The International Lyme and Associated Diseases Society

Evidence-based guidelines for the management of Lyme disease

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Summary & disclaimer

These guidelines represent an evidence-based review of Lyme and associated tickborne diseases by the International Lyme and Associated Diseases Society (ILADS). Although the guidelines present evidence-based approaches to the diagnosis and treatment of Lyme and associated tickborne diseases, they were not intended to be a standard of medical care. Physicians must use their own judgment based on a thorough review of all available clinical information and the Lyme disease literature to decide on the best course of treatment for an individual patient.

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Section I: Introduction to guidelines

This report, completed in November 2003, is intended to serve as a resource for physicians, public health officials and organizations involved in the evaluation and treatment of Lyme disease.

1. International Lyme and Associated Diseases Society (ILADS)

ILADS is an interdisciplinary organization of health science professionals established in 1999 to accomplish the following objectives:

- Analyze the medical literature, position statements and practice parameters related to Lyme and associated diseases
- Improve the management of these diseases through evaluation of established and innovative therapies
- Educate a broad range of healthcare providers and serve as an effective advocate for clinicians seeking cost-effective state-of-the-art treatment regimens

ILADS identified the need for new and expanded guidelines for the diagnosis and treatment of Lyme and associated diseases. In 2001, a working party was formed to evaluate current practices and to encourage new standards of care. This report, completed in November 2003, is intended to serve as a resource for physicians, public health officials and organizations involved in the evaluation and treatment of Lyme disease.

2. Chronic Lyme disease: a growing epidemic

The Centers for Disease Control and Prevention (CDC) consider Lyme disease the fastest growing vector-borne disease in the USA. By conservative estimate, the number of new Lyme disease infections per year may be ten times higher than the 17,730 cases reported to the CDC during 2000 [1,2].

The prevalence of chronic Lyme disease ranges from 34% in a population-based, retrospective cohort study [3] to 62% in a specialty clinic located in an area endemic for Lyme disease [4]. Clinic patients presented with arthralgia, arthritis, cardiac and neurologic symptoms [4].

A widening array of chronic presentations is associated with the Lyme spirochete, *Borrelia burgdorferi*. There are great challenges in determining optimal cost-effective means for appropriate diagnosis, clinical management and public health control of Lyme disease throughout the world. Additional problems include the identification and management of tickborne coinfections including *Ehrlichia*, *Babesia* and *Bartonella* species [5].

3. The need for new guidelines

Guidelines of the Infectious Disease Society of America (IDSA) fall short of meeting the needs for diagnosis and treatment of individuals with chronic Lyme disease [6]. The latest IDSA Guidelines (2000) fail to take into account the compelling, peer-reviewed, published evidence confirming persistent, recurrent and refractory Lyme disease and, in fact, deny its existence [6].

The IDSA's symptomatic approaches to Lyme disease are limited and exclude many individuals with persisting clinical and laboratory evidence of active *B. burgdorferi* infection. In addition, physicians treating individuals with Lyme and other tick-borne infections recognize the need for new guidelines to better serve the patient population [6].

Previous guidelines for management of Lyme disease have been published in the *New England Journal of Medicine* in 1990 by Rahn [7]; in *Conn's Current Therapy* in 1997 by Burrascano and in 1998 by Steere [8,9]; in Burrascano's Guidelines on the ILADS website (www.ilads.org); and in the *Journal of Infectious Diseases* by Wormser and colleagues in 2000 [6]. The ILADS Guidelines expand on these protocols using the evidence-based approach and Cochrane methodology employed by the IDSA [6,10].

Our goal is to present practitioners with practical and defensible guidelines for treating all individuals with Lyme disease including those with persistent, recurrent and relapsing symptoms of *B. burgdorferi* infection.

The ILADS Guidelines focus on which patients to evaluate, what tests to order, what antibiotics to use and what steps to take to ensure that concerns over antibiotic use are addressed.

The ILADS Working Group that formulated these guidelines included primary care clinicians, researchers, community healthcare providers and patient advocates. In developing these treatment guidelines, the group considered factors such as incidence of Lyme disease; severity of disease in terms of morbidity; comorbidities and determinants of when Lyme disease is most likely to become chronic; feasibility, efficacy and cost of antibiotic treatment; impact of antibiotic therapy on quality of life, including adverse drug events; and the potential for drug resistance to develop.

Because of the complexity and variability of Lyme disease symptoms, the guidelines are flexible. Treatment depends on the severity of each case, the patient's response to therapy and the physician's own clinical judgment.

4. A problem of definitions

Lyme disease was initially investigated by CDC epidemiologists focusing on erythema migrans, heart block, meningitis and arthritis. The ELISA test and later, the western blot, were introduced for seroepidemiologic studies. Chronic, persistent, recurrent and refractory Lyme disease were not included in these studies; consequently cases of chronic Lyme disease still go unrecognized.

