

**CHARLES RAY JONES, M.D.**

Pediatric & Adolescent Medicine  
Lyme Disease

Madison Towers  
111 Park Street, 1<sup>st</sup> Floor  
New Haven, Connecticut 06511

Tel (203) 772-1121  
Fax (203) 772-068

May 17, 2007

To: Section of the Committee on Petition  
European Parliament  
Attn: Karen Chioti  
Petition #151/2007

Re: Aeneas Heller  
DOB 4/17/95, 12 1/12 years old

On 8/12/04, I received a telephone call from 9 year old Aeneas Heller's mother, Petra Heller, informing me that her son had been taken away from her because she was accused of "mistreating him with prolonged use of unnecessary IV antibiotics for treating his Lyme disease". Obviously, Petra was upset and crying and was desperately trying to find out where her son had been taken and how she could get him back. She was concerned about Aeneas' reaction to being taken from his mother and that his Lyme disease would worsen if IV antibiotics were discontinued prematurely. She asked me to intercede on Aeneas' behalf.

I have been advising Petra Heller appropriately about treatment of her son's chronic, persisting Lyme disease since 2002. Aeneas had improved since being treated with IV Rocephin and vancomycin. He had more energy. He had less joint pain. He was reading better and had fewer headaches. Petra Heller sought my advice because she wanted the best care from a professional with expertise in treating Lyme disease.

Please allow me to clarify my experience in this case. I am a physician in the practice of pediatric and adolescent medicine. I have evaluated and treated over 10,000 children between one day and 18 years old with Lyme and other tick-borne diseases from every state in America and every continent abroad. No other physician has my experience in treating children with tick-borne diseases. At Columbia University, there are several endowed funds to support research and education. One of these funds is

Heller, Aeneas 5/17/07 2

called the "Charles Ray Jones Endowment Fund". The purpose of this fund is to educate medical students about Lyme disease and other tick-borne diseases. The fund was named after me to honor my dedication and pioneering work as a pediatrician devoted to helping children with chronic Lyme disease and related disorders. Medical students from Columbia who are awarded this fellowship spend time learning about Lyme disease from me in my office at 111 Park Street, New Haven, Connecticut 06511. I am also a charter member of The International Lyme and Associated Diseases Society (ILADS).

Aeneas has ample evidence supporting the clinical diagnosis of Lyme disease and has laboratory evidence indicating exposure to the *Borrelia burgdorferi* spirochete, the bacterium that causes Lyme disease. The CDC stipulates that the diagnosis of Lyme disease remains clinical and the rigid CDC surveillance criteria, including ELISA and Western Blot, should not be used to make a diagnosis of Lyme disease.

Aeneas Heller has had two significant epidemiological risks for exposure to the *Borrelia burgdorferi* spirochete, the Lyme bacterium: 1.) through gestational transmission, and 2.) from *Ixodes scapularis* tick attachments. Aeneas' mother, Petra Heller, has had Lyme disease since 1985. Her Lyme disease was not treated until long after Aeneas was born. Aeneas has had 3 known *Ixodes scapularis* tick attachments: in 1995 (below his clavicle), in 1998 (on his hand), and in 2001 (on his arm).

Aeneas has clinical symptoms and responses compatible with Lyme disease: fevers, night sweats, chills, weight gain, fatigue and tiredness, sore throat, swollen glands, pelvic pain, irritable bladder, abdominal pain, diarrhea, chest wall (rib) pain, shortness of breath, bradycardia, apnea, joint pain and swelling (knees, toes), stiffness (neck, back), daily headaches since 1998 when he was 3 years old, tingling paresthesias in his fingers and toes, light sensitivity, floaters, impaired hearing, motion sickness, poor balance, tremor, confusion, difficulty thinking, difficulty with reading due to an increase in headache if he reads more than 2-4 minutes, disorientation, going to the wrong places, disturbed sleep, Jarisch-Herxheimer reactions, and improvement on antibiotics, especially IV antibiotics.

