Appendix I: Comparison of ILADS and IDSA Treatment Recommendations by Clinical Situation

Conflicting guidelines exist for over 25 conditions, including Lyme disease. The Institute of Medicine (IOM) explains that conflicting guidelines most often result "when evidence is weak; developers differ in their approach to evidence reviews (systematic vs. nonsystematic), evidence synthesis or interpretation; and/or developers have varying assumptions about intervention benefits and harms."[191] There is no current system for reconciling conflicting guidelines.[191] The IOM and other health policy analysts suggest that guideline developers acknowledge the existence of conflicting guidelines and be transparent in their processes, thus enabling readers to understand how recommendations were derived and who developed them.[191][192] This table sets forth the differences between the Lyme disease guidelines of the IDSA and ILADS. Appendix II, which follows this appendix, attempts to explicate the divergent values underlying IDSA and ILADS guideline recommendations.

ILADS	IDSA	Comments on Differences
Management of Ixodes species Bites		
1. Recommends against single 200 mg dose of doxycycline 2. Recommends prompt prophylaxis with doxycycline 100 -200 mg twice daily for a minimum of 20 days for all *Ixodes* tick bites in which there is evidence of tick feeding, regardless of the degree of tick engorgement or the infection rate in the local tick population.[a] 3. Recommends patient education on prevention of future tick bites, on the manifestations of Lyme and other *Ixodes*-borne diseases and the manifestations and prevention of antibiotic-associated *C. difficile* infections. .	1. Strongly Recommends Single 200 mg dose of oral doxycycline for Ixodes scapularis if the following criteria are met: a. Tick attached for minimum of 36 hours b. Tick infection rate > 20% in local where bite occurred c. Treatment can begin within 72 hours of tick removal 2. Recommends education of healthcare providers 3. Recommends various preventative strategies	Opposing recommendations on single dose doxycycline reflect differing evaluations of the evidence from the single dose doxycycline trial with regard to effectiveness and therapeutic risks.
Management of Erythema Migrans		

1. Recommends against treatment regimens using 20 or fewer days of phenoxymethylpenicillin, amoxicillin, cefuroxime or doxycycline and 10 or fewer days of azithromycin. 2. Recommends A minimum of 4 -6 weeks of Amoxicillin, cefuroxime or doxycycline or a minimum of 3 weeks of azithromycin. 3. Recommends ongoing assessments to detect persistence, progression or relapse of Lyme disease or the presence of other tick-borne illnesses. The initial assessment follows the completion of therapy; subsequent evaluations are done on an as needed basis. 4. Recommends extending treatment in patients who remain symptomatic after initial therapy. 5. Recommends retreatment of persistent, recurrent or newly developed manifestations of Lyme disease. 6. Recommends patient education regarding potential manifestations of Lyme disease and other Ixodes-transmitted infections as well as the manifestations and prevention of antibiotic-associated *C. difficile* infections.	1. Strongly recommends: Doxycycline for 10 – 21days, amoxicillin or cefuroxime axetil for 14 -21 days. 2. Strongly recommends against using macrolides as first-line agents. 3. Strongly recommends against any use of first-generation cephalosporins and use of IV ceftriaxone for EM unless AV block or neurologic involvement present. Also strongly recommends cefuroxime or amoxicillin-clavulanic acid when clinicians cannot determine whether lesion is an EM or cellulitis. 4. Recommends pregnant/lactating patients, with the exception of avoiding doxycycline, be treated the same as non-pregnant patients. 5. Strongly recommends against a wide range of agents regardless of disease stage; see comments. 6. Strongly recommends clinicians consider the possibility that patients may have other tick-borne diseases.	Differing recommendations regarding the duration of therapy reflect differences in how the organizations viewed the trial designs, which used disease-centered outcome definitions and non-ITT methodology. IDSA accepted the outcomes as reported while ILADS did not. ILADS reanalyzed the data after applying patient-centered definitions, (which resulted in the recategorization of some outcomes) and conservative methodology for calculating outcomes. The resulting success rates were substantially lower than the originally reported rates. IDSA recommendation against macrolides may be the result of not considering outcomes from the four European trials included in ILADS' GRADE analysis.[b] ILADS recommends extending treatment or retreating in appropriate clinical situations. IDSA recommends against both approaches yet researchers in seven of the nine trials included in this GRADE analysis offered such therapy. IDSA expressly prohibits the use of several therapies.[c] ILADS agrees that first-generation cephalosporins, intravenous hydrogen peroxide and bismuth injections are not recommended. However, ILADS has concluded that it is premature to exclude other potentially beneficial therapies based on the evidence to date. Therefore, ILADS contends that the use of such agents should not be precluded until studies have demonstrated their ineffectiveness in the treatment of Lyme disease.
Management of Patients with Persistent Post-treatment Manifestations		
1. Strongly recommends discussing the possibility of antibiotic retreatment with all patients and performing individualized risk-benefit assessments for patient-appropriate options. Information on reducing the risk of antibiotic-associated *C.difficile* infections should be included in these discussions. 2. Recommends 4-6 weeks of antibiotics when retreatment is undertaken, with antibiotic	1. Strongly recommends against antibiotic retreatment for patients with persistent post-treatment manifestations of Lyme disease.	Opposing recommendations regarding antibiotic retreatment reflect differences in evidence quality ratings and risk-benefit analyses. ILADS found that primary endpoints were often inadequately designed or underpowered while the IDSA apparently did not note these limitations or thought they were insignificant. The IDSA risk-benefit assessment minimized the severity of patients' quality of life impairments, highlighted adverse

