# LYME DISEASE MANAGEMENT PART II

## ILADS- Antwerp, Belgium

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## Disclosure Statement

**I do not have any financial arrangements or affiliations with any commercial entities whose products, research or services may be discussed in these materials.**

# LYME DISEASE
## MANAGEMENT

- Clinical Judgment
- Short term antibiotics in late stage disease
- Evidence of persistent infection
- Treatment
  - Prophylaxis
  - Acute Lyme-with or without an EM Rash
- Long term treatment
  - "No Benefit" -analysis of these studies
  - Positive outcomes of retreatment
- Antimicrobials
- Clinical Oversight

# Clinical Judgment

"Clinical judgment is a central element of the medical profession, essential for the performance of the doctor, and potentially generating information also for other clinicians and for scientists and health care managers."

Gunver S Kienle, MD and Helmut Kiene, MD Clinical judgment and the medical profession J Eval Clin Pract. 2011 August; 17(4): 621–627

# Lyme Disease

## Clinical Judgment

Until technological advances provide reliably sensitive and specific diagnostics, some patients will continue to have a diagnosis that remains unclear.

# Clinical Judgment

- Clinical presentation consistent with the Dx
- Exclusion of other potential causes
- Chronic and relapsing
- Risk of exposure
- Clinical response to intervention
- Diagnostics supportive, not required

# LYME DISEASE
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# LYME DISEASE
## EFFICACY OF SHORT TERM ANTIBIOTICS

Short term antibiotics fail in 25%-71% of patients with late stage disease [1-4]


1. Stricker et al. Research Journal of Infectious Diseases 2013, http://www.hoajonline.com/journals/pdf/2052-5958-1-2.pdf
2. Embers ME, et al. Persistence of *Borrelia burgdorferi* in rhesus macaques following antibiotic treatment of disseminated infection. PLoS One. 2012;7(1):e29914. Epub 2012 Jan 11.
3. Hodzic E, et al. Resurgence of Persisting Non-Cultivable Borrelia burgdorferi following Antibiotic Treatment in Mice. PLoS ONE 9(1): e86907. doi:10.1371/journal.pone.0086907, 2014
4. Treib J, Fernandez A, Haass A, Grauer MT, Holzer G, Woessner R. Clinical and serologic follow-up in patients with neuroborreliosis. *Neurology*. 1998 Nov;51(5):1489-91.

# LYME DISEASE
## MANAGEMENT

Short term antibiotics fail in 25%-71% of patients with late stage disease [1-4]


1. Steere AC, Berardi VP, Weeks KE, Logigian EL, Ackermann R. Evaluation of the intrathecal antibody response to Borrelia burgdorferi as a diagnostic test for Lyme neuroborreliosis. *J Infect Dis* 1990 Jun;161(6):1203-9.
2. Dvorakova J, Celer V. Pharmacological aspects of Lyme borreliosis. *Ceska Slov Farm*. 2004 Jul;53(4):159-64.
3. Kaiser R. Clinical courses of acute and chronic neuroborreliosis following treatment with ceftriaxone. *Nervenarzt*.2004 Jun;75(6):553-7.
4. Berglund J, Stjernberg L, Ornstein K, Tykesson-Joelsson K, Walter H. 5-y Follow-up study of patients with neuroborreliosis. *Scand J Infect Dis*. 2002;34(6):421-5.

# LYME DISEASE
## MANAGEMENT

Short term antibiotics fail in 25%-71% of patients with late stage disease [1-2]


1. Valesová H, Mailer J, Havlík J, Hulínská D, Hercogová J. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. *Infection*. 1996 Jan-Feb;24(1):98-102.
2. Rohácová H, Hancil J, Hulinská D, Mailer H, Havlík J. Ceftriaxone in the treatment of Lyme neuroborreliosis. *Infection*. 1996 Jan-Feb;24(1):88-90