For the purpose of the ILADS guidelines, 'chronic Lyme disease' is inclusive of persistent symptomatologies including fatigue, cognitive dysfunction, headaches, sleep disturbance and other neurologic features, such as demyelinating disease, peripheral neuropathy and sometimes motor neuron disease; neuropsychiatric presentations; cardiac presentations including electrical conduction delays and dilated cardiomyopathy; and musculoskeletal problems. Symptoms may continue despite 30 days of treatment (persistent Lyme disease). The patient may relapse in the absence of another tickbite or erythema migrans rash (recurrent Lyme disease), or be poorly responsive to antibiotic treatment (refractory Lyme disease).

By these definitions, almost two-thirds of 215 Lyme disease patients in a recent retrospective cohort from an endemic region had chronic Lyme disease [4]. Case definitions for Lyme disease have evolved and will continue to develop as a better understanding of chronic Lyme disease emerges to shape a common lexicon.

5. Competency and training

The appropriateness of treatment hinges on the clinician's experience in treating Lyme disease. Competence requires diagnostic and treatment skills heretofore not offered in medical school or postresidency training.

Clinicians more practiced in treating Lyme disease achieve better outcomes and encounter fewer complications because of an enhanced ability to interpret clinical data, the prompt prescription of antibiotics and the use of measures to reduce adverse events, e.g., employing acidophilus to replace normal intestinal flora that is depleted by antibiotics.

6. The increasing role of primary care

The primary care physician has an important role as the first and at times, the principal medical contact for the person with Lyme disease.

Primary care physicians focus on the resolution of symptoms, monitoring for side effects, maintenance or improvement of functional status and prevention of recurrent symptoms.

These guidelines incorporate the evidence used by primary care physicians for the care of patients with Lyme disease.

7. Highlights of guidelines

- Since there is currently no definitive test for Lyme disease, laboratory results should not be used to exclude an individual from treatment
- Lyme disease is a clinical diagnosis and tests should be used to support rather than supersede the physician's judgment
- The early use of antibiotics can prevent persistent, recurrent and refractory Lyme disease
- The duration of therapy should be guided by clinical response, rather than by an arbitrary (i.e., 30 day) treatment course
- The practice of stopping antibiotics to allow for delayed recovery is not recommended for persistent Lyme disease. In these cases, it is reasonable to continue treatment for several months after clinical and laboratory abnormalities have begun to resolve and symptoms have disappeared

Section II: New presentatons

Lyme disease was first described in 1977 as 'Lyme arthritis' among patients initially thought to have arthritis or juvenile rheumatoid arthritis [11]. It was later renamed 'Lyme disease' following recognition of a combination of cardiac, neurologic and rheumatologic presentations, including heart block, meningitis and Bell's palsy. For more than 10 years, variable symptomatic conditions have been recognized including encephalopathy and neuropsychiatric presentations.

8. Symptomatic presentation

Variable symptomatic presentations have been increasingly documented in Lyme disease, with the best example being encephalopathy [12]. Encephalopathic presentations were described in an initial cohort of 27 patients as a symptom complex including memory loss (81%), fatigue (74%), headache (48%), depression (37%), sleep disturbance (30%) and irritability (26%), often without objective markers [12]. Only two of the 27 patients presented with objective findings on lumbar puncture: one had pleocytosis (seven cells) and a second had an antibody index of greater than one [12].

Neuropsychiatric presentations in acute and chronic Lyme disease have been increasingly recognized and can include depression, anxiety and rage [13]. These are presumably related to persistent infection and are potentially reversible with antibiotics. Neuropsychiatric symptoms may reflect additional psychosocial processes including the stress of coping with a chronic illness.

Asch and colleagues found that more than half of 215 patients in a Lyme-endemic region had symptomatic presentations of chronic Lyme disease [4]. The patients presented with chronic fatigue, headaches and joint pain (but not headaches alone) in this retrospective cohort study.

9. Symptoms of Lyme disease

- Fatigue
- Low grade fevers, 'hot flashes' or chills
- Night sweats
- Sore throat
- Swollen glands
- Stiff neck
- Migrating arthralgias, stiffness and, less commonly, frank arthritis
- Myalgia
- Chest pain and palpitations
- Abdominal pain, nausea
- Diarrhea
- Sleep disturbance
- Poor concentration and memory loss
- Irritability and mood swings
- Depression
- Back pain
- Blurred vision and eye pain
- Jaw pain
- Testicular/pelvic pain
- Tinnitus
- Vertigo
- Cranial nerve disturbance (facial numbness, pain, tingling, palsy or optic neuritis)
- Headaches
- 'Lightheadedness'
- Dizziness

10. Increasing evidence of persistent infection

Persistent, recurrent and refractory presentations from ongoing infection are the most feared of the long-term complications of Lyme disease.

