

Epidemiologic Assessment of the 2006 IDSA Lyme Disease Guidelines

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I am here to express my concerns as a:

Physician

My patients are being denied treatment based on the IDSA guidelines

President of ILADS

ILADS is an international, multi-disciplinary medical society, dedicated to the diagnosis and appropriate treatment of Lyme and its associated diseases.

Epidemiologist

1. Cameron et al: ILADS guidelines
2. Cameron: Consequences of treatment delay in LD
3. Cameron: Insufficient evidence to deny antibiotics to CLD patients
4. Cameron: Clinical trial validate the severity of persistent LD symptoms
5. Cameron: Generalizability in two clinical trials of LD

1) 2004 Expert Review Anti Infect Ther, 2) 2007 Jour Eval Clin Med, 3) 2009 Med Hypotheses, 4) 2009 Med Hypotheses, 5) 2006 Epidemiol Perspec Innovations

Examples of contested recommendations

Contested recommendations

Laboratory test is required to confirm diagnosis of non-EM Lyme

Prophylaxis

Short term treatment regimens 14-21 days for early Lyme disease

Treatment modality restrictions

Definition of late Lyme disease requires objective findings

Short term treatment regimens for late Lyme

No evidence of persistence

Post Lyme Disease Syndrome Definition

Did 2006 IDSA Lyme disease guidelines meet Dr. Sackett's goals for evidence based medicine?



David Sackett, founder of the EBM movement

“Integrate best research evidence with clinical expertise and patient values” Sackett 2000

- **Evidence**
- **Clinical expertise**
- **Patient values**

All four CLD trials were small

Only the Krupp trial enrolled the appropriate sample size to achieve adequate power

Trial	Calculated sample size	Actual sample size
Klempner seropositive	194	70
Klempner seronegative	66	45
Fallon	45	37
Krupp	55	55

Insignificant findings do not have the precision to conclude:
“Antibiotic therapy has not proven to be useful and is not recommended” for CLD

Heterogeneous outcomes between CLD trials

Outcome	Score	Control	Significance
Fatigue Krupp	64%	18	p<0.001
Fatigue Fallon	66.7	25%	P = 0.05
Physical component score (PCS) Klempler	31 to 41	22 to 29	Not significant
Mental component score (MCS) Klempler	31 to 36	26 to 46	Not significant

Krupp and Fallon: Fatigue improved with treatment
Klempler trials: No treatment effect

The evidence is too heterogeneous for the IDSA 2006 panel to conclude: “Antibiotic therapy has not proven to be useful and is not recommended” for CLD

Poor generalizability of CLD trials

Duration of illness

- Klemmner subjects: ill 4.7 years
- Klemmner subjects: received 3 courses of Rx
- Fallon subjects: symptomatic 9 years

Study subjects represent “Tip of the iceberg”

- Fallon: only 1% of screened subjects met inclusion criteria

“Applying the findings to target populations with characteristics that differ from those included in these trials is inappropriate and may limit options for chronic Lyme disease patients who might benefit from antibiotic treatment.” (Cameron 2006 Generalizability)

The evidence not sufficiently generalizable to conclude: “Antibiotic therapy has not proven to be useful and is not recommended” for CLD

Treatment delay: confounder in CLD trials

Fallon RCT described delays of 1.8 years without discussing whether the delay affected the outcome.

Consecutive case series of LD patients, confirmed by IgG WB
Treatment delay of 1.8 years; strongly associated with treatment failure. (Cameron Med Hypotheses 2007)

Treatment delay was not considered a confounder when concluding: “Antibiotic therapy has not proven to be useful and is not recommended” for CLD

Prophylaxis recommendation: based on a poorly designed trial

Single human trial

Subjects assessed only 6 weeks

Trial could not assess the risk of:

- A rash beyond 6 weeks
- Neurologic manifestation of LD
- Psychiatric manifestation of LD
- Arthritic manifestation of LD
- Chronic manifestations of LD

Evidence has too many limitations to recommend:

“A single dose of doxycycline may be offered”

No evidence to limit most treatment options on “not recommended” list

The 2006 IDSA panel:

- Did not cite Level 1 or II evidence
- Did not give specific reason why agent/modality on list