# LYME DISEASE
## MANAGEMENT

- Clinical Judgment
- Short term antibiotics in late stage disease
- Evidence of persistent infection-previously described
- Treatment
  - Prophylaxis
  - Acute Lyme-with or without an EM Rash
- Long term treatment
  - "No Benefit" -analysis of the retreatment trials
  - Positive outcomes of retreatment
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# LYME DISEASE
## PROPHYLAXIS

IDSA Recommendations

SINGLE STAT dose of Doxycycline 200mg if within 72 hours of a tick bite

Nadelman RB, Nowakowski J, Fish D, et al Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. N Engl J Med 2001; 345: 79-84

# LYME DISEASE
## PROPHYLAXIS

## IDSA Recommendations

### Major Flaws in design:

- End point of no EM rash is flawed
- According to health department statistics from multiple states including Connecticut, that only 35-59% of Lyme disease patients present with an EM rash [1,2]. In essence, ~1/2 of the participants wouldn't develop a rash regardless of whether they were treated


1. Johnson L, Stricker RB Treatment of Lyme disease: a medicolegal assessment. *Expert Rev. Anti Infect. Ther.* 2(), 533-557 (2004)
2. Stricker RB, Phillips SE. Lyme disease without erythema migrans: cause for concern? *Am J. Med.* 115, 72 (2003)

# LYME DISEASE
## PROPHYLAXIS

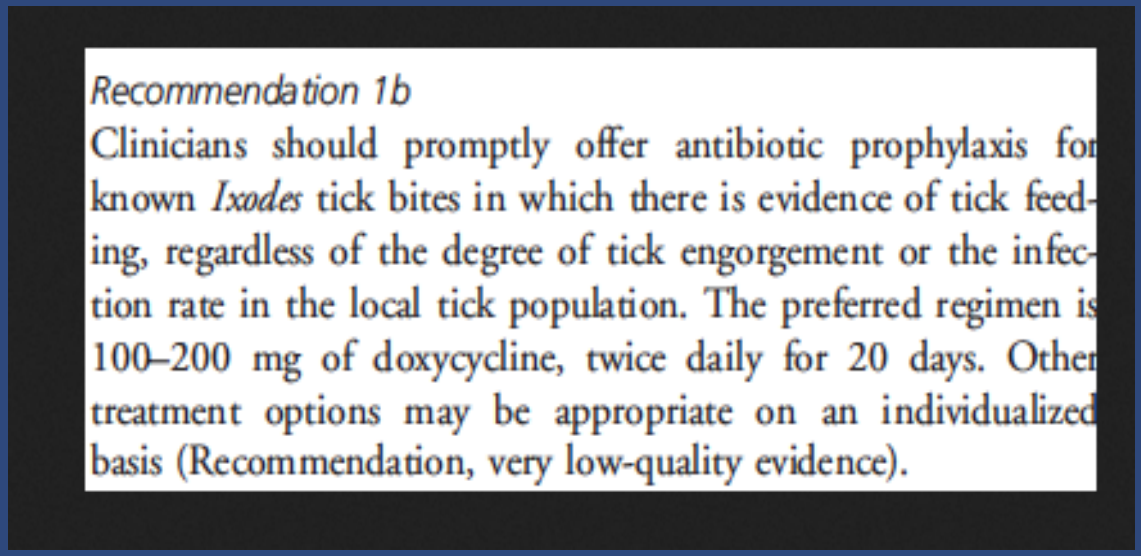
## IDSA Recommendations

### Major Flaws in design:

- Duration of follow up was inadequate-Patients may be assymptomatic early in the infection only to develop symptoms of late disease after a latent period lasting months to years [1-6] In essence, validation of efficacy was not adequately employed