Laboratory culture of *B. burgdorferi* has documented persistent infection in chronic Lyme disease patients, but the yields are quite low by current methods [14]. In fact, there is no reliable, commercially available culture assay that can confirm the eradication of the organism. Using experimental techniques, however, *B. burgdorferi* has been detected in virtually every organ in the body, and the spirochete has a strong predilection for the central nervous system. Oral antibiotic levels in the central nervous system are low, and this fact may necessitate the addition of drugs with good penetration across the blood–brain barrier [15], such as intravenous ceftriaxone or cefotaxime.

Most studies demonstrate a beneficial effect of antibiotics in the management of chronic Lyme disease, but the extent of optimal treatment is still uncertain [4,12,13,16–22]. Recent clinical trials questioning the benefits of antibiotics have been criticized for enrolling patients with refractory Lyme disease who were sick for a mean of 4.7 years despite an average of three courses of antibiotics, and for relying only on one treatment protocol (1 month of i.v. ceftriaxone followed by 2 months of low-dose oral doxycycline) [23]. In view of these methodological problems, persistent infection remains a continued concern for physicians.

11. Disappointing results of symptomatic treatment

A theoretical immune mechanism has been proposed to explain persistent symptoms in chronic Lyme disease, but no clinical or laboratory test can confirm this theory. The immune mechanism theory is based on physiological events (often in the form of cascades) that are not reversed by simply killing the infecting organism.

The presentation of chronic Lyme disease can be identical to that of other multisystem disorders, including systemic lupus erythematosus, rheumatoid arthritis and fibromyalgia. In the seminal article describing fibromyalgia in a Lyme disease population, antibiotic treatment failure and relapse of symptoms were considered to be proof of the absence of *B. burgdorferi* infection, and persistent symptoms were assumed to be due to postinfectious sequelae [24]. However, the failure of short-course (2–4 week) antibiotic treatment in 14 (94%) of 15 fibromyalgia patients is consistent with a persistent, inadequately treated infection with *B. burgdorferi* [24].

The increasing successes of repeated and prolonged antibiotic treatment in chronic Lyme disease are more consistent with a persistent infection mechanism.

12. Severity of chronic Lyme disease

For patients with chronic Lyme disease, the quality of life has been evaluated in a clinical trial sponsored by the National Institutes of Health (NIH) using a standardized questionnaire [23]. The quality of life of the 107 individuals with chronic Lyme disease was worse than that of patients with Type 2 diabetes or a recent heart attack, and equivalent to that of patients with congestive heart failure or osteoarthritis. Moreover, the average Lyme disease duration of 4.7 years in subjects enrolling in the study emphasized the chronic nature of the condition. Finally, the failure of 1 month of i.v. ceftriaxone followed by 2 months of oral doxycycline delineated the potential for a poor outcome in chronic Lyme disease [25].

Section III: Diagnostic concerns

The most important method for preventing chronic Lyme disease is recognition of the early manifestations of the disease.

13. Atypical early presentations

Early Lyme disease classically presents with a single erythema migrans (EM or 'bullseye') rash. The EM rash may be absent in over 50% of Lyme disease cases, however [25]. Patients should be made aware of the significance of a range of rashes beyond the classic EM, including multiple, flat, raised or blistering rashes. Central clearing was absent in over half of a series of EM rashes [26]. Rashes can also mimic other common presentations including a spider bite, ringworm, or cellulitis. One series of eleven EM rashes was misdiagnosed and treated as cellulitis, with all eleven patients showing clinical evidence of Lyme disease progression [27].

Physicians should be aware that fewer than 50% of all Lyme disease patients recall a tickbite [28]. Early Lyme disease should also be considered in an evaluation of 'off-season' onset when flu-like symptoms, fever and chills occur in the summer and fall. Early recognition of atypical early Lyme disease presentation is most likely to occur when the patient has been educated on this topic.

14. New chronic Lyme disease presentations

A detailed history may be helpful for suggesting a diagnosis of chronic Lyme disease. Headache, stiff neck, sleep disturbance and problems with memory and concentration are findings frequently associated with neurologic Lyme disease. Other clues to Lyme disease have been identified, although these have not been consistently present in each patient: numbness and tingling, muscle twitching, photosensitivity, hyperacusis, tinnitus, lightheadedness and depression.

Most patients diagnosed with chronic Lyme disease have an indolent onset and variable course. Neurologic and rheumatologic symptoms are characteristic, and increased severity of symptoms on wakening is common. Neuropsychiatric symptoms alone are more often seen in chronic than acute Lyme disease. Although many studies have found that such clinical features are often not unique to Lyme disease, the striking association of musculoskeletal and neuropsychiatric symptoms, the variability of these symptoms and their recurrent nature may support a diagnosis of the disease.

15. The limitations of physical findings

A comprehensive physical examination should be performed, with special attention to neurologic, rheumatologic and cardiac symptoms associated with Lyme disease.