Panel’s conclusion: “Selected antimicrobials, drug regimens, or other modalities not recommended for the treatment of Lyme disease”

is NOT supported

Examples of concerns with evidence grade

Condition	2006 IDSA
Antibiotic therapy for individual with symptoms beyond 6 months	E-1 E- Strongly against I – Strongest evidence
Other antimicrobial, drug regimens, or other modalities	E-III E- Strongly against III – Weakest evidence

IDSA Evidence Grading Scheme

Grade Quality of evidence

- I Evidence from at least one properly randomized, controlled trial
- II Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from >1 center), from multiple time-series studies, or from dramatic results of uncontrolled experiments
- III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Category Strength of recommendation

- A Strongly in favor
- B Moderately in favor
- C Optional
- D Moderately against
- E Strongly against

Suggested changes to evidence grade

Condition	2006 IDSA	Suggested changes
Antibiotic therapy for individual with symptoms beyond 6 months	E-1 E- Strongly against I – Strongest evidence	B-II B- Moderately in favor II– Moderate evidence (Supports treatment)
Other antimicrobial, drug regimens, or other modalities	E-III E- Strongly against III – Weakest evidence	B-II B- Moderately in favor II - Moderate evidence (Supports use)

Did 2006 IDSA Lyme disease guidelines meet Dr. Sackett's goals for clinical expertise?



- Evidence
- **Clinical expertise**
- Patient values

Clinical expertise refers to the clinician's cumulated experience, education and clinical skills.

NOT “aches and pains of daily living”

Symptoms of CLD severe in Klempner, Krupp, Fallon

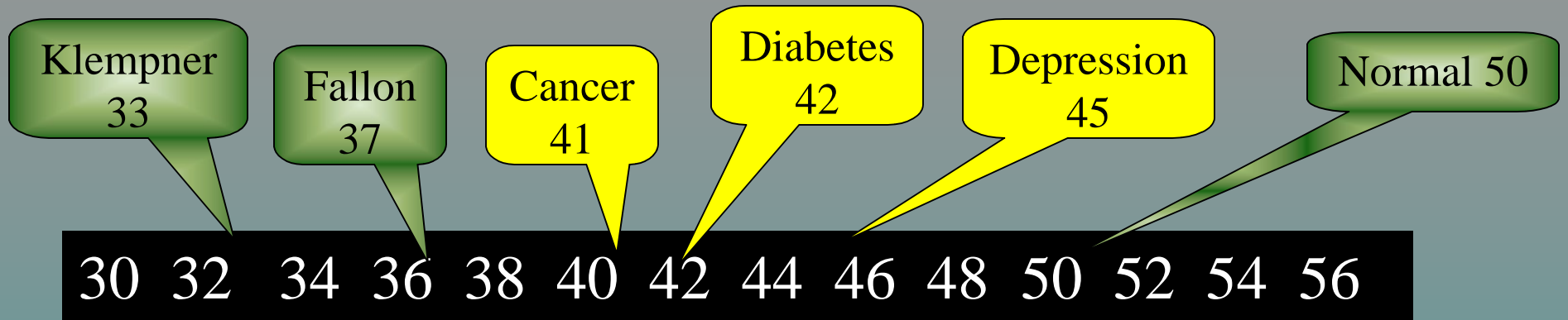
- significant deficits in all 22 standardized measures of:

QOL ✓ **Fatigue** ✓ **Pain** ✓
Cognition ✓ **Role function** ✓ **Psychopathology** ✓