Aeneas has serological evidence of exposure to the *Borrelia burgdorferi* spirochete, the bacterium that causes Lyme disease; 7/7/00 Laboratoriumsmedizin Lyme Western Blot IgG 34 39 41. Bands 34 and 39 are genus specie specific for *Borrelia burgdorferi* and confirm the clinical diagnosis of Lyme disease.

*There are nine known Borrelia burgdorferi genus specie specific KDA Western Blot antibodies (bands): 18 23 30 31 34 37 39 83 and 93. Only one of these Borrelia burgdorferi genus specie specific bands is needed to confirm that there is serological evidence of exposure to the Borrelia burgdorferi spirochete and can confirm a clinical diagnosis of Lyme disease. CDC Western Blot IgM surveillance criteria includes only two Borrelia burgdorferi genus specie specific antibodies for IgM 23 and 39 and excludes the other seven Borrelia burgdorferi genus specie specific antibodies. CDC Western Blot IgG surveillance criteria includes 18 23 30 37 39 and 93 and excludes bands 31 34 and 83. It does not make sense to exclude any Borrelia burgdorferi genus*

Heller, Aeneas 5/17/07 3

*specie specific antibodies in a Lyme Western Blot IgG and to include only two of these antibodies in IgM because all the antibodies in IgG were once IgM. IgM converts to IgG in about two months unless there is a persisting infection driving a persisting IgM reaction. This is the case with any infection including the Borrelia burgdorferi induced Lyme disease. CDC wrongfully includes five non-specific cross-reacting antibodies in its Western Blot surveillance criteria: 28 41 45 58 and 66. This leads to the possibility of false positive Lyme Western Blots. There can be no false positives if only Borrelia burgdorferi genus specie specific antibodies are considered. One can have a CDC surveillance positive IgG Lyme Western Blot with the five non-specific antibodies without having any Borrelia burgdorferi genus specie specific antibodies. This does not make sense. CDC recommends that the Lyme Western Blot be performed only if there is a positive or equivocal Lyme ELISA. In my practice of over 7000 children with Lyme disease, 30% with a CDC positive Lyme Western Blot have negative ELISA's. The Lyme ELISA is a poor screening test. An adequate screening test should have false positives not false negatives.*

Aeneas was responding to IV Rocephin and vancomycin when he was abducted from his mother. These, or other, antibiotics should be continued for at least two months after his Lyme symptoms and signs have resolved. If antibiotics are stopped prematurely, such as they have been, he will relapse and have more body and brain injury from a more resistant, difficult to treat residual Borrelia burgdorferi spirochete. Aeneas must not become a victim of the erroneous concept that all Lyme disease can be successfully treated and all Borrelia burgdorferi spirochetes eradicated with an arbitrary 3-6 week course of antibiotic therapy. There is ample evidence in the peer reviewed medical literature that the Borrelia burgdorferi spirochete can survive prolonged antibiotic therapy of one month, six months and even several years of intensive IV antibiotic therapy. This evidence must not be ignored in any objective determination of what constitutes adequate, curative therapy for treating Lyme disease. Enclosed is a recent expert consensus panel report published on the treatment of chronic Lyme disease by ILADS, which supports the use of long-term antibiotic therapy in chronic Lyme disease. It should also be noted that longer courses of antibiotic therapy are appropriate when indicated for other disorders as well, such as acne, malaria, tuberculosis, leprosy, etc. Three-quarters of the over 10,000 children I have treated for Lyme disease have been treated with 3 months to 7 years of continuous oral, and/or IM, or IV antibiotic therapy. These children are well and without symptoms 2-15 years after stopping adequate antibiotic therapy. A more typical duration of treatment of children with persisting Lyme disease is 2-3 years unless a child has gestational Lyme disease. Children with gestational Lyme disease require longer treatment to eradicate their Lyme infection. None of these children on appropriate long-term antibiotic therapy have had damage to any organ or system as a result of antibiotic treatment. However, these children with chronic Lyme disease have brain, spinal cord, eye, thyroid, lung, heart, GI tract, and GU tract damage if treatment is not long enough to eradicate all of the Borrelia burgdorferi spirochete. Aeneas is one of these children who require prolonged antibiotic treatment. Any interruption of his antibiotic therapy and/or emotional trauma will cause him to have a Lyme relapse with more brain and body injury.