Physical findings are nonspecific and often normal, but arthritis, meningitis and Bell's palsy may sometimes be noted. Available data suggest that objective evidence alone is inadequate to make treatment decisions, because a significant number of chronic Lyme disease cases may occur in symptomatic patients without objective features on examination or confirmatory laboratory testing.

Factors other than physical findings, such as a history of potential exposure, known tickbites, rashes or symptoms consistent with the typical multisystem presentation of Lyme disease, must also be considered in determining whether an individual patient is a candidate for antibiotic therapy.

16. Sensitivity limitations of testing

Treatment decisions should not be based routinely or exclusively on laboratory findings [2,25]. The two-tier diagnostic criteria, requiring both a positive ELISA and western blot, lacks sensitivity and leaves a significant number of individuals with Lyme disease undiagnosed and untreated [29,30]. These diagnostic criteria were intended to improve the specificity of tests to aid in identifying well-defined Lyme disease cases for research studies [31]. Though arbitrarily chosen, these criteria have been used as rigid diagnostic benchmarks that have prevented individuals with Lyme disease from obtaining treatment. Diagnosis of Lyme disease by two-tier confirmation fails to detect up to 90% of cases and does not distinguish between acute, chronic, or resolved infection [21].

The CDC considers a western blot positive if at least 5 of 10 IgG bands or 2 of 3 IgM bands are positive [31]. However, other definitions for western blot confirmation have been proposed to improve the test sensitivity [30,32–36]. In fact, several studies showed that sensitivity and specificity for both the IgM and IgG western blot range from 92 to 96% when only two specific bands are positive [34–36].

Lumbar puncture has also been disappointing as a diagnostic test to rule out concomitant central nervous system infection. In Lyme disease, evaluation of cerebrospinal fluid is unreliable for a diagnosis of encephalopathy and neuropathy because of poor sensitivity (see Section II.8). For example, pleocytosis was present in only one of 27 patients (sensitivity 3%) and with only seven cells [12]. The antibody index was positive (>1) in only one of 27 patients (sensitivity 3%) [12]. An index is the ratio between Lyme ELISA antibodies in the spinal fluid and Lyme ELISA antibodies in the serum. The proposed index of 1.3 would be expected to have even worse sensitivity.

Several additional tests for Lyme disease have been evaluated. These include antigen capture, urine antigen and polymerase chain reaction. Each has advantages and disadvantages in terms of convenience, cost, assay standardization, availability and reliability. These tests remain an option to identify people at high risk for persistent, recurrent and refractory Lyme disease but have not been standardized.

17. Seronegative Lyme disease

A patient who has tested seronegative may have a clinical presentation consistent with Lyme disease, especially if there is no evidence to indicate another illness.

Although many individuals do not have confirmatory serologic tests, surveillance studies show that these patients may have a similar risk of developing persistent, recurrent and refractory Lyme disease compared with the seropositive population. A prospective observational study of 1094 patients [21] and the Klempner clinical trials [23] found no difference in measured outcomes (e.g., success of retreatment) among seropositive or seronegative Lyme disease patients.

18. Continued importance of differential diagnosis

The differential diagnosis of Lyme disease requires consideration of both infectious and noninfectious etiologies. Among noninfectious causes are thyroid disease, degenerative arthritis, metabolic disorders (vitamin B12 deficiency, diabetes), heavy metal toxicity, vasculitis and primary psychiatric disorders.

Infectious causes can mimic certain aspects of the typical multisystem illness seen in chronic Lyme disease. These include viral syndromes such as parvovirus B19 or West Nile virus infection, and bacterial mimics such as relapsing fever, syphilis, leptospirosis and mycoplasma.

The clinical features of chronic Lyme disease can be indistinguishable from fibromyalgia and chronic fatigue syndrome. These illnesses must be closely scrutinized for the possibility of etiological *B. burgdorferi* infection.

19. Clinical judgment

Clinical judgment remains necessary in the diagnosis of late Lyme disease. A problem in some studies that relied on objective evidence was that treatment occurred too late, leaving the patient at risk for persistent and refractory Lyme disease.

As noted, time-honored beliefs in objective findings and two-tier serologic testing have not withstood close scrutiny [21,30,34,37]. Lyme disease should be suspected in patients with newly acquired or chronic symptoms (headaches, memory and concentration problems and joint pain). Management of patients diagnosed on the basis of clinical judgment needs to be tested further in prospective trials, and diagnostic reproducibility must be verified.

20. Testing for coinfection

Polymicrobial infection is a new concern for individuals with Lyme disease, and coinfection is increasingly reported in critically ill individuals [25,38]. Although *B. burgdorferi* remains the most common pathogen in tickborne illnesses, coinfections including *Ehrlichia* and *Babesia* strains are increasingly noted in patients with Lyme disease, particularly in those with chronic illness. *Bartonella* is another organism that is carried by the same ticks that are infected with *B. burgdorferi,* and evidence suggests that it is a potential coinfecting agent in Lyme disease [25].

