitoring Boards (DSMB) for Biogen, Genzyme/Sanofi, Genentech, EMD Serono, Shire, Wave Life Sciences, Pfizer, Atara, and Mitsubishi Tanabe and IQVIA (formerly Quintiles); serves on Progressive Multifocal Leukoencephalopathy (PML) adjudication committees for Amgen, GlaxoSmithKline, EMD Serono, *Bristol Myers Squibb*, Roche and the Takeda Oncology (formerly Millennium) Adjudication Committee-FDA, as well as Dr. Reddy's Laboratories; has previously received research funding from the NIH; and his spouse formerly held stock in Johnson & Johnson. F. J. D. has received research funding from Novartis. Y. F. Y. serves as director of the Evidence Foundation and the GRADE Network; conducts GRADE workshops with the Evidence Foundation; has served as the chair of the Guidelines Committee for the American Gastroenterological Association; and has received research funding from the Cleveland VA Medical Research and Education Foundation. J. J. H. serves as an Editorial Board Member of *Neurology*, and Vice Chair of the American Academy of Neurology (AAN) Guideline Subcommittee; has stock in Abbott Labs, AbbVie, Merck, and Johnson & Johnson; provides and has previously provided legal expert testimony defending physicians in medical malpractice cases on various neurological issues, including Lyme disease; has received research funding from NIH, the Centers for Disease Control and Prevention (CDC); has served as a section editor of neuroinfectious diseases in *Neurology & Neuroscience Reports*. P. J. K. receives research funding from the National Institutes of Health (NIH), the Gordon and Llura Gund Foundation, and the Yale Emerging Infections Program; receives remuneration from Gold Standard Diagnostics for a collaborative research project; has stock in Gilead Sciences and First Trust NASDAQ Pharmaceuticals ETF; has received research funding from NIH, the Centers for Disease Control and Prevention (CDC), the Gordon and Llura Gund Foundation, and L2 Diagnostics for NIH-sponsored research; has served as a scientific consultant and provided medical education and training for Oxford Immunotec, Inc.; has a patent pending (Enhanced Chemiluminescent enzyme-linked immunosorbent assay for detection of antibodies against *Babesia microti*), for which U.S. Provisional Patent Application No. 62/580,588, was filed on November 2, 2017; serves on the Board of Directors for the American Lyme Disease Foundation and the Editorial Boards of *Pathogens and Plos Neglected Tropical Diseases*, the Editorial Advisory Board of *Clinical Infectious Diseases*; was on the Editorial Board of Journal of *Clinical Microbiology*, and will be on the Editorial Board of *Clinical Microbiology Reviews* starting January 2021. P. M. L. has received research funding from the National Cytomegalovirus Foundation and from the NIH and educational funding from Duke University; and has served as a consultant and reviewed trial protocol for Frederick O'Connor Medical Consultants, LLC. M. H. L. has stock in Johnson & Johnson; received research funding from the Veterans Health Administration, the Arthritis Foundation and the NIH; has served on the FDA Advisory Panel, Institute of Medicine panels; served as a scientific reviewer for the Research Grant Council of Hong Kong, and the NIH; served on the Board of the Lupus Clinical Trials Consortium, Beacon Hill Villages, Rx Foundation and advised the Institute for Clinical and Economic Review and the China Medical Board; previously had stock in Sequenom and his spouse has stock in Johnson & Johnson. H. C. M. is a current member of the CDC Workgroups; serves as a volunteer consultant on the American Academy of Pediatrics Committee on Infectious Diseases, and the NIH DSMB. L. E. N. receives research funding from the NIH, Department of Defense and the NIH Center for Research Resources and for Advancing Translational Sciences (NCATS), Global Lyme Alliance and Peabody Foundation; serves on the Editorial Board for *Annals of Emergency Medicine*; has served as scientific consultant for Adaptive Technologies; has received research funding from the NIH, Provider and Payer Quality Initiative (PPQI) Research Foundation, Harvard Catalyst, Hood Foundation, Bay Area Lyme Foundation, CDC, Emergency Medical Services for Children (EMSC), the National Patient-Centered Clinical Research Network (PCORNet), Milton Foundation and Boston Children's Hospital. J. J. N. receives research funding from Bristol Myers Squibb; serves as a member of the Subboard of Pediatric Rheumatology of the American Board of Pediatrics; has received research funding from AbbVie, NIH, and the Arthritis Foundation. A. A. P. has received research funding from Teva Pharmaceuticals and has served on the AAN Editorial Board of *Neurology Clinical Practice*. L. E. N. serves as a Council Member of the American College of Cardiology; has stock in Abbott, Proctor & Gamble, and General Electric; has received Fellowship Support from Boston Scientific, Medtronic, and Abbott Laboratories (formerly St. Jude Medical); has received research funding from Boehringer Ingelheim Pharmaceuticals, Inc.; and has served on the Program Committee and the Patient and Caregivers Committee of the Heart Rhythm Society. J. R. has received research funding from the Center for AIDS Research, Biogen Idec, Hoffmann-LaRoche, Sun Pharmaceutical Industries Ltd., Genzyme, the Alzheimer's Association, and the American College of Radiology; has served as a speaker for Teva Pharmaceuticals. M. L. S. serves on the American Academy of Family Physicians (AAFP) Board of Directors, as an ex-officio Board member of Delaware Academy of Family Physicians (DAFP), as the Chair of the Centers for Medicare and Medicaid Services (CMS) Advisory Panel on Outreach and Education, and as Secretary of the Board of Directors of the Association of Departments of Family Medicine; receives honoraria from AAFP, DAFP, CMS and Merck; has served on an Advisory Council for Highmark Health and as an advisor to the AAFP Adolescent Immunization Project; has received honoraria from AAFP; has served as the President of DAFP, as Editor of *DelFamDoc* and as a member of AAFP Commissions. S. K. S. has received research funding from the NIH; and has provided expert testimony for Danaher Lagnese, P.C. A. C. 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S. receives research funding from the NIH, and AbbVie, Inc.; serves as a content author and editor for UpToDate; provides expert testimony to Chin-Caplan, P.C.; has provided expert testimony for Conway Homer, P.C.; has served as an advisor for Paul Hastings, LLC; has served as a content editor for SimulConsult and as a Medical Education Resources lecturer for CME-granting educational courses; has received remuneration from SimulConsult as a co-investigator for an NIH-sponsored grant; and has received research funding from the NIH. J. T. receives research funding from the National Science Foundation,

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