selection based on several factors. 3. Recommends reassessment immediately following the initial course of retreatment and basing decisions regarding the subsequent modification or discontinuation of treatment on several factors.		events and discounted positive treatment effects; its recommendation is based on a generalized risk-benefit assessment. ILADS' risk-benefit analysis recognizes the positive treatment effect seen in two of the trials and that significant quality of life impairments may justify the higher risk of adverse events. ILADS notes the heterogeneity within this patient population regarding several clinical characteristics, most importantly, quality of life impairments and the acceptance of/aversion to treatment risk. For this reason its recommendation mandates individualized risk-benefit assessments. Opposing recommendations also reflect different values regarding: 1) the use of clinical judgment when the evidence is uncertain, 2) the need for individualized, patient-centered care and 3) the role of patient preferences in medical decision-making. See Appendix II, which compares ILADS and IDSA values.

[a] In cases where prophylaxis is not utilized, the immediate reporting of any Lyme-related symptom is emphasized.
[b] Strle F, Ruzic E, Cimperman J. Erythema migrans: comparison of treatment with azithromycin, doxycycline and phenoxymethylpenicillin. *J Antimicrob Chemother.* Oct 1992;30(4):543-550; Strle F, Preac-Mursic V, Cimperman J, Ruzic E, Maraspin V, Jereb M. Azithromycin versus doxycycline for treatment of erythema migrans: clinical and microbiological findings. *Infection.* Mar-Apr 1993;21(2):83-88; Weber K, Wilske B, Preac-Mursic V, Thurmayr R. Azithromycin versus penicillin V for the treatment of early Lyme borreliosis. *Infection.* Nov-Dec 1993;21(6):367-372; Barsic B, Maretic T, Majerus L, Strugar J. Comparison of azithromycin and doxycycline in the treatment of erythema migrans. *Infection.* May-Jun 2000;28(3):153-156.
[c] Table 4 of the IDSA guidelines.

Appendix II: ILADS' Guideline Development Process in Relationship to the Institute of Medicine Standards for Trustworthy Guidelines

The Institute of Medicine report Clinical Practice: Guidelines We Can Trust was published in 2011 and represents a substantial advance in delineating standards for developing guidelines.[1] This appendix discusses the guideline development process that ILADS followed to produce its guidelines, Evidence Assessments and Guideline Recommendations in Lyme disease: The Clinical Management of Known Tick Bites, Erythema Migrans Rashes and Persistent Disease, and its conformity to the standards proposed by the IOM.

STANDARD 1: Establishing transparency

No outside funding was used for the development of the guidelines. The guidelines were developed using the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE) to ensure a high quality evidence review and transparency.[2-5] The GRADE system has been adopted by over 25 organizations, including the World Health Organization, the American College of Physicians, and the Cochrane Collaboration. It has also recently been adopted by the Infectious Diseases Society of America (IDSA), which has produced guidelines on Lyme disease that conflict with those of ILADS. It was thought that adoption of the same scheme of review would increase the transparency of the guideline development process and make value differences between the two organizations transparent.

The guidelines were developed by a three member working group which met every other week over a period of two years. The working group included an epidemiologist/physician, a physician educator, and a patient advocate. This group reported back to the full guidelines panel, which consisted of the board of directors of ILADS. The working group identified three questions for the guidelines to address, anticipating that additional questions related to Lyme disease would be addressed in future guidelines. The working group assessed the available evidence for each question using the GRADE process. A literature search using Pubmed and question-specific criteria was performed for each question; search criteria are set forth listed in the guidelines. The working group a) assessed the quality of the available evidence, b) performed a risk/benefit assessment for each question, and c) evaluated whether the role of patient preferences and values for each question was low, moderate or high. Recommendations were made based on these assessments, followed by a discussion of scientific and clinical factors concerning the recommendations.