Recent animal and human studies suggest that Lyme disease may be more severe and resistant to therapy in coinfected patients [25,38]. Thus, concurrent testing and treatment for coinfection is mandatory in Lyme disease patients.

Section IV: Treatment considerations

Since Lyme disease can become persistent, recurrent and refractory even in the face of antibiotic therapy, evaluation and treatment must be prompt and aggressive.

21. Prompt use of antibiotics

Although no well designed studies have been carried out, the available data support the prompt use of antibiotics to prevent chronic Lyme disease. Antibiotic therapy may need to be initiated upon suspicion of the diagnosis, even without definitive proof. Neither the optimal antibiotic dose nor the duration of therapy has been standardized, but limited data suggest a benefit from increased dosages and longer treatment, comparable to the data on tuberculosis and leprosy which are caused by similarly slow-growing pathogens [25].

22. Choosing an antibiotic

In acute Lyme disease, the choice of antibiotics should be tailored to the individual and take into account the severity of the disease as well as the patient's age, ability to tolerate side effects, clinical features, allergy profile, comorbidities, prior exposure, epidemiologic setting and cost.

Conversely, persistent and refractory Lyme disease treatment is more likely to include intravenous and/or intramuscular antibiotics. The choices depend in part on the patient's response to antibiotic therapy and on the success of antibiotics in treating other Lyme disease patients (see below).

Therapy usually starts with oral antibiotics, and some experts recommend high dosages. The choice of antibiotic therapy is guided by weighing the greater activity of intravenous antibiotics in the central nervous system against the lower cost and easy administration of oral antibiotics for *B. burgdorferi*.

23. Oral antibiotic options

For many Lyme disease patients, there is no clear advantage of parenteral therapy. Along with cost considerations and pressure to treat patients with Lyme disease with the least intervention, there is growing interest in the use of oral therapy.

First-line drug therapies for Lyme disease may include (in alphabetical order): oral amoxicillin, azithromycin [39–41], cefuroxime [42], clarithromycin [43], doxycycline and tetracycline. These antibiotics have similar favorable results in comparative trials of early Lyme disease. In one study, azithromycin performed slightly less well when compared to amoxicillin and doxycycline. However, the efficacy of azithromycin was underestimated because the antibiotic was only given for 10 days [39].

One study has suggested that oral doxycycline (100 mg twice daily for 30 days) is as effective as intravenous ceftriaxone (2 g daily for 30 days) in early disseminated Lyme disease [40]. Two European studies have demonstrated similar efficacy of oral doxycycline and parenteral penicillin and ceftriaxone in early Lyme disease [44,45].

There are no studies comparing oral with intravenous antibiotics for persistent, recurrent and refractory Lyme disease.

24. Intravenous antibiotic options

It is common practice to consider intravenous antibiotics upon failure of oral medications in patients with persistent, recurrent or refractory Lyme disease, and as the first line of therapy for certain conditions, (i.e., encephalitis, meningitis, optic neuritis, joint effusions and heart block).

Ideally, the intravenous antibiotic should be selected on the basis of *in vitro* sensitivity testing or clinical experience [101]. Intravenous antibiotics are also justified by concern for penetration into the central nervous system [15].

Until recently, ceftriaxone, cefotaxime and penicillin were the only intravenous antibiotics routinely studied for use in Lyme disease. Intravenous imipenem, azithromycin and doxycycline have an adequate antispirochetal spectrum of activity and may represent suitable alternative therapies. However, the latter two drugs are often considered for intravenous use only if they are not tolerated orally.

There is a paucity of data on alternative intravenous antibiotics, and their success is less predictable in chronic Lyme disease.

25. Intramuscular antibiotic options

Intramuscular benzathine penicillin (1.2 to 2.4 million units per week) is sometimes effective in patients who do not respond to oral and intravenous antibiotics. If intramuscular benzathine penicillin is used, long-term therapy may be necessary due to the low serum concentration of this form of penicillin [46]. Luft and colleagues report, "It was demonstrated that while *B. burgdorferi* may be sensitive to relatively small concentrations of penicillin and ceftriaxone, the organism is killed slowly. This implies that, as in syphilis, prolonged blood levels of these drugs may be necessary in order to ensure cure" [46].

One-third of a chronic Lyme disease population responded to intramuscular benzathine penicillin (1.2 to 2.4 million units per week) [16–18]. Benzathine penicillin has mainly been used in patients who have had multiple relapses while receiving oral or intravenous antibiotic therapy or who are intolerant of oral or intravenous antibiotics.

26. Combination antibiotic treatment

Combination therapy with two or more antibiotics is now increasingly used for refractory Lyme disease [11,41,45,46–49] and has also been given as initial therapy for some chronic presentations.