1. Steere A, Bartenhagen N, Craft J, Hutchinson GJ, Newman JH, Rahn DW et al.. The early clinical manifestations of Lyme disease. Ann Inter Med 1983 ;99:76-82.
2. Halperin JJ; Little BW; Coyle PK; Dattwyler RJ. Lyme disease: Cause of a treatable peripheral neuropathy. Neurology 1987; 37:1700-6
3. Duray PH. Clinical pathologic correlations of Lyme disease. Rev Infect Dis 1989; 11(Suppl.6):S1487-93.
4. Coyle PK; Schutzer SE. Neurologic presentations in Lyme disease. Hospital Practice 1991; 26(11):55-66.
5. Lo R; Menzies DJ; Archer H; Cohen TJ. Complete heart block due to Lyme carditis. Journal of Invasive Cardiology 2003; 15(6):367-9.
6. Fallon, BA. Lyme Borreliosis: Neuropsychiatric aspects and Neuropathology. Psychiatric Annals 2006; 36(2):120-8.

# Lyme Disease Prophylaxis



*Recommendation 1b*

Clinicians should promptly offer antibiotic prophylaxis for known *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. The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis (Recommendation, very low-quality evidence).

## ILADS Guidelines:

Cameron DJ, Johnson, LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Review of Anti-Infective Therapy September 2014, Vol. 12, No. 9 , Pages 1103-1135

# LYME DISEASE
## PROPHYLAXIS

### ILADS Recommendations [1]

- Any individual with an attached tick and evidence of feeding, regardless of attachment time
- Preferred regimen for post exposure to a tick bite: Doxycycline 100mg twice daily for 20 days [2,3]


1. Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)
2. Zeidner NS, Brandt KS, Dadey E, et al. Sustained-release formulation of doxycycline hyclate for prophylaxis of tick bite infection in a murine model of Lyme borreliosis. Antimicrob Agents Chemother 2004;48(7): 2697-9
3. Zeidner NS, Massung RF, Dolan MC, et al. A sustained-release formulation of doxycycline hyclate (Atridox) prevents simultaneous infection of Anaplasma phagocytophilum and Borrelia burgdorferi transmitted by tick bite. J Med Microbiol 2008;57(Pt 4):463-8

# LYME DISEASE
## PROPHYLAXIS

ILADS Recommendations

- Alternative options (20 days):
  - Amoxicillin 1500-2000mg/day in divided doses
  - Cefuroxime 500mg twice daily

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

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# LYME DISEASE
## MANAGEMENT
## ILADS 2014 GUIDELINES
## TREATMENT OF EM RASH

- Treat based upon Clinical Judgment
  - 4-6 weeks
  - Dosages differ-Doxycycline 100-200mg bid
- Risk-benefit assessment
  - Harms associated with restriction of treatment vs risk of treatment
  - High failure rates for treatment <=20 days
  - Probiotic use to decrease risk of Cdiff colitis

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

# Lyme Disease
# Treatment early disease

Feder advised that "… patients from LD endemic areas who have fever and fatigue, especially within a month following a deer tick bite, should be considered for empiric antibiotic therapy for early localized Lyme disease"

i.e. Do not delay treatment for test results
Even without a rash

Feder, H.M., Jr., et al., *Early Lyme disease: a flu-like illness without erythema migrans*. Pediatrics, 1993. **91**(2): p. 456-9.

# LYME DISEASE
## MANAGEMENT
## ILADS 2014 GUIDELINES
## TREATMENT OF EM RASH

- Common ERROR
- Clinicians confusing the "2 STAT dosing" for prophylaxis actually being used to treat EM.
- Not only is that not likely adequate in many cases of RISK of exposure, it is LIKELY FAR from adequate for ACTUAL INFECTION

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# LYME DISEASE
## RETREATMENT TRIALS

## Management

"To date there are no convincing published data that repeated or prolonged courses of either oral or iv antimicrobial therapy are effective for such patients. The consensus of the Infectious Diseases Society of America (IDSA) expert-panel members is that there is insufficient evidence to regard 'chronic Lyme disease' as a separate diagnostic entity."

