Evidence-based Analysis of the 2006 IDSA Lyme Disease Guidelines

for

IDSA Review Panel Hearing of July 30, 2009

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Written Submissions

- Challenge to the Recommendation Restricting the Use of Clinical Judgment
- Challenge to the Recommendation on the Prophylaxis of Lyme Disease
- Challenge to the Recommendation Limiting the Duration of Treatment for Early Lyme Disease
- Challenge to the Recommendation Limiting the Duration of Treatment for Early Lyme Disease
- Challenge to the Recommendation Restricting Specific Therapeutic Options in the Treatment of Lyme Disease
- Challenge to the Recommendation Regarding Post-treatment Lyme Disease Symptoms

Evidence Review

Evidence is:

- Insufficient
- Misrepresented
- Misapplied
- Missing
- Evolving

Insufficient Evidence

2006 Guidelines Evidence:

- 72 graded recommendations
  - Level I 16
  - Level II 17
  - Level III 39
- **54% recommendations based on opinion, clinical experience and descriptive studies**

Evidence Misrepresented

- **Strength of studies over-rated**
  - Design flaws, poor execution
  - Missing data excessive
  - Poor external validity
- **Inappropriate statistical analysis**
  - Complete-case
  - Last-observation-carried-forward
  - Intent-to-treat analysis ⟶ preferred method

Inappropriate Outcome Analyses

Complete response to treatment

Doxycycline for 10 days

Evaluation Point	% Response	Complete-case	Intent-to-treat
Baseline	NA	61 patients	61 patients
20 days	71%	34/48 (71%)	34/61 (56%)
3 month	77%	36/47 (77%)	36/61 (59%)
12 months	84%	36/43 (84%)	36/61 (59%)
30 months	90%	28/31 (90%)	28/61 (46%)

Wormser GP. Ann Intern Med 2003; 138:697-704.

Evidence Misrepresented

- Study definitions
- Prejudicial terms

  - case reports from European journals called anecdotal (p 1098, 1118)
  - non-IDSA theories called “notions” (1118)

- Vague phrases, not statistics

  - “vast majority” = 60% (page 1107)
  - “great majority” = 68% (page 1099)

Evidence Misapplied

- Trials yielding poor outcomes called supportive
  - Treatment trials for early and late disease
- Cited references not truly supportive
  - Zeidner prophylaxis in mice
- Errors in reasoning
  - Circular logic
  - Faulty deductive reasoning

    restrictions to use of prophylaxis

Evidence Misapplied

CDC Surveillance case definition

NOT

intended for clinical diagnosis

Evidence Missing

Available but omitted

- *Borrelia burgdorferi* complexity
  - Intracellular location
  - Pleomorphic nature
  - Implications of strain variation
  - Mechanisms of immune system evasion
- Persistence evidence
- Studies demonstrating poor sensitivity of two-tier testing

Evidence Missing

Not fully known

- Numbers and location of *B. burgdorferi* species
- Incidence and prevalence data
  - under-reporting
  - CDC definition doesn't include encephalopathy, other neurologic or psychiatric syndromes
- Management of multiply co-infected patients

Prophylaxis Challenge

Recommendation 2, page 1100

A single dose of doxycycline may be offered when all of the following circumstances exist:

(a) tick attached for >36 h

(b) prophylaxis can be started within 72 h of removal

(c) local rate of infection of these ticks with *B. burgdorferi* is >20%

(d) doxycycline is not contraindicated

Prophylaxis Challenge

- **Insufficient evidence**
  - Single human trial
  - Time restriction unsupported
- **Misrepresented: Strength of Nadelman study**
  - Poor external validity
    - entomologist assessed ticks
    - rates of local tick infection often unavailable

Nadelman RB. N Engl J Med 2001; 345: 79–84.

Prophylaxis Challenge

- **Misrepresented: Strength of Nadelman study**
  - Significant design flaws
    - 6 wk follow-up
    - EM as primary endpoint

Study design only allows for conclusions regarding prevention of EM

Claims that single dose oral doxycycline prevents all Lyme disease are not scientifically grounded

Prophylaxis Challenge

- **Misrepresented: Outcomes in Nadelman**
  - Incorrect statistical analysis
    - placebo risk higher than stated
    - effectiveness overstated
- **Misapplied: Zeidner mouse studies**
  - **DO NOT** support single-dose oral regimen

Zeidner N. Antimicrob Agents Chemother 2004; 48:2697-9.