This approach is already used for another tickborne illness, babesiosis [50]. Oral amoxicillin, cefuroxime or (more recently) cefdinir combined with a macrolide (azithromycin or clarithromycin) are examples of combination regimens that have proven successful in clinical practice, although controlled clinical trials are lacking in persistent, recurrent and refractory Lyme disease.

Combination therapy in patients with Lyme disease raises the risk of adverse events. This risk must be weighed against the improved response to combination therapy in Lyme disease patients failing single agents [47–49].

27. Sequential treatment

Clinicians increasingly use the sequence of an intravenous antibiotic followed by an oral or intramuscular antibiotic [19,37,101,47,48]. In two recent case series that employed combination therapy and sequential therapy, most patients were successfully treated [19,47]. A logical and attractive sequence would be to use intravenous therapy first (e.g., intravenous ceftriaxone), at least until disease progression is arrested and then follow with oral therapy for persistent and recurrent Lyme disease.

28. Dosage

Increasingly, clinicians recommend that certain drugs used for Lyme disease be given at higher daily doses: for example, 3000–6000 mg of amoxicillin, 300–400 mg doxycycline and 500–600 mg of azithromycin. Some clinicians prescribe antibiotics using blood levels to guide higher doses. Close monitoring of complete blood counts and chemistries are also required with this approach.

With higher doses, there may be an increase in adverse events in general and gastrointestinal problems in particular. Acidophilus has reportedly reduced the incidence of *C. difficile* colitis and non-*C. difficile* antibiotic-related diarrhea.

Serious adverse effects of antibiotics, however, were less common than previous estimates. In a recent clinical trial of chronic Lyme disease, the overall serious adverse event rate was 3% after three months of antibiotics, including 1 month of intravenous antibiotics [23]. Clinicians who have experience with higher-dose antibiotic therapy must balance the benefit of higher drug levels achieved with this therapy against the modest risk of gastrointestinal and other side effects.

Research is needed to determine the added benefits of higher doses of antibiotics in chronic Lyme disease.

29. Duration of therapy

Because of the disappointing long-term outcome with shorter courses of antibiotics, the practice of stopping antibiotics to allow for a delayed recovery is no longer recommended for patients with persistent, recurrent and refractory Lyme disease. Reports show failure rates of 30–62% within 3 years of short-course treatment using antibiotics thought to be effective for Lyme disease [3,4,12]. Conversely for neurologic complications of Lyme disease, doubling the length of intravenous ceftriaxone treatment from 2 to 4 weeks improved the success rate from 66 to 80% [12,51].

The management of chronic Lyme disease must be individualized, since patients will vary according to severity of presentation and response to previous treatment.

Concurrent risk factors (i.e., coinfections, previous treatment failures, frequent relapses, neurologic involvement, or previous use of corticosteroids) or evidence of unusually severe Lyme disease should lead to the initiation of prolonged and/or intravenous antibiotic treatment. Physicians should always assess the patient's response to treatment before deciding on appropriate duration of therapy (i.e., weeks versus months).

30. Empiric treatment

The importance of establishing the diagnosis of Lyme disease is heightened in light of increasing concern about antibiotic overuse. After an appropriate history, physical examination and laboratory testing are completed, empiric antimicrobial therapy should be initiated on the basis of clinical clues, the severity of the patient's acute illness, underlying disease and the likelihood of *B. burgdorferi* infection. The ILADS working group recommends that empiric treatment be considered routine for patients with a likely diagnosis of Lyme disease.

31. Persistent Lyme disease

Persistent Lyme disease is more resistant to treatment and more likely to produce a relapse. Although persistent Lyme disease may resolve without additional therapy, many experts believe that this condition should be treated with repeated and prolonged antibiotics. Physicians should extend the duration of antibiotics to prevent or delay recurrent and refractory Lyme disease.

32. Recurrent Lyme disease

Despite previous antibiotic treatment, Lyme disease has a propensity for relapse and requires careful follow-up for years. The data suggest that failure to eradicate the organism may be the reason for a recurrence of symptoms [12]. Early and aggressive treatment with antibiotics is indicated for recurrent Lyme disease. The ultimate impact from retreating each episode of recurrent Lyme disease is currently unclear.

33. Refractory Lyme disease

Refractory Lyme disease is a devastating condition that usually affects patients with persistent symptomatology and long-term disability. Prompt and aggressive institution of antibiotic therapy may be essential to prevent refractory disease. Increasing evidence shows that antibiotics have a beneficial effect on the course of refractory Lyme disease even in cases where the patient is intolerant of antibiotics or when a previous regimen has failed. Several months of therapy are often required to produce clear evidence of improvement. During this time, symptomatic treatment may be combined with antibiotic treatment.