Wormser PG et al The Clinical Assessment, Treatment and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babebiosis: Clinical Practice Guidelines by the Infectious Disease Society of America *CID* 2006. 43:1089-1134

# LYME DISEASE
## RETREATMENT TRIALS

| | N | N |
|---|---|---|
| Klempner MS et al [1] | | |
| seropositive to Bb IgG | 78 | |
| seronegative to Bb IgG | 51 | |
| total enrolled in both studies: | | 129 |
| | | |
| Krupp LB et al [2] | | 55 |
| Fallon BA et al [3] | | 37 |
| | | |
| **TOTAL in all FOUR studies:** | | **221** |


1. Klempner MS, et al Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001 Jul 12;345(2):85-92
2. Fallon BA et alA randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2007 Oct 10
3. Krupp LB, et al Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30

# LYME DISEASE
# RETREATMENT TRIALS

## Klempner study- Design [1]

- Randomized, controlled study
  - 1 month on IV ceftriaxone, followed by
  - 2 months on doxycycline 100mg bid
- Follow-up with SF-36 questionnaire


1. Klempner MS, et al Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001 Jul 12;345(2):85-92

# LYME DISEASE RETREATMENT TRIALS

## Klempner study- Flaws [1,2]

- Small sample size
- Selection bias and questionable generalizability
  - Patients had been ill for an average of 4.7 years
  - Previously failed an average of 3 courses of abx, often including the protocol employed
  - 30% had failed IV treatment of 30 days or more
  - median number of days of failed treatment was 71 days (seropositive group) and 54 days seronegative group


1. DeLong AK, et al. Antibiotic retreatment of Lyme disease: review of randomized, placebo-controlled, clinical trials. *Contemp Clin Trials* 2012;epub ahead of print. http://dx.doi.org/10.1016/j.cct.2012.08.009
2. Cameron DJ. Generalizability in two clinical trials of Lyme disease. *Epidemiol Perspect Innov*. 2006 Oct 17;3:12

# LYME DISEASE RETREATMENT TRIALS

## Klempner study- Flaws [1,2]

- Treatment doses and duration may have been sub-therapeutic
- Inadequate statistical power-Studies to detect changes in SF-36 physical component must be many times larger than the sample size
- No coinfection studies or treatment


1. DeLong AK, et al. Antibiotic retreatment of Lyme disease: review of randomized, placebo-controlled, clinical trials. *Contemp Clin Trials* 2012;epub ahead of print. http://dx.doi.org/10.1016/j.cct.2012.08.009
2. Cameron DJ. Generalizability in two clinical trials of Lyme disease. *Epidemiol Perspect Innov*. 2006 Oct 17;3:12

# LYME DISEASE
## EVIDENCE OF PERSISTENCE

*EMBERS*

Non-human primate model

Design:

- 12 Rhesus monkeys treated with the equivalent regimen as the Klempner human study
- 12/12 positive skin culture 4 weeks after treatment

Embers ME, et al. Persistence of *Borrelia burgdorferi* in rhesus macaques following antibiotic treatment of disseminated infection. PLoS One. 2012;7(1):e29914. Epub 2012 Jan 11.

# LYME DISEASE RETREATMENT TRIALS

## Fallon study- Design [1]

- Participants had prior history of Lyme disease and had received at least 3 weeks of IV ceftriaxone
- Persistent IgG positivity on Western Blot
- Objective memory impairment
- 10 weeks of treatment with IV ceftriaxone 2gm daily

1. Fallon BA et alA randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2007 Oct 10

# LYME DISEASE RETREATMENT TRIALS

## Fallon study [1] Outcomes
**statistically significant benefits**

- Pain and physical functioning improved at 12 and 24 weeks
- Fatigue improved at 12 weeks but not sustained at 24 weeks
- Cognition
  - Improvement measurable at 12 weeks; relapsed at 24 weeks
  - Objective improvements in cognitive functioning correlated with changes in blood flow to the brain as measured by SPECT scan

1. Fallon BA et al A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2007 Oct 10

# LYME DISEASE RETREATMENT TRIALS

## Fallon study [1]

"…the beneficial effect of drug over placebo increased as baseline severity increased…"