A preliminary draft of the guidelines was distributed to the full guideline panel for comments and the guidelines were then refined by the working group and resubmitted to the full guidelines panel for additional comments and approval. In addition, for each recommendation, each member of the full guidelines panel was polled to determine whether they agreed with the recommendation to assure consensus. Copies of these documents have been retained by ILADS administration.

Once this process was completed, the guidelines were distributed to outside reviewers for further comment on the guidelines as well as on each recommendation. Fourteen of the seventeen people selected as outside reviewers responded with comments. The outside reviewers included a patient advocacy organization, researchers, treating physicians, a psychologist, a psychiatrist, and individual patients. Comments from each reviewer were anonymously posted on a log, which the working group responded to, making any modifications to the recommendations that the working group deemed necessary.

STANDARD 2: Management of conflict of interest (COI)

Members of the working group and the full guidelines panel were asked to declare all interests and activities potentially resulting in a conflict of interest (COI) with development of the guidelines, by written disclosure. The disclosure form reflected all current and planned commercial interests. Written conflict of interest forms were completed and are on file at ILADS. Although the panel determined that payments to physicians that are inherent in the provision of healthcare did not disqualify experienced clinicians from serving on the guideline panel or working group, other forms of financial relationships exceeding $10,000 that were not intrinsic to medical practice and accordingly were avoidable were taken into account.[6] No panel members held such financial conflicts-of-interest of $10,000 or more. All members of the panel were members of ILADS and none reported any other potential institutional conflicts. To ensure clinical

expertise, the panel included clinicians who treat Lyme disease; 7 of 10 panel members are physicians who treat patients with Lyme disease.

Several panel members, including members of the working group, serve on non-profit boards related to Lyme disease. The panel did not consider these interests sufficient to exclude participation by these panel members.

STANDARD 3: Guideline development group composition

The panel is multidisciplinary and balanced. It included a methodologist, clinicians, and populations expected to be affected by the guidelines. Specifically, the panel included a clinical epidemiologist (DC), a consumer representative (LJ), and clinicians with expertise in the diagnosis and treatment of Lyme disease. The panel considered strategies to increase the participation of patient and consumer representatives and included a consumer advocate and representative on both the working group and the full guidelines panel. In addition, the panel included individual patients as reviewers of the final draft of the guidelines. Some panel members had attended Cochrane Collaboration conferences and training sessions regarding GRADE or had an epidemiological background. In addition, the working group engaged in a journal club regarding GRADE methodology for a number of months before beginning the assessment of evidence for the review.

STANDARD 4: Clinical practice guideline–systematic review intersection

The guidelines panel utilized the GRADE system of evidence assessment. The full GRADE analysis was performed by the working group. Members of the panel were also educated on the GRADE process. The working group completed the assessment of evidence prior to determining appropriate treatment recommendations. The MEDLINE and clinicaltrial.gov database were used to locate articles published between June 1976 and March 5, 2013 that are relevant to the prevention, assessment, and treatment of Lyme disease for all age groups. The query was restricted to articles published in the English language. Priority was given to publications reporting original research, review articles, and, results of previous guidelines.

STANDARD 5: Establishing evidence foundations for and rating the strength of recommendations

The working group used the GRADE scheme to analyze the quality of the available evidence and summarize its findings. The group chose to include only evidence from RCTs and meta-analyses in its assessment. GRADE classifies the quality of the available evidence, in aggregate, as either high, moderate, low, or very low. In assessing individual studies, RCTs are typically rated as being of high quality but this rating may be downgraded due to limitations in design or execution. The working group's assessment of the overall quality of the relevant evidence was based on the quantity, consistency, precision, generalizability and biases of the studies under consideration. The evidence for each of the three clinical questions had several limitations; therefore, the working group determined the evidence was of very low quality.(Tables 2, 4, 6)

In keeping with GRADE, ILADS' treatment recommendations accounted for the quality of the evidence, the risk-benefit assessments of the various therapeutic strategies and patient values and preferences; organizational values pertaining to treatment decisions were also

noted. Recommendations are patient-centered and each includes an assessment of the role of patient values in choosing a therapeutic approach. In making these assessments, the panel considered whether patients would likely have divergent views regarding risk/benefit trade-offs.