Heller, Aeneas 5/17/07 4

I am impressed with the responsible care provided by Petra Heller for her son. She has actively sought the best care for Aeneas from professionals with special expertise in treating Lyme disease. She does not suffer from Munchausen by proxy. She should not be penalized for having more knowledge about Lyme disease than many physicians and for using this knowledge in seeking appropriate medical care for her son's chronic persisting Lyme disease.

I am available to help in any way necessary to resolve this tragic error.

  
Charles R. Jones, M.D.

**Commissioning Editor**

Laura Savill

**Production Editor**

Karen Blatchford

**Drug Profile Editor**

Vivien Griffiths

**Publisher**

David Hughes

**Editorial Advisory Panel**

- Appay V, John Radcliffe Hospital, Oxford, UK  
 Burchmore R, University of Glasgow, UK  
 Cohen S, UC Davis Medical Center, CA, USA  
 Chopra I, University of Leeds, UK  
 Donald PR, University of Stellenbosch, South Africa  
 Gootz T, Pfizer Inc., CT, USA  
 Guérin P, Epicentre, France  
 Labro MT, INSERM, Paris, France  
 Montefiori DC, Duke University Medical Center, NC, USA  
 O'Brien SJ, Central Public Health Laboratory, UK  
 Oxford J, School of Medicine and Dentistry, UK  
 Perfect JR, UCLA, CA, USA  
 Peters CJ, University of Texas Medical Branch, TX, USA  
 Quinn TC, National Institute of Health, USA  
 Schang LM, University of Alberta, Canada  
 Sidwell RW, Institute for Antiviral Research, UT, USA  
 Stanhope MJ, GlaxoSmithKline, PA, USA  
 Threlfall J, Central Public Health Laboratory, UK  
 Turpin J, TherImmune Research Corp., USA  
 van Heeswijk RPG, The Ottawa Hospital, The Netherlands  
 Wendel K, Johns Hopkins University School of Medicine, USA  
 Will R, National Creutzfeldt-Jakob Disease Surveillance Unit, UK  
 Yewdell J, National Institute of Allergy & Infectious Diseases, MA, USA

**Supplement proposals:**

Genevieve Eastwood  
 Special Projects Editor  
 Future Drugs Ltd, Unitec House,  
 3rd Floor, 2 Albert Place,  
 Finchley Central,  
 London N3 1QB, UK  
 Fax: +44 (0)20 8343 2313  
 g.eastwood@future-drugs.com

**Reprint purchase enquiries:**

reprints@future-drugs.com

**General enquiries:**

info@future-drugs.com

## Expert Review of Anti-infective Therapy

www.future-drugs.com

**Aims and scope**

*Expert Review of Anti-infective Therapy* provides a centralized resource of commentary and debate to inform clinical and economic decision-making in the treatment of infectious diseases. Members of the International Editorial Advisory Panel identify the most important and topical review themes and the corresponding experts most appropriate to provide their opinion and perspective. All articles are subject to rigorous peer-review.

The Journal concentrates on a structured program of authoritative review articles, addressing:

- Therapeutic overviews of specific therapeutic areas, highlighting optimal therapy
- Performance and benefits of newly-approved anti-infective therapeutic agents
- Prospects for new therapies
- Psychosocial aspects
- Epidemiological studies and trends
- New diagnostic approaches, screening and patient stratification
- Pharmacoeconomics and outcomes

**Editorial policy:** Articles published in *Expert Review of Anti-infective Therapy* are commissioned by the Editor in collaboration with the Editorial Advisory Panel. Authors who wish to contribute should contact the Commissioning Editor with an outline proposal in the first instance. Guidelines are available on request or at our website.