34. Treatment failure

When patients fail to respond or their conditions deteriorate after initiation of empiric therapy, a number of possibilities should be considered other than Jarisch-Herxheimer reaction. These include adverse events that limit treatment, allergic history to medication, inappropriate or inadequate dosing regimen, compliance problems, incorrect medication, immune sequelae and sequestering of the organism (e.g., in the central nervous system). An alternative diagnosis or coinfection should also be considered.

35. Symptomatic treatment

Although there may be a potential role for symptomatic treatment in chronic Lyme disease, this approach has little support due to the strong possibility of persistent infection. Owing to the potential hazard of immunosuppression and the poor outcome in

one study, steroid therapy is not recommended [52]. Surgical synovectomy is associated with significant morbidity and does not address neurologic presentations; it should be reserved for knee pain failing antibiotic treatment [53]. Intra-articular steroid injection may be useful as a temporizing procedure in patients with persistent knee pain but this runs the risk of masking persistent infection.

Symptomatic therapy (particularly anti-inflammatory medications, tricyclic antidepressants, selective serotonin re-uptake inhibitors and hydroxychloroquine) may be useful in concert with antibiotics and in individuals failing antibiotics.

Hyperbaric oxygen therapy (HBOT) is under study but is not recommended for routine therapeutic use [25,54]. Other treatments, including cholestyramine (CSM), antifungal therapy and antiviral agents require further study.

Since patients are becoming more interested in alternative therapies (e.g., traditional Chinese medicine, anti-oxidants, hyperthermia, bee venom, naturopathy and homeopathy), physicians should be prepared to address questions regarding these topics.

36. Fibromyalgia

The outcome of treating fibromyalgia secondary to Lyme disease with nonantibiotic regimens has been poor. The most encouraging clinical trial showed success in only one of 15 patients and only modest improvement in 6 of 15 individuals with fibromyalgia despite 2 years of treatment [24].

Antibiotic therapy has been much more effective than supportive therapy in symptomatic patients with fibromyalgia secondary to Lyme disease.

Fibromyalgia treatment alone without antibiotics raises the risk of conversion to refractory chronic Lyme disease and/or exacerbation of an undiagnosed persistent infection and is not recommended. Increasingly, clinicians do not feel comfortable treating fibromyalgia in Lyme disease without antibiotics.

37. Decision to stop antibiotics

Several studies of patients with Lyme disease have recommended that antibiotics be discontinued after 30 days of treatment. Complicating the decision to stop antibiotics is the fact that some patients present with disease recurrence after the resolution of their initial Lyme disease symptoms. This is consistent with incomplete antibiotic therapy. Although the optimal time to discontinue antibiotics is unknown, it appears to be dependent on the extent of symptomatology, the patient's previous response to antibiotics and the overall response to therapy (see below).

Rather than an arbitrary 30-day treatment course, the patient's clinical response should guide duration of therapy. Patients must therefore be carefully evaluated for persistent infection before a decision is made to withhold therapy.

The decision to discontinue antibiotics should be made in consultation with the patient and should take into account such factors as the frequency and duration of persistent infection, frequency of recurrence, probability of refractory Lyme disease, gains with antibiotics, the importance to the patient of discontinuing antibiotics and potential for careful follow-up.

The ideal approach would be to continue therapy for Lyme disease until the Lyme spirochete is eradicated. Unfortunately there is currently no test available to determine this point [25]. Therefore, the clinician must rely on the factors outlined above to decide on the length of antibiotic therapy for chronic Lyme disease.

38. Alternative antibiotics

There is compelling evidence that Lyme disease can result in serious and potentially refractory illness. Use of alternative antibiotics to treat early Lyme disease with erythema migrans is generally not indicated unless coinfection is suspected.

The ILADS Working Group believes that the risk of alternative antibiotics is acceptable in selected Lyme disease patients presenting with chronic Lyme disease. Alternative antibiotics include less commonly used oral antibiotics (cefixime, cefdinir, metronidazole) and intravenous antibiotics (imipenem, azithromycin). The role of alternative antibiotics in low-risk patients is less certain and there is less consensus within the Working Group as to whether the potential benefits outweigh the risks.

39. Therapy for coinfection

Therapy for polymicrobial infection in Lyme disease is a rapidly changing area of clinical practice [25]. Uncomplicated Lyme disease may be managed without addressing coinfection by means of standard oral or parenteral antibiotic therapy. Some but not all experts recommend therapy for subclinical or chronic coinfection with *Ehrlichia*, *Babesia* or *Bartonella* on the basis of their belief that responses are more prompt with this approach.

The dose, duration and type of treatment for coinfections have not been defined. Published reports of coinfection are limited to a small number of patients treated in open-label, nonrandomized studies. Doxycycline has been indicated for *Ehrlichia*. A recently published randomized trial determined that treatment of severe *Babesia microti* with the combination of atovaquone and azithromycin was as effective as the use of standard oral therapy with clindamycin and quinine [55].