Given the low quality of the evidence, the panel rated the strength of each recommendation based on the extent to which the risk-benefit assessment favored a particular course of action and aligned with the values of most patients. The guidelines make a "strong recommendation" in instances where risk-benefit analyses favor a particular intervention such that most patients would choose it. When the risks and benefits of an intervention are balanced or less clear, the panel determined that the choices of individual patients are likely to diverge. In these instances the guidelines make a "recommendation" that identifies treatment options.

There are substantial differences of opinion between the IDSA and ILADS regarding the diagnosis and treatment of Lyme disease. To assist reader comparisons of the recommendations issued by the two organizations, the ILADS guidelines include an appendix summarizing these differences. There are also substantial differences between the values held by IDSA and ILADS and these are reflected in the guidelines of the two medical societies. The ILADS guidelines contain an appendix that attempts to make the differing values transparent to the reader.

STANDARD 6: Articulation of recommendations

The recommendations have a standardized format and each recommendation includes precise details regarding the recommended action and when it should be implemented. The panel identified key implementation strategies targeting outcomes that matter to patients with Lyme disease. The guidelines aimed at ""bridging the gap between best evidence and actual practice".[7] Web-based educational material, including complete guideline documents and informational brochures for clinicians and the public, will be available on the ILADS website - www.ILADS.org. International professional conferences, grand rounds, webinars, and other regional programs will encourage an ongoing dialogue and assist in translating guideline recommendations into clinical practice. Compliance with strong recommendations is easily evaluable.

STANDARD 7: External review

A draft of the guidelines and summary tables was made available to researches, healthcare professionals, patients, and community organizations for comments prior to publication. The authorship of external reviewer comments has been kept in a confidential log. The working group reviewed and responded to the comments from external reviewers, with some comments prompting modifications to the guidelines. A log of the working group's responses to the comments was also prepared; both documents are on file at ILADS.

STANDARD 8: Updating

The literature will be monitored regularly following guideline publication to identify the emergence of new, potentially relevant evidence and to evaluate the continued validity of the guideline. A formal reassessment of the guideline will be conducted in 2018 or sooner, if new evidence emerges which necessitates the modification of a clinically important recommendation.

1. Clinical Practice Guidelines we can trust , Available from http://www.nap.edu/catalog.php?record_id=13058, last accessed 3/1/14. (Ed.^(Eds)
2. Guyatt GH, Oxman AD, Vist GE *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 336(7650), 924-926 (2008).
3. Guyatt G, Gutterman D, Baumann MH *et al.* Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. *Chest*, 129(1), 174-181 (2006).
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6. Institute of Medicine (Committee on Conflict of Interest in Medical Research Education and Practice). ***Conflict of interest in medical research, education, and practice*** (eds. Lo, B, Field, M) (National Academies Press., Washington, DC, 2009).
7. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. *Jama*, 268(2), 240-248 (1992).

Appendix III: Patient-centered Outcomes in Trials of Erythema Migrans Treatment

Author	Agent; Duration, in days	N	Complete (%)	Total Non-complete[a]	Wrongly Enrolled	AE	Non-comply	Lost	Retreat[b]	Symptom /findings[c]	Original Trial Failed + Retreat	Complete Success[d], (%) 95% binomial CI	Total Failure[e], (%) 95% binomial CI
Strle 1992	Azith 10d	22	20 (90.9%)	2	1	0	0	1	0	3	0	17/22, (77.3%) CI: 54.6,92.2	5/22, **(22.7%)** CI: 7.8, 45.4
Strle 1992	Doxy 14d	23	23 (100%)	0	0	0	0	0	0	4	2	17/23, (73.9%) CI: 51.6, 89.2	6/23, (**26.1%)** CI: 10.2, 48.4
Strle 1992	PMP 14d	23	21 (91.3%)	2	0	2	0	0	0	7	2	12/23, (52.2%) CI: 30.6, 73.3	11/23, **(47.8%)** CI: 26.8, 69.4
Massarotti 1992	Azithro 10d	16[f]	16 (100%)	0	0	0	0	0	4	0	4	12/16, (75.0%) CI: 47.6, 92.7	4/16, **(25.0%)** CI: 7.3, 52.4
Massarotti 1992	Amox + proben 10d	19[f]	19 (100%)	0	0	2[g]	0	0	4	0	4	13/19, (68.4%) CI: 43.4, 87.4	6/19, **(31.6%)** CI: 12.6, 56.6
Massarotti 1992	Doxy 10 d	22[f]	22 (100%)	0	0	0	0	0	8	0	8	14/22, (63.6%) CI: 40.7, 82.8	8/22, **(36.4%)** CI: 17.2, 59.3
Nadelman 1992	Cefur 20d	63	52 (82.5%)	11	0	1	?	?	0-9[h]	9[i]	9	34/63, (54.0%) CI: 40.9, 66.6	29/63, **(46.0%)** CI: 33.4, 59.1
Nadelman 1992	Doxy 20d	60	44 **(72.3%)**	16	1	0	?	?	0-9[h]	6[i]	9	29/60, (48.3%) CI: 35.2, 61.6	31/60, (51.7%) CI: 38.4, 64.8
Strle 1993	Azith 5d	55	55 (100%)	0	0	0	0	0	1	10	1	44/55, (80.0%) CI: 67.0, 89.6	11/55, **(20.0%)** CI: 10.4, 33.0
Strle 1993	Doxy 14d	52	52 (100%)	0	0	0	0	0	7	15	7	30/52, (57.7%) CI: 43.2, 71.3	22/52, **(42.3%)** CI: 28.7, 56.8
Weber	Azith 10d	33	32[j]	1	0	1	0	0	4[k]	3[k]	4	25/33, (75.8%)	8/33[j], **(24.2%)**