**Copyright:** Conditions of sale - *Expert Review of Anti-infective Therapy* may be circulated only to those members of staff who are employed at the site at which the subscription is taken out. Readers are reminded that, under internationally agreed copyright legislation, photocopying of copyright materials is prohibited other than on a limited basis for personal use. This means that making copies of any article published in *Expert Review of Anti-infective Therapy* is a breach of the law and can be prosecuted. Whilst every effort is made by the publishers and advisory board to ensure that no inaccurate or misleading data, opinions or statements appear in this journal, they wish to make it clear that the data and opinions appearing herein are the responsibility of the contributor concerned. Accordingly, the publishers, advisory board, editors and their respective employees, officers and agents accept no liability whatsoever for the consequences of any inaccurate or misleading data, opinions or statements. Approved product information should always be reviewed prior to prescribing.

**Contributions to *Expert Review of Anti-infective Therapy*:** We welcome suggestions or recommendations for Guest Editorials, Meeting Reports or Reviews for publication in *Expert Review of Anti-infective Therapy*. In the first instance, please contact the Editor, Laura Savill, with a brief outline of the proposed contribution.

Please direct the proposal to:  
 Laura Savill, Commissioning Editor,  
 Future Drugs Ltd, Unitec House, 3rd Floor, 2 Albert Place  
 Finchley Central, London N3 1QB, UK  
 Tel: +44 (0)20 8349 2033; Fax: +44 (0)20 8343 2313  
 lsavill@future-drugs.com

## The International Lyme and Associated Diseases Society

### 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](http://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 symptomatology 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).

## ILADS guidelines for 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 presentations

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

## The International Lyme and Associated Diseases Society

### 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 [19], 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 waking 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.

## ILADS guidelines for 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 coinfecting patients [25,38]. Thus, concurrent testing and treatment for coinfection is mandatory in Lyme disease patients.

## The International Lyme and Associated Diseases Society

### 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 [10]. Intravenous antibiotics are also justified by concern for penetration into the central nervous system [13].

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].

## ILADS guidelines for Lyme disease

**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% [12,31].

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

## The International Lyme and Associated Diseases Society

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, non-randomized 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.

## ILADS guidelines for Lyme disease

### 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 retreatment of 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](http://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.