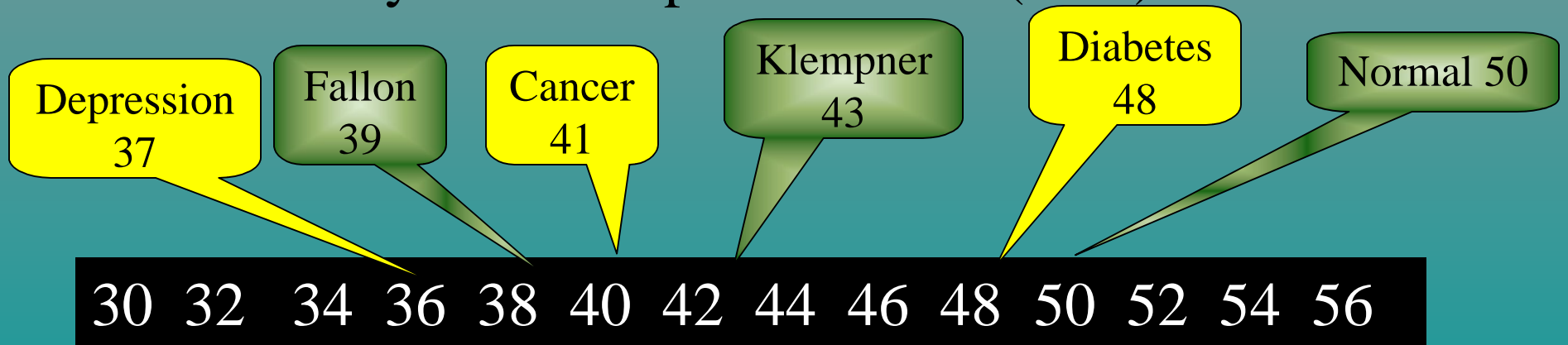
- *“The deficits in physical health status as measured by the SF-36 were equivalent to those observed in patients with congestive heart failure or osteoarthritis”* Klempner, NEJM, 2001

- *“Compared with published samples, reports of pain were similar to those of postsurgery patients, fatigue was similar to that of patients with multiple sclerosis, and limitations in physical functioning were comparable with those of patients with congestive heart failure.”* Fallon, Neurology 2008

Poor quality of life in CLD on SF-36



Physical Component Score (PCS)



Mental Component Score (MCS)

Evidence: CLD not uncommon

- **34%** of a population-based, retrospective cohort study in Massachusetts had long-term sequelae from Lyme disease 6.2 years after treatment.
(Shadick 1994)
- **62%** of a cohort of 215 consecutively treated LD patients in Westchester County remained ill 3.2 years after treatment. (Asch 1994)
- CLD subjects in Klempner, Krupp and Fallon trials

Bayes' theorem not applicable

Denominator (the actual number of LD) **unknown**.

- CDC reported cases continue to rise
- Studies of incidence over 10 years old (Meeks, 1996; Orioski, 1998)
- Incidence estimates 6-12 fold higher than reported

Pretest Probability **unknown**

- Evidence shows CLD patient with subjective symptoms are far sicker than the general population
- Pretest probability based on disease prevalence in population under investigation, not general population
- Predictive value of a positive test does not factor in physician experience in recognition of symptom clusters or ruling out other conditions ie thyroid, anemia, lupus, migraine

Defining CLD

- CLD definition has clinical/financial implications
- 2006 IDSA guideline recommends CLD be defined as “once having objective evidence of B infection must be a condition sine qua non”
- “Sine qua non” means “something absolutely indispensable or essential” (Merriam-Webster, 2009)
- Insufficient evidence on CLD to adequately inform on what types of objective evidence, if any, are appropriate to require
- “Instead, what is needed is scientific thinking that is open-minded and humble as well as methodologically rigorous and informed in order to develop the most appropriate guidelines about what kinds of evidence best identifies CLD.” (Koopman: Submission to IDSA Review Panel 2009)

Did 2006 IDSA Lyme disease guidelines meet Dr. Sackett's goals for patient values?



- Evidence
- Clinical expertise
- **Patient values**

Risks and benefits considered by the IDSA panel

- Adverse effects of antimicrobial therapy
- Complications associated with the use of intravenous catheters
- Inconvenience of prolonged therapies
- The potential impact of the indiscriminate use of antibiotics on the development of antibiotic resistance in the community
- The economic cost of treatment

The desired outcome is to eliminate or alleviate symptoms without causing harm to the patient.

Risks not considered by the IDSA panel

- 34% risk of persistent symptoms at 6.2 years (Shadick 1994)
- 62% risk of persistent symptoms at 3.2 years (Asch 1994)
- 4.7–9 years mean duration of illness (Klempner and Fallon trials)
- Severity of symptoms (Klempner, Fallon and Krupp trials)

Cost not considered by the IDSA panel

\$16,199 per patient - Average annual economic impact of CLD

95% of cost of CLD - Indirect medical costs
Non-medical costs
Productivity losses

\$203 million - The annual economic impact of LD in the US based on 23,763 CDC reported cases

\$2 billion - The annual economic impact of LD in the US based on estimates that the actual number of cases is ten fold higher

Zhang et al. Economic cost of Lyme disease. 2006 Emerg Infect Dis

Heterogeneity not considered by the IDSA panel

- Responsiveness to treatment
- Coinfections
- Comorbidities
- Strain virulence
- Quality of life tradeoffs
- Degree of functional impairment

"Patient heterogeneity requires individualized care and the treating physician's clinical judgment. Risk/Benefit can only be done at the patient-physician level."