"These benefits were felt to be independent of carefully assessed placebo effects"

1. Fallon BA et alA randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2007 Oct 10

# LYME DISEASE RETREATMENT TRIALS

## Krupp [1] Methods

- 55 patients with persistent severe fatigue 6 or more months following antibiotic therapy
- IV ceftriaxone for 28 days
- Monitor fatigue and cognitive function

1. Krupp LB, et al Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30

# LYME DISEASE RETREATMENT TRIALS

## Krupp [1] Results

- Significant improvement in fatigue, sustained at 6 months

1. Krupp LB, et al Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30

# LYME DISEASE RETREATMENT TRIALS

## Therapeutic benefit of retreatment

Fallon [1]

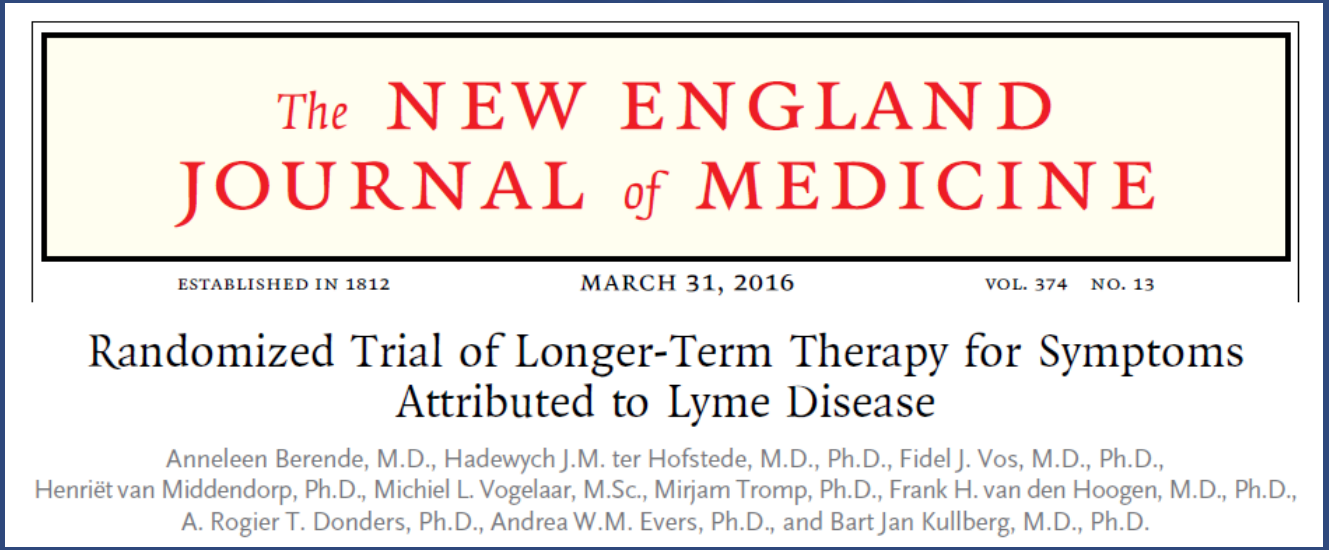
- Fatigue
- Pain and functionality
- Cognition

Krupp [2]

- Fatigue


1. Fallon BA et alA randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2007 Oct 10
2. Krupp LB, et al Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30

# LYME DISEASE



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 31, 2016 VOL. 374 NO. 13

Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease

Anneleen Berende, M.D., Hadewych J.M. ter Hofstede, M.D., Ph.D., Fidel J. Vos, M.D., Ph.D., Henriët van Middendorp, Ph.D., Michiel L. Vogelaar, M.Sc., Mirjam Tromp, Ph.D., Frank H. van den Hoogen, M.D., Ph.D., A. Rogier T. Donders, Ph.D., Andrea W.M. Evers, Ph.D., and Bart Jan Kullberg, M.D., Ph.D.