The decision to use alternative antibiotics should be based on the individual case, including a careful assessment of the patient's risk factors and personal preferences. Patients managed in this way must be carefully selected and considered reliable for follow-up. Further controlled studies are needed to address the optimal antimicrobial agents for coinfections and the optimal duration of therapy.

Additional research is needed to determine which antibiotics work best for *Bartonella,* but fluoroquinolones, azithromycin, doxycycline and rifampin have good *in vitro* activity.

Section V: Research needs

The ILADS Working Group encourages centers that treat large numbers of Lyme disease patients symptomatically using IDSA treatment guidelines to perform a formal evaluation of their own programs. This will allow researchers to compare the results of treatment guidelines that use more antibiotics with those that do not.

40. Ongoing development of treatment guidelines

The IDSA guidelines recommending one-time short-term antibiotic therapy have not been successful. Physician demands for better outcomes have led to the development of the ILADS guidelines, and the continued evolution of an evidence-based approach is critical for the treatment of persistent, recurrent and refractory Lyme disease.

41. Validation of guidelines

Most studies of Lyme disease were retrospective, unblinded and uncontrolled. Furthermore, the antibiotic dose and duration of therapy were not standardized.

The first double-blind clinical trial found that weekly benzathine penicillin for 3 weeks was more effective than placebo for Lyme arthritis [56]. At the other end of the spectrum, a recently completed randomized clinical trial failed to demonstrate any efficacy of 90 days of antibiotic therapy in previously treated patients with neurologic Lyme disease [23].

Two additional randomized trials are examining the practice of retreating chronic Lyme disease patients with antibiotics, and these results should be available shortly [57,58]. The retreatment approach is being validated using a single-center, prospective surveillance database.

42. Comparative studies

The IDSA and ILADS Guidelines differ substantially, revealing the wide variation in diagnosis and treatment (TABLE 1) [59,60]. This variation suggests that physicians do not use a uniform strategy to diagnose and treat Lyme disease. Physicians often treat for Lyme disease longer than 4 weeks and also retreat [8,19,47,48,57–62]. These decisions are made despite warnings against overdiagnosis and overtreatment [63–65].

Community-based clinicians and academic centers often have different criteria for diagnosis and divergent goals of care [8]. The guidelines and standards of practice used for diagnosis of Lyme disease in academic research settings may not be applicable or appropriate for community-based settings. Moreover, the clinical manifestations of Lyme disease are often subtle or atypical in the community.

Because important data concerning the treatment of chronic Lyme disease was not considered by the IDSA expert panel, ILADS introduced an evidence-based review to determine which recommendations warranted revision. This evidence-based review gave rise to the current guidelines.

Section VI: Periodic review of guidelines

New data on treatment of Lyme disease is emerging, and randomized controlled trials that address various unresolved issues in Lyme disease are ongoing. The ILADS Working Group has therefore developed a mechanism for routinely and periodically reviewing this information and for updating the guidelines on a regular basis. The most recent information will be available from the ILADS website at www.ILADS.org.

43. Grading system for evidence-based guidelines

The ILADS system for grading recommendations is similar to that used by the expert panel of the IDSA. However, the ILADS panel includes primary care clinicians, researchers and international leaders in the treatment of Lyme disease. Thus, the ILADS group is more inclusive and clinically oriented than the IDSA panel, and the ILADS guidelines reflect this diversity.

44. Table 1. Comparison of key IDSA and ILADS guidelines.

Condition	IDSA	ILADS
Lyme arthritis	B - II	A - II
Encephalopathy	A - II	A - II
Retreatment	None	A - II
Prolonged antibiotics	None	A - II
Benzathine penicillin	D - III	B - III
Intra-articular steroid	B - III	D - III
Arthroscopic Synovectomy	B - II	D - II
Coinfection	B - III	B - III
Seronegative Lyme disease	None	A - III
Combination treatment	None	B - III
Empiric treatment	None	B - III

45. Criteria for evidence-based guidelines

The ILADS recommendations are based on two criteria [10]:

- The strength of the evidence (denoted by categories A–E)
- The quality of the data (denoted by Roman numerals I–III)

Recommendations rated 'A' are considered good evidence to support the recommendation. Those rated 'B' have moderate evidence to support the recommendation. Those rated 'C' are considered optional. Measures designated 'D' generally should not be offered; those designated 'E' are contraindicated.

A rating of I indicates that at least one randomized controlled trial supports the recommendation; II, evidence from at least one well-designed clinical trial without randomization supports the recommendation; and III, 'expert opinion'.

Sources

Our data sources are English-language articles published from 1975 to 2003. The selection panel synthesized the recommendations from published and expert opinion. Human studies of Lyme disease were identified from MEDLINE (1975 to 2003) and from references in pertinent articles and reviews. Also included are abstracts and material presented at professional meetings and the collective experience of the ILADS Working Group treating tens of thousands of Lyme disease patients.

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