Zeidner N. J Med Microbio 2008; 57:463–8

Prophylaxis Challenge

- **Misdirection: Adverse events**
  - Guidelines repeatedly stress risk of treatment
  - **Risk-benefit analysis should weigh consequences**: adverse event from antibiotic vs. Lyme disease
- **Missing from Guidelines**
  - Discussion of unintended consequences: seronegative Lyme
  - Acknowledgement that risk of late Lyme from failed prophylaxis unknown

Early Lyme Disease Challenge

Recommendation 1, page 1104:

"Doxycycline (100 mg twice per day), amoxicillin (500 mg 3 times per day), Or cefuroxime axetil (500 mg twice per day) for 14 days (range for doxycycline, 10–21 days; range for amoxicillin or cefuroxime axetil, 14–21 days) is recommended for treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans in the absence of specific neurologic manifestations (see Early Neurologic Lyme Disease) or advanced atrioventricular heart block (tables 2 and 3) (A-I).

Ten days of therapy is sufficient if doxycycline is used; however, given the much shorter halflife of b-lactam drugs, such as amoxicillin or cefuroxime axetil, it is unclear whether a 10-day course of these drugs would be as effective.

Therefore, for uniformity, a 14-day course of therapy is recommended for all of the first-line oral agents.

Early Lyme Disease Challenge

- **Insufficient Evidence**
  - No trials used solely amoxicillin or cefuroxime for < 20 days
  - 10d doxycycline recommendation based on 87 patients
    - 26 from Massarotti
    - 61 from Wormser 2003

Massarotti EM Am J Med 1992; 92:396-403.

Wormser GP Ann Intern Med 2003; 138:697-704.

Early Lyme Disease Challenge

Massarotti 1992

- Comparative study; 6 month follow-up
  - 10d Doxy or Amox + probenecid or azithro x5d
- Reported 5% failure rate in each group
- Doxycycline 100mg BID x 10 days
  - 26 pts doxycycline; only 22 followed
  - 7 immediately retreated with oral antibiotics
  - 1 other retreated later with ceftriaxone

Early Lyme Disease Challenge

Wormser 2003

- Comparative study; 30 mo follow-up
- Reported satisfactory outcomes as:

  - 86.5% doxycycline 100mg BID x 10d +ceftriaxone x1d

  - 90.3 % doxycycline 100mg BID x 10d

  - 83.9% doxycycline 100mg BID x 20d

Early Lyme Disease Challenge

Intent-to-treat Analysis

Doxycycline 100mg BID x 10 days

Author	N	Success	Improved	Uneval	Clinical Failure	Total Failure
Massarotti 1992	26	14 (54%)	-	4 (15%)	8 (31%)	12 (**46%**)
Wormser* 2003	61	36 (59%)	6 (10%)	18 (29%)	1 (2%)	19 (**31%**)

*Data from 12 month evaluation

Early Lyme Disease Challenge

Intent-to-treat Analysis

Doxycycline 100mg BID/TID x 20-21 days

Author	N	Success	Improve	Uneval	Failed	Total Failure
Dattwyler 1990	37	35 (95%)	-	2 (5%)	-	2 (**5%**)
Dattwyler 1997	72	58 (81%)	-	13 (18%)	1 (1%)	14 (**19%**)
Nadelman 1992	45	29 (64%)	6 (13%)	7 (16%)	3 (7%)	10 (**22%**)
Luger 1995	89	48 (54%)	5 (6%)	36 (40%)	-	36 (**40%**)
Wormser* 2003	59	30 (51%)	10 (17%)	19 (32%)	-	19 (**32%**)

*Data from 12 month evaluation

Late Neurologic Lyme Challenge

Recommendation 3, page 1113

"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)."