Patient Autonomy not considered by the IDSA panel

Respects patient's integrity

- Capacity to self-govern
 - choose from alternative options

Physician Responsibility

- Describe medical facts accurately
- Outline therapeutic choices
- Discuss benefits, risks, and costs
- Make recommendations
- Acknowledge patient's right to self-decision

AMA Principle regarding informed consent

Recommendation: The IDSA guideline should be revised to reflect Dr. Sackett's goals for evidence based medicine:



“Integrate best research evidence
with clinical expertise and
patient values” Sackett 2000

The following is a list of contested recommendations and flaws to be discussed today followed by suggested language

Overview of contested recommendations with flaws

Contested recommendations	Flaws
Laboratory test is required to confirm diagnosis of non-EM Lyme	Laboratory tests too insensitive to rule out diagnosis
Prophylaxis	Single study using inappropriate end point—development of EM rash with no assessment after 6 weeks
Short term treatment regimens 14-21 days for early Lyme disease	Unacceptably high treatment failures rates ranging from 5-40% on intent to treat analysis
Treatment modality restrictions	Scientific studies support many of these modalities
Definition of late Lyme disease requires objective findings	Requirements of objective findings are premature. Appropriate objective markers not yet been determined. Studies support subjective symptoms as part of spectrum of disease.
Short term treatment regimens for late Lyme	Unacceptably high treatment failure rates (exceed 65%) Aggregate sample size 96 patients
No evidence of persistence	Persistence has been demonstrated in animals (mice, dogs, ponies) and some humans Invasive human studies not feasible
Post Lyme Disease Syndrome Definition	Research entrance criteria only Hypothesis not validated Patients with subjective symptoms occur

Recommendation

Challenge to Prophylaxis of Lyme disease--Page 1100

“For prevention of Lyme disease after a recognized tick bite, routine use of antimicrobial prophylaxis or serologic testing is not recommended (E-III).

A single dose of doxycycline may be offered to adult patients (200 mg dose) and to children >8 years of age (4 mg/kg, up to a maximum dose of 200 mg) (B-I) when all of the following circumstances exist: (a) the attached tick can be reliably identified as an adult or nymphal I. scapularis tick that is estimated to have been attached for >36 h on the basis of the degree of engorgement of the tick with blood or on certainty about the time of exposure to the tick, (b) prophylaxis can be started within 72 h of the time that the tick was removed, (c) ecologic information indicates that the local rate of infection of these ticks with *B. burgdorferi* is >20%, and (d) doxycycline is not contraindicated.

ILADS Suggested Recommendation

Physicians should exercise clinical judgment when considering prophylactic antimicrobial treatment for a tick bite. There is insufficient evidence at this time to recommend a single dose of doxycycline as a prophylaxis and it may abrogate the immune response in patients. The optimal duration of prophylactic treatment has not been determined and further research is necessary. Clinical judgment and monitoring of patients is advised.

Rationale: See written submission of Dr. Maloney and PowerPoint submission of Drs. Stricker and Cameron.

Recommendation

Post Lyme Disease Syndrome Treatment

Limitation—Recommendation 2, Pages 1120-1121

To date, there is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease.

ILADS Suggested Recommendation

There is biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after the receipt of recommended antibiotic treatment regimens for Lyme disease. There is no diagnostic test available to prove the eradication of the organism.

Rationale: See written and PowerPoint submissions of Drs. Stricker and Phillips.

Recommendation

Late Neurologic Lyme Disease--Recommendation 3, Page 1113

(See also, Challenge to Implausibility of Persistence)

“Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone (2 g once per day intravenously for 2–4 weeks) (tables 2 and 3) (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-II).

Response to treatment is usually slow and may be incomplete. Re-treatment is not recommended unless relapse is shown by reliable objective measures.

Ceftriaxone is also recommended for children with late neurologic Lyme disease (tables 2 and 3) (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-III).”