Study Design:

- Chronic symptoms-with h/o EM and/or positive serologies
- All treated with 2wks IV Ceftriaxone
- Randomized 12 additional weeks:
  - Doxycycline (100mg BID)
  - Clarithromycin(500mg BID)/Hydrochlorquin (200mg/d)
  - Placebo

# LYME DISEASE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Results

- SF 36 quality of life assessment
- No significant differences in the 3 groups

Conclusion of the authors:

- 12 additional weeks of either Doxycycline or Clarithromycin/Hydroxochloroquine compared to placebo were not felt to improve outcomes beyond that seen from 2 weeks of IV Ceftriaxone

# LYME DISEASE


The NEW ENGLAND JOURNAL of MEDICINE

MARCH 31, 2016

Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease

- Clinical benefit to 2.0gms of IV Ceftriaxone
  - Baseline vs post treatment SF 36 analysis, there were clear improvements from baseline

| Outcome | Doxycycline Group (N=86) | Clarithromycin–Hydroxychloroquine Group (N=96) | Placebo Group (N=98) |
|---|---|---|---|
| BASELINE | | | |
| Total score | 101.9±19.4 | 96.5±20.7 | 99.3±22.3 |
| Fatigue-severity scale | 46.0±8.1 | 42.7±10.7 | 43.8±10.6 |
| POST Rx: | | | |
| Total score | 88.7 (84.4 to 92.9) | 87.1 (83.0 to 91.1) | 88.4 (84.4 to 92.4) |
| Fatigue-severity scale | 39.4 (37.3 to 41.5) | 38.6 (36.6 to 40.5) | 38.3 (36.3 to 40.2) |

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Given the lack of differences in the 3 study groups, the one constant was the 2 weeks of IV Ceftriaxone.

THIS would support that <u>there was an active infectious process</u> responsive to that intervention.

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The lack of statistically significant response to an additional 12 weeks of either Doxycycline 100mg bid or clarithyromycin (500mg bid)/hydrochlorquine (200mg/day) could be interpreted

- Unresponse to those specific agents
- At the doses chosen
- For this select population

To extrapolate any other statements regarding long term therapy we believe would be misleading

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The enrollment criteria did not:

1) sufficiently screen subjects for other etiologies of their illnesses, including tick-borne co-infections
2) designate a pre-enrollment antibiotic treatment status (i.e. treated or untreated)
3) disqualify those functioning better than the mean of the general population
4) Include a true placebo group (all patients received 14 days of intravenous ceftriaxone)

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## Possible problems with this analysis

- Potentially inadequate coverage
  - for either different strains of *Borrelia* [1]
  - Co-Infections-not addressed [2]
- Possible inadequate duration of treatment
  - particularly given delayed efficacy of hydrochloroquine


1. Khasnatinov MA, Danchinova GA, Takano A, Kawabata H, Ohashi N, Masuzawa T.Prevalence of Borrelia miyamotoi in Ixodes persulcatus in Irkutsk City and its neighboring territories, Russia. Ticks Tick Borne Dis. 2016 Mar;7(2):394-7. doi: 10.1016/j.ttbdis.2015.12.016. Epub 2015 Dec 21.
2. Schouls LM, Van De Pol I, Rijpkema SG, Schot CS. Detection and identification of Ehrlichia, Borrelia burgdorferi sensu lato, and Bartonella species in Dutch Ixodes ricinus ticks. J Clin Microbiol. 1999 Jul;37(7):2215-22.