1993			(97.0%)									CI:57.7, 88.9	CI: 11.1, 42.3
Weber 1993	PMP 10d	33	33[j] (100%)	0	0	0	0	0	1[k]	4[k]	1	28/33, (84.8%) CI: 68.1, 94.9	5/33[j], **(15.2%)** CI: 5.1, 31.9
Luft 1996	Azith 7d	124	111 (89.5%)	13	3	2	0	8	2	17	3	91/124, (73.4%) CI: 64.7, 80.9	33/124, **(26.6%)** CI: 19.1, 35.3
Luft 1996	Amox 20d	122	106 (86.9%)	16	0	5	2	9	0	4	0	102/122, (83.6%) CI:75.8, 89.7	20/122, (**16.4%)** CI: 10.3, 24.2
Barsic 2000	Azithro 5d	48	47 (97.9%)	1	0	0	0	1	0	6	1	40/48, (83.3%) CI: 69.8, 92.5	8/48, **(16.7%)** CI: 7.5, 30.2
Barsic 2000	Doxy 14d	40	35 (87.5%)	5	0	1	0	4	0	3	2	30/40, (75.0%) CI: 58.8, 87.3	10/40, **(25.0%)** CI: 12.7, 41.2
Eppes 2002	Cefur 20d 30mg/kg	15	15 (100%)	0	0	0	0	0	1	0	1	14/15, (93.3%) CI: 68.1, 99.8	1/15, **(6.7%)** CI: 0.2, 31.9
Eppes 2002	Amox 20d	13	12 (92.3%)	1	0	0	0	1	0	0	0	12/13, (92.3%) CI: 64.0, 99.8	1/13, **(7.7%)** CI: 0.2, 36.0
Eppes 2002	Cefur 20d 20mg/kg	15	12 **(80.0%)**	3	0	2	0	1	0	0	0	12/15, (80.0%) CI: 51.9, 95.7	3/15, (20.0%) CI: 4.3, 48.1
Cerar 2010	Cefur 15d	140	114 (81.4%)	26	0	0	0	26	0	4	0	110/140, (78.6%) CI: 70.8, 85.1	30/140, **(21.4%)** CI: 14.9, 29.2
Cerar 2010	Doxy 15d	145	116 **(80.0%)**	29	0	0	0	29	2	1	2	113/145, (77.9%) CI: 70.3, 84.4	32/145, (22.1%) CI: 15.6, 29.7

Adverse events (AE) [a] Total non-complete includes subjects that were wrongly enrolled, withdrawn secondary to adverse events, noncompliant or lost to follow-up. [b] Subjects retreated by investigators during trial. [c] Subjects symptomatic at the final endpoint. [d] Complete success = resolution of all signs and symptoms, without retreatment, and no evidence of relapse during observation period. [e] Total failure includes investigator-identified failures, the retreated and those symptomatic at the final endpoint as well as subjects wrongly enrolled, withdrawn prematurely due to adverse events, lost to follow-up and those labeled as "unevaluable" for any reason. [f] Includes only subjects who received treatment; some non-EM subjects were originally enrolled but subsequently dropped when their baseline serology was negative. [g] Although 4 subjects discontinued treatment prematurely due to AE, the 2 who were not retreated yet were asymptomatic at the final endpoint were not included here. [h] 13 subjects were retreated but the authors did not break this down by agent. [i] Subjects "improved" at 1 month were not considered failures and were included in the group assessed at 12 months. [j] Trial data at 3 months, Table 2, [k] Trial data at 3 months, Table 3.