ILADS Suggested Recommendation

The optimal agent, combination of agents, duration, and modality for the treatment of late neurologic Lyme disease has not yet been determined. There is evidence of treatment failures following current treatment regimens. Moreover, there is evidence supporting longer therapeutic regimens in some patients. Clinicians should be aware that treatment failure and the persistence of signs and/or symptoms occur in patients treated for Late neurologic Lyme disease and that clinical reassessment and additional treatment is indicated in for some patients. Further research is necessary to determine the optimal regimen for late neurologic Lyme disease.

Rationale: See written submission of Allison DeLong and Drs. Maloney, Cameron, Liegner, Phillips, and Green. See also PowerPoint presentations of Drs. Stricker, Cameron, Liegner, and Phillips.

Recommendation

Challenge to Restrictions on the Use of Clinical Judgment—Pages 1089-90

“Clinical findings are sufficient for the diagnosis of erythema migrans, but clinical findings alone are not sufficient for diagnosis of extracutaneous manifestations of Lyme disease or for diagnosis of HGA or babesiosis. Diagnostic testing performed in laboratories with excellent quality-control procedures is required for confirmation of extracutaneous Lyme disease, HGA, and babesiosis.”

ILADS Suggested Recommendation

“Diagnostic testing performed in CLIA certified laboratories should be sought and may support a diagnosis but a negative test does not rule out Lyme disease, which is a clinical diagnosis. The presence of an erythema migrans alone is sufficient for the diagnosis of cutaneous Lyme disease and laboratory tests are not advised because antibody response in early Lyme disease may not have developed. Research is urgently need for improved diagnostic methods for all stages of Lyme disease.”

Rationale: See written submissions of Drs. Maloney, Stricker and Liegner and PowerPoint presentations of Drs. Stricker and Liegner.

Recommendation

Arthritis –Recommendations 1 and 2, Page 1113

1. Lyme arthritis can usually be treated successfully with antimicrobial agents administered orally (tables 2 and 3). Doxycycline (B-I), amoxicillin (B-I), or cefuroxime axetil (B-III) for 28 days is recommended for adult patients without clinical evidence of neurologic disease. For children, amoxicillin (B-I), cefuroxime axetil (B-III), or doxycycline (if ≥ 8 years of age) (B-I) is recommended (tables 2 and 3). Oral therapy is easier to administer than intravenous antibiotics, is associated with fewer serious complications, and is considerably less expensive. However, it is important to recognize that a small number of patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require intravenous therapy with a b-lactam antibiotic for successful resolution. Further controlled trials are needed to compare the safety and efficacy of oral therapy with intravenous therapy for Lyme arthritis. Neurologic evaluation that may include lumbar puncture should be performed for patients in whom there is a clinical suspicion of neurologic involvement. Adult patients with arthritis plus objective evidence of neurologic disease should receive parenteral therapy with ceftriaxone (tables 2 and 3) (AII). Cefotaxime or penicillin G administered parenterally is an acceptable alternative (B-II). For children, intravenous ceftriaxone or intravenous cefotaxime is recommended (B-III); penicillin G administered intravenously is an alternative (B-III) (tables 2 and 3).

2. Patients who have persistent or recurrent joint swelling after a recommended course of oral antibiotic therapy should be re-treated with another 4-week course of oral antibiotics or with a 2–4-week course of intravenous ceftriaxone (B-III) (tables 2 and 3). A second 4-week course of oral antibiotic therapy is favored by panel members for the patient whose arthritis has substantively improved but has not yet completely resolved, reserving intravenous antibiotic therapy for those patients whose arthritis failed to improve at all or worsened. Clinicians should consider waiting several months before initiating re-treatment with antimicrobial agents because of the anticipated slow resolution of inflammation after treatment. During this period, NSAIDs may be used, but intra-articular injections of corticosteroids are not recommended (D-III). If patients have no resolution of arthritis despite intravenous therapy, and if PCR results for a sample of synovial fluid (and synovial tissue, if available) are negative, symptomatic treatment is recommended (B-III). Symptomatic therapy might consist of NSAIDs, intra-articular injections of corticosteroids, or DMARDs, such as hydroxychloroquine; expert consultation with a rheumatologist is recommended. If persistent synovitis is associated with significant pain or limitation of function, arthroscopic synovectomy may reduce the duration of joint inflammation (B-II). should be performed for patients in whom there is a clinical suspicion of neurologic involvement. Adult patients with arthritis plus objective evidence of neurologic disease should receive parenteral therapy with ceftriaxone (tables 2 and 3) (AII). Cefotaxime or penicillin G administered parenterally is an acceptable alternative (B-II). For children, intravenous ceftriaxone or intravenous cefotaxime is recommended (B-III); penicillin G administered intravenously is an alternative (B-III) (tables 2 and 3).