## The International Lyme and Associated Diseases Society

## References

- 1 Goldoft MJ, Schulze TL, Parkin WE, Gunn RA. Lyme disease in New Jersey. *NJ Med.* 87, 579-584 (1990).
- 2 CDC. Lyme disease-United States, 2000. *MMWR* 51, 29-31 (2002).
- 3 Shadick NA, Phillips CB, Logigian EL *et al*. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. *Ann. Intern. Med.* 121, 560-567 (1994).
- 4 Asch ES, Bujak DJ, Weiss M, Peterson MGE, Weinstein A. Lyme disease: an infectious and postinfectious syndrome. *J. Rheumatol.* 21, 454-456 (1994).
- 5 Parola B, Raoult D. Ticks and tickborne bacterial diseases in humans: an emerging infectious threat. *Clin. Infect. Dis.* 32, 897-928 (2001).
- 6 Wormser GP, Nadelman RB, Dattwyler RJ *et al*. Practice guidelines for the treatment of Lyme disease. The Infectious Diseases Society of America. *Clin. Infect. Dis.* 31(Suppl. 1), 1-14 (2000).
- 7 Rahn DW, Malawista SE. Lyme disease: recommendations for diagnosis and treatment. *Ann. Intern. Med.* 114, 472-481 (1991).
- 8 Feder HM Jr. Differences are voiced by two Lyme camps at a Connecticut public hearing on insurance coverage of Lyme disease. *Pediatrics* 105(4 Pt 1), 855-857 (2000).
- 9 Burtascano JJ. Lyme disease. In: *Conn's Current Therapy*. WB Saunders Company, PA, USA 140-143 (1997).
- 10 Kish MA. Guide to development of practice guidelines. *Clin. Infect. Dis.* 32, 851-854 (2001).
- 11 Steere AC, Malawista SE, Snyderman DR, Shope RE, Andiman WA, Ross MR, Steele FM. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Arthritis Rheum.* 20, 7-17 (1977).
- 12 Logigian EL, Kaplan RE, Steere AC. Chronic neurologic manifestations of Lyme disease. *N. Engl. J. Med.* 323, 1438-1444 (1990).
- 13 Fallon BA, Nields JA. Lyme disease: a neuropsychiatric illness. *Am. J. Psychiatry* 151, 1571-1583 (1994).
- 14 Tylewska-Wierzbanowska S, Chmielewski T. Limitation of serological testing for Lyme borreliosis: evaluation of ELISA and western blot in comparison with PCR and culture methods. *Wien Klin Wochenschr.* 114, 601-605 (2002).
- 15 Halperin JJ. Neuroborreliosis. *Am. J. Med.* 98(4A), 52S-59S (1995).
- 16 Bartaglia HR, Alvarez G, Mercuq A, Fay M, Campoñónico M. Psychiatric symptomatology associated with presumptive Lyme disease: Clinical evidence. *J. Spiro Tick Dis.* 7, 22-25 (2000).
- 17 Corsaro L. Intramuscular Bicillin for persistent pediatric Lyme disease. Proceedings of the 9th International Conference on Lyme Borreliosis & Other Tick-borne Disorders (1999).
- 18 Cimmino MA, Accardo S. Long-term treatment of chronic Lyme arthritis with benzathine penicillin. *Ann. Rheum. Dis.* 51, 1007-1008 (1992).
- 19 Fallon BA, Tager F, Keily J, Weiss N, Liebowitz MR, Fein L, Liegner K. Repeated antibiotic treatment in chronic Lyme disease. *J. Spiro Tick Dis.* 6, 94-102 (1999).
- 20 Lawrence C, Lipton RB, Lowy FD, Coyle PK. Seronegative chronic relapsing neuroborreliosis. *Eur. Neurol.* 35, 113-117 (1995).
- 21 Cameron DJ. Monitoring Lyme disease in the community - First surveillance database sentinel health site. Proceedings of the 12th Annual International Scientific Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders (1999).
- 22 Fallon BA, Kochevar JM, Gaito A, Nields JA. The underdiagnosis of neuropsychiatric Lyme disease in children and adults. *Psychiatr. Clin. North Am.* 21, 693-703 (1998).
- 23 Klemmner MS, Hu LT, Evans J *et al*. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N. Engl. J. Med.* 345, 85-92 (2001).
- 24 Dincerman H, Steere AC. Lyme disease associated with fibromyalgia. *Ann. Intern. Med.* 117, 281-285 (1992).
- 25 Stricker RB, Laitin A. The Lyme wars: time to listen. *Expert Opin. Investig. Drugs* 12, 1609-1614 (2003).
- 26 Nadelman RB, Wormser GP. Erythema migrans and early Lyme disease. *Am. J. Med.* 98(4A), S15-S24 (1995).
- 27 Nowakowski J, McKenna D, Nadelman RB *et al*. Failure of treatment with cephalexin for Lyme disease. *Arch. Fam. Med.* 9, 563-567 (2000).
- 28 Steere AC, Broderick TE, Malawista SE. Erythema chronicum migrans and Lyme arthritis: epidemiologic evidence for a tick vector. *Am. J. Epidemiol.* 108, 317-321 (1978).
- 29 Petrovic M, Vogelers D, Van Renterghem L, Carton D, De Reuck J, Afsharif M. Lyme borreliosis - a review of the late stages and treatment of four cases. *Acta Clin. Belg.* 53, 178-183 (1998).
- 30 Tilton RC, Sand MN, Manak M. The Western immunoblot for Lyme disease: determination of sensitivity, specificity and interpretive criteria with use of commercially available performance panels. *Clin. Infect. Dis.* 25(Suppl. 1), S31-S34 (1997).
- 31 CDC. Recommendations for test performance and interpretation from the second national conference on serologic diagnosis of Lyme disease. *MMWR* 44, 590-591 (1995).
- 32 Trevejo RT, Krause PJ, Sikand VK, Schriefer ME, Ryan R, Lepore T, Porter W, Dennis DT. Evaluation of two-test serodiagnostic method for early Lyme disease in clinical practice. *J. Infect. Dis.* 179, 931-938 (1999).
- 33 Agucro-Rosenfeld ME, Nowakowski J, McKenna DE, Carbonaro CA, Wormser GP. Serodiagnosis in early Lyme disease. *J. Clin. Microbiol.* 31, 3090-3095 (1993).
- 34 Harris N. An understanding of laboratory testing for Lyme disease. *J. Spiro Tick Dis.* 5, 16-26 (1998).
- 35 Ma B, Christen B, Leung D, Vigo-Pelfrey C. Serodiagnosis of Lyme borreliosis by Western immunoblot: reactivity of various significant antibodies against *Borrelia burgdorferi*. *J. Clin. Microbiol.* 30, 370-376 (1992).
- 36 Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. *J. Clin. Microbiol.* 33, 419-427 (1995).
- 37 Magnarelli LA. Laboratory analyses for Lyme disease. *Conn. Med.* 53, 331-334 (1989).
- 38 Krause PJ, Telford S, Spielman A, Sikand VJ, Ryan R, Christianson D, Burke G, Brassard R, Pollack R, Peck J, Persing DH. Concurrent Lyme disease and Babesiosis: Evidence for increased severity and duration of illness. *JAMA* 275, 1657-1660 (1996).
- 39 Luft BJ, Dattwyler RJ, Johnson RC *et al*. Azithromycin compared with amoxicillin in the treatment of erythema migrans: a double-blind, randomized, controlled trial. *Ann. Intern. Med.* 124, 785-791 (1996).
- 40 Dattwyler RJ, Luft BJ, Kunkel M *et al*. Ceftriaxone compared with doxycycline for the treatment of acute disseminated Lyme disease. *N. Engl. J. Med.* 337, 289-294 (1997).