# LYME DISEASE
## MANAGEMENT

- Clinical Judgment
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  - Acute Lyme-with or without EM rash
- Long term treatment
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# LYME DISEASE
## MANAGEMENT

### Therapeutic benefit of retreatment

- Methods
  - 84 patients with persistent symptoms following treatment for acute Lyme disease
  - 52 received amoxicillin 3gms daily
  - 32 received placebo

Cameron D. Severity of Lyme Disease with Persistent Symptoms. Insights from a double-blind placebo-controlled trial. Minerva Med 2008;99:489-96

# LYME DISEASE
## MANAGEMENT
## Therapeutic benefit of retreatment

- Results
  - **Pre-treatment** SF-36 quality of life both physically and mentally were worse than the general population and worse than individuals with heart disease, diabetes, depression, osteoarthritis and rheumatoid arthritis
  - **Post-treatment** SF-36 improved significantly in the treated vs. placebo group: 46% vs. 18%

Cameron D. Severity of Lyme Disease with Persistent Symptoms. Insights from a double-blind placebo-controlled trial. Minerva Med 2008;99:489-96

# LYME DISEASE
## MANAGEMENT

## Therapeutic benefit of retreatment

### Methods:

Response to 3 interventions:

| **14 days of intravenous ceftriaxone alone** |
| --- |
| 14 days of IV ceftriaxone followed by 100days of Cefodroxil |
| 14 days of IV ceftriaxone followed by 100days of Amoxicillin |

With evaluation of clinical and serologic response

Wahlberg P. et al, Treatment of late Lyme borreliosis. J Infect, 1994. 29(3): 255-61

# LYME DISEASE
## MANAGEMENT

## Therapeutic benefit of retreatment

Methods:

First consecutive 100 patients from the Aland Islands with late Lyme borreliosis, followed for at least 1 year after treatment

Wahlberg P. et al, Treatment of late Lyme borreliosis. J Infect, 1994. 29(3): 255-61

# LYME DISEASE
## MANAGEMENT
## Therapeutic benefit of retreatment

Results:

"Short periods of treatment were not generally effective."

| | | |
|---|---|---|
| **14 days of intravenous ceftriaxone alone** | 4 of 13 | **31%** |
| 14 days IV ceftriaxone followed by 100days Cefodroxil | 50 of 56 | 89% |
| 14 days IV ceftriaxone followed by 100days Amoxicillin | 19 of 23 | 83% |

Wahlberg P. et al, Treatment of late Lyme borreliosis. J Infect, 1994. 29(3): 255-61

# LYME DISEASE
## MANAGEMENT

### Therapeutic benefit of retreatment

Methods

- 277 patients-Univ Connecticut Lyme Clinic
- Clinical Dx: At least 2 of 3:
  - Fatigue
  - Neurological complaints (cognitive/paresthesias, etc)
  - Musculoskeletal (myalgais/arthralgias)
- Symptoms persisting > 3 months

Donta ST., Tetracycline therapy for chronic Lyme disease. Clin Infect Dis, 1997. 25 Suppl 1: p.S52-6

# LYME DISEASE
## MANAGEMENT

## Therapeutic benefit of retreatment

### Results

Improvement frequently did not take place for several months

| Significant Clinical improvement | |
|---|---|
| After 2 months | 33% |
| After 3 months | 61% |

Donta ST., Tetracycline therapy for chronic Lyme disease. Clin Infect Dis, 1997. 25 Suppl 1: p.S52-6

# LYME DISEASE
## MANAGEMENT

## Therapeutic benefit of retreatment

Conclusions:

These results support the use of longer courses of treatment in the management of patients with chronic Lyme disease

Donta ST., Tetracycline therapy for chronic Lyme disease. Clin Infect Dis, 1997. 25 Suppl 1: p.S52-6

# LYME DISEASE
## MANAGEMENT

## Therapeutic benefit of retreatment

Methods:

Disseminated Lyme *borreliosis* (mainly neurologic and musculoskeletal)

- Group1, N=30: Oral cefixime 200mg with Probenecid 500mg TID x 100days
- Group2, N=30: IV Ceftriaxone 2.0gms/day x 14days, followed by oral amoxicillin 500mg with Probenecid 500mg TID for 100days

Oksi J et al., Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. Eur J Clin Microbiol Infect Dis, 1998. 17(10): 715-9

# LYME DISEASE
## MANAGEMENT

### Therapeutic benefit of retreatment

Findings:

- No statistical difference in outcomes
- However, the total number of patients with relapse or no response at all and number of positive PCR findings after therapy were > in the cefixime group