ILADS Suggested Recommendation
The optimal agent, combination of agents, duration, and modality for the treatment of Lyme arthritis has not yet been determined. There is evidence of treatment failures following current treatment regimens. Clinicians should be aware that treatment failure and the persistence of signs and/or symptoms occur in patients treated for Lyme arthritis and that clinical reassessment and additional treatment may be an option for some patients. Further research is necessary to determine the optimal regimen for arthritic Lyme disease.

Rationale: See written submission of Dr. Zackrison.

Recommendation

Challenge to Restriction on Specific Therapeutic Options--Recommendation 5, Page 1105

“Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are not recommended for treatment of patients with any manifestation of Lyme disease: first generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G, combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), long-term antibiotic therapy, anti-Bartonella therapies, hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, specific nutritional supplements, and others (see table 4) (EIII).”

ILADS Suggested Recommendation

There is insufficient evidence to support this recommendation. It should be deleted from the guidelines.

Rationale: The optimal agent, combination of agents, duration, and modality for the treatment of Lyme disease has not yet been determined. There is evidence supporting the efficacy of some of these agents. Further research studies are needed before recommendations restricting treatment modalities can be made.

See submission of Drs. Maloney and Phillips and PowerPoint presentations of Drs. Liegner and Cameron.

Recommendation

Post Lyme Disease Syndrome Definition—

Recommendation 1, Page 1120

(See also, Challenge to Implausibility of Persistence)

There is no well-accepted definition of post-Lyme disease syndrome. This has contributed to confusion and controversy and to a lack of firm data on its incidence, prevalence, and pathogenesis. In an attempt to provide a framework for future research on this subject and to reduce diagnostic ambiguity in study populations, a definition for post-Lyme disease syndrome is proposed in table 5. Whatever definition is eventually adopted, having once had objective evidence of *B. burgdorferi* infection must be a condition sine qua non.

Furthermore, when laboratory testing is done to support the original diagnosis of Lyme disease, it is essential that it be performed by well-qualified and reputable laboratories that use recommended and appropriately validated testing methods and interpretive criteria [117, 118]. Unvalidated test methods (such as urine antigen tests or blood microscopy for detection of *Borrelia* species) should not be used [337].

ILADS Suggested Recommendation

It is premature to require that patients have had prior objective evidence of Lyme disease as a sine qua non of post Lyme disease syndrome, including supportive laboratory testing. Any definition of post-Lyme disease syndrome should include the full spectrum of disease, including persistent symptoms and neuro-psychiatric manifestations. This term “post Lyme disease syndrome” implies a lack of infectious etiology and is premature. A more appropriate term, which does not predetermine the etiological cause of the condition, should be established. Further research is essential to determine the full spectrum of objective and subjective manifestations of Lyme disease for research, diagnostic and treatment purposes.

Rationale: See written submissions of Drs. Cameron, Phillips, Maloney and Green. See PowerPoint submissions of Drs. Cameron and Phillips.

Recommendation

Post Lyme Disease Syndrome Treatment

Limitation—Recommendation 2, Pages 1120-1121

Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (6 months) subjective symptoms after administration of recommended treatment regimens for Lyme disease (E-I).

ILADS Suggested Recommendation

Antibiotic therapy has been useful for some patients with chronic manifestations of Lyme disease (A-I). However, optimal treatment regimens have not been established for this condition. Research to develop improved approaches to treat chronic manifestations of Lyme disease is urgently needed.

Rationale: A risk/benefit analysis based on the individual patient presentation, functional impairment, and quality of life should include the risk of treatment as well as the risk of not treating a chronic condition. The societal risk of antimicrobial resistance must be weighed against the burden on society of a chronically ill population with long term severe disability equivalent to that of congestive heart failure and that resultant productivity loss.

See written submissions of Allison DeLong, and Drs. Phillips, Green and Cameron and PowerPoint presentations of Allison DeLong, and Drs. Phillips and Cameron.

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