## ILADS guidelines for Lyme disease

41. Barsic B, Maretic T, Majerus L, Strugar J. Comparison of azithromycin and doxycycline in the treatment of erythema migrans. *Infection* 28, 153-156 (2000).
42. Scott LJ, Ormrod D, Goa KL. Cefuroxime axetil: an updated review of its use in the management of bacterial infections. *Drugs* 61, 1455-1500 (2001).
43. Dattwyler RJ, Grunwaldt E, Luft BJ. Clarithromycin in treatment of early Lyme disease: a pilot study. *Antimicrob. Agents Chemother.* 40, 468-469 (1996).
44. Karlsson M, Hammers-Berggren S, Lindquist L *et al.* Comparison of iv. penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. *Neurology* 44, 1203-1207 (1994).
45. Dotevall L, Hagberg L. Successful oral doxycycline treatment of Lyme disease-associated facial palsy and meningitis. *Clin. Infect. Dis.* 28, 569-574 (1999).
46. Luft BJ, Volkman DJ, Halperin JJ, Dattwyler RJ. New chemotherapeutic approaches in the treatment of Lyme borreliosis. *Ann. NY Acad. Sci.* 539, 352-361 (1988).
47. Barzaglia HR, Alvarez G, Mercou A, Fay M, Campodónico M. Psychiatric symptomatology associated with presumptive Lyme disease: clinical evidence. *J. Spirol. Tick Dis.* 7, 22-25 (2000).
48. Ziska MH, Donta ST, Demarest FC. Physician preferences in the diagnosis and treatment of Lyme disease in the United States. *Infection* 24, 182-186 (1996).
49. Culp RW, Eichenfield AH, Davidson RS, Drummond DS, Christofersen MR, Goldsmith DP. Lyme arthritis in children. An orthopedic perspective. *J. Bone Joint Surg. Am.* 69, 96-99 (1987).
50. Weiss LM. Babesiosis in humans: a treatment review. *Expert Opin. Pharmacother.* 3, 1109-1115 (2002).
51. Logigian EL, Kaplan RF, Steere AC. Successful treatment of Lyme encephalopathy with iv. ceftriaxone. *J. Infect. Dis.* 180, 377-383 (1999).
52. Dattwyler RJ, Halperin JJ, Volkman DJ, Luft BJ. Treatment of late Lyme borreliosis - randomized comparison of ceftriaxone and penicillin. *Lancet* 1191-1194 (1988).
53. Schoen RT, Aversa JM, Rahn D'W, Steere AC. Treatment of refractory chronic Lyme arthritis with arthroscopic synovectomy. *Arthritis Rheum.* 34, 1056-1060 (1991).
54. Pavia CS. Current and novel therapies for Lyme disease. *Expert Opin. Investig. Drugs* 12, 1003-1016 (2003).
55. Krause PJ, Lepore T, Sikand VK *et al.* Arovaquone and azithromycin for the treatment of babesiosis. *N. Engl. J. Med.* 343, 1454-1458 (2000).
56. Steere AC, Green J, Schoen RT *et al.* Successful parenteral penicillin therapy of established Lyme arthritis. *N. Engl. J. Med.* 312, 869-874 (1985).
57. Fallon BA. Chronic Lyme Disease Research Study. A double-blind placebo-controlled randomized clinical trial evaluating the efficacy of ten weeks of iv. ceftriaxone and effects on brain imaging. Enrollment since 2000.
58. Cameron DJ. Lyme Disease Retreatment Study. A double-blind placebo-controlled randomized clinical trial evaluating the efficacy of oral amoxicillin for seropositive and seronegative Lyme disease. Enrollment since 2001.
59. Eppes SC, Klein JD, Caputo G, Rose CD. Physician beliefs, attitudes and approaches toward Lyme disease in an endemic area. *Clin. Pediatr.* 33, 130-134 (1994).
60. Peña CA, Mathew AA, Siddiqi NH, Strickland GT. Antibiotic therapy for Lyme disease in a population-based cohort. *Clin. Infect. Dis.* 29, 694-695 (1999).
61. Wahlberg R, Granlund H, Nyman D, Panelius J, Seppala I. Treatment of late Lyme borreliosis. *J. Infect.* 29, 255-261 (1994).
62. Donta ST. Tetracycline therapy for chronic Lyme disease. *Clin. Infect. Dis.* 25(Suppl. 1), S52-S56 (1997).
63. Reid MC, Schoen RT, Evans J, Rosenberg JC, Horwitz RL. The consequences of overdiagnosis and overtreatment of Lyme disease: an observational study. *Ann. Intern. Med.* 128, 354-362 (1998).
64. Steere AC, Taylor E, McHugh GL, Logigian EL. The overdiagnosis of Lyme disease. *JAMA* 269, 1812-1816 (1993).
65. Sigal LH. Anxiety and persistence of Lyme disease. *Ann. J. Med.* 98(4A), 74S-78S (1995).

## Website

101. Burrascano JJ Jr. Managing Lyme disease: diagnostic hints and treatment guidelines for Lyme borreliosis, 2003. Accessed at [www.ILADS.org](http://www.ILADS.org) on November 1, 2003.