Oksi J et al., Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. Eur J Clin Microbiol Infect Dis, 1998. 17(10): 715-9

# LYME DISEASE
## MANAGEMENT

### Therapeutic benefit of retreatment

Conclusion:

"General outcomes after 3-4 months of therapy indicate that prolonged courses of antibiotics may be beneficial in this setting, since 90% showed excellent or good treatment response"

Oksi J et al., Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. Eur J Clin Microbiol Infect Dis, 1998. 17(10): 715-9

# LYME DISEASE MANAGEMENT

## Therapeutic benefit of retreatment

Caveat:

"although recommendations were for one month, most physicians practicing in this area believe that longer duration of treatment is needed"

Ziska MH, Donta ST, Demarest F A survey of physician opinions and preferences in the diagnosis and treatment of Lyme disease Infection 1995;23:1-5

# CHRONIC FATIGUE SYNDROME AND LYME DISEASE IS THERE A RELATIONSHIP?

Could Lyme disease **CAUSE** some cases of CFS?

# Lyme Disease-DUE DILIGENCE Original peer review published data

Test Hypothesis:

- That a cohort of CFS patients actually have perpetuation of symptoms in part due to ongoing occult "seronegative" Lyme disease
- In essence, active "seronegative" Lyme disease

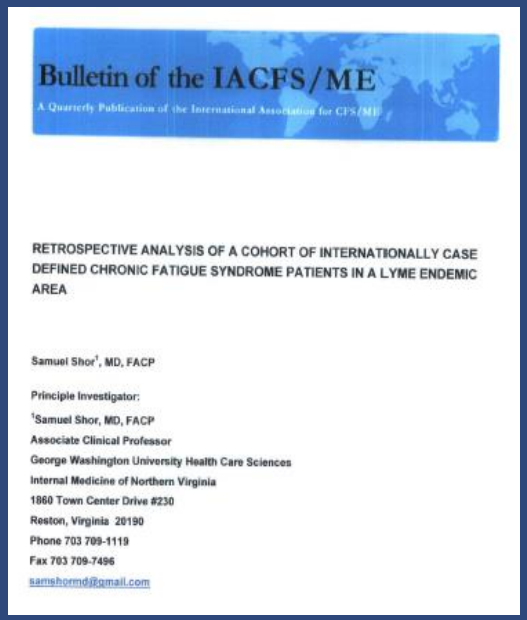
Need to assess this possible relationship

Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123

# Chronic Fatigue Syndrome presenting as "Seronegative" Lyme Disease

**March 2011**

Peer reviewed
Original research



Bulletin of the IACFS/ME

A Quarterly Publication of the International Association for CFS/ME

RETROSPECTIVE ANALYSIS OF A COHORT OF INTERNATIONALLY CASE DEFINED CHRONIC FATIGUE SYNDROME PATIENTS IN A LYME ENDEMIC AREA

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Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123

# CFS/Lyme
## Retrospective/Observational Study

- Define the study population
  - International Case Defined CFS
    - Including negative Lyme "two tiered" criteria
  - "seronegative" Lyme-
    - POSITIVE alternative criteria

| Presence ANY highly specific band 23-25,31,34,39,83-93 | Presence of ANY co-infection | Low CD57 |
|---|---|---|

- Response to therapeutic intervention

# CFS/Lyme
## Retrospective/Observational Study

- Define the study population
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# CFS/Lyme
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    - POSITIVE alternative criteria

| Presence ANY highly specific band 23-25,31,34,39,83-93 | Presence of ANY co-infection | Low CD57 |
|---|---|---|

- Response to therapeutic intervention

# Test Hypothesis: Lyme/CFS

## METRIC-response to therapeutic intervention

- Initial small test population
- Track clinical response to intervention:
- Symptom questionnaires completed at <u>each</u> office visit, in an attempt to "quantify" subjective symptomotology contemporaneously.
- The more symptoms present, the higher the score.