Late Neurologic Lyme Challenge

- **Insufficient evidence**
  - 4 open-label trials for analysis
  - 96 patients
  - Ceftriaxone of various duration
- **Evidence misapplied**
  - Poor outcomes:

    only 7-35% back to pre-morbid baseline

Restrictive recommendation not supported

Dattwyler RJ. J Infect Dis 1987;155:1322–5.

Dattwyler RJ. Lancet 1988; 1:1191–4.

Logigian EL. N Engl J Med 1990; 323:1438–44.

Logigian EL. J Infect Dis 1999; 180:377–83.

Late Neurologic Lyme Challenge

- **Evidence misrepresented**
  - Retreatment can be helpful
  - Treatment response times vary
  - Anecdotes re: panel members' case types uninformative and out-of-sync with CDC data

Logigian EL. J Infect Dis 1999; 180:377–83.
MMWR. 2008; 57 (SS-10):1-10.
Halperin JJ. Neurology. 1987; 37(11):1700-6.
Halperin JJ. Neurology. 1989; 39:753-759.

Post-treatment Lyme Challenge

Recommendation 2, page 1120-21

"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.

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).

Post-treatment Lyme Challenge

- **No evidence**: **“post-Lyme syndrome”**
  - No markers of “post-Lyme syndrome”
  - No markers of eradication
- **Evidence misrepresented: “aches and pains”**
  - Klempner, Krupp and Fallon:
    subjects’ health scores worse than controls
  - Inappropriate cohorts
    arthritis in Asch vs. aged-matched general public
    41% vs. 7.8%

Klempner MS. N Engl J Med 2001;

Fallon BA . Neurology 2008;70:992-1003.

Krupp LB. Neurology 2003;60(12):1923–30.

Asch ES. J Rheumatol 1994; 21:454–61.

Post-treatment Lyme Challenge

- **Evidence misrepresented: Retreatment**
  - Krupp and Fallon: positive effects from retreatment
    - improved fatigue in both
    - Fallon: improved pain and physical well being

Krupp LB. Neurology 2003;60(12):1923–30.

Fallon BA . Neurology 2008;70:992-1003.

Not Recommended Challenge

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:

Not Recommended Challenge

Recommendation 5, page 1105 (cont.)

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).”

Not Recommended Therapeutics

- **Insufficient evidence**: Level III
- **Evidence missing:**
  - for “everything but kitchen sink” nature of list
  - for disqualification
  - Literature supports use of:

  fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, ketolides, fluconazole, benzathine penicillin G, combinations of antimicrobials, pulsed-dosing, long-term antibiotic therapy and anti-Bartonella therapies

Clinical Judgment Challenge

- **Guidelines restrict judgment in diagnosis**
  - Do not permit consideration of all clinical data
  - Inappropriately emphasize serologic testing
  - Require physicians to misapply CDC surveillance case definition
- **Guidelines restrict judgment in management**
  - Prescribe specific treatments based on generalized characteristics of illness
  - No management options based on clinical response

Clinical Judgment Challenge

Worthwhile to consider:

- Science unsettled in many aspects of illness
- No evidence for lab requirement
- RCT evidence is scant and weak
- Treatment trial outcomes inadequate

Clinical Judgment Challenge

Integrating evidence quality with policy – AAP

Strong Evidence (Level I)

+

Obvious benefit or harm

Strong recommendation for or against treatment

Weak Evidence (Level III)

+

Obvious benefit or harm

Option

When benefit/harm is balanced, then

Option

No recommendation

AAP: Steering Committee on Quality Improvement and Management. Pediatrics 2004; 114:874-877.

Conclusions from the Evidence

- Supportive evidence is insufficient across all challenged recommendations
- Serologic testing not superior to clinical diagnosis; its limited sensitivity should have discussed
- Evidence was missing, misapplied, misrepresented
- Treatment trials flawed, numbers were low and conclusions uncertain
- Some patients remain symptomatic post-treatment
- Successful trial outcomes were low

Conclusion-based Commentary

Given those circumstances -

- Risk-benefit performed at patient-physician level
- Physician innovation encouraged, not restricted
- Primary goal: Relief of suffering

The evidence and clinical reality is clear; the challenged recommendations must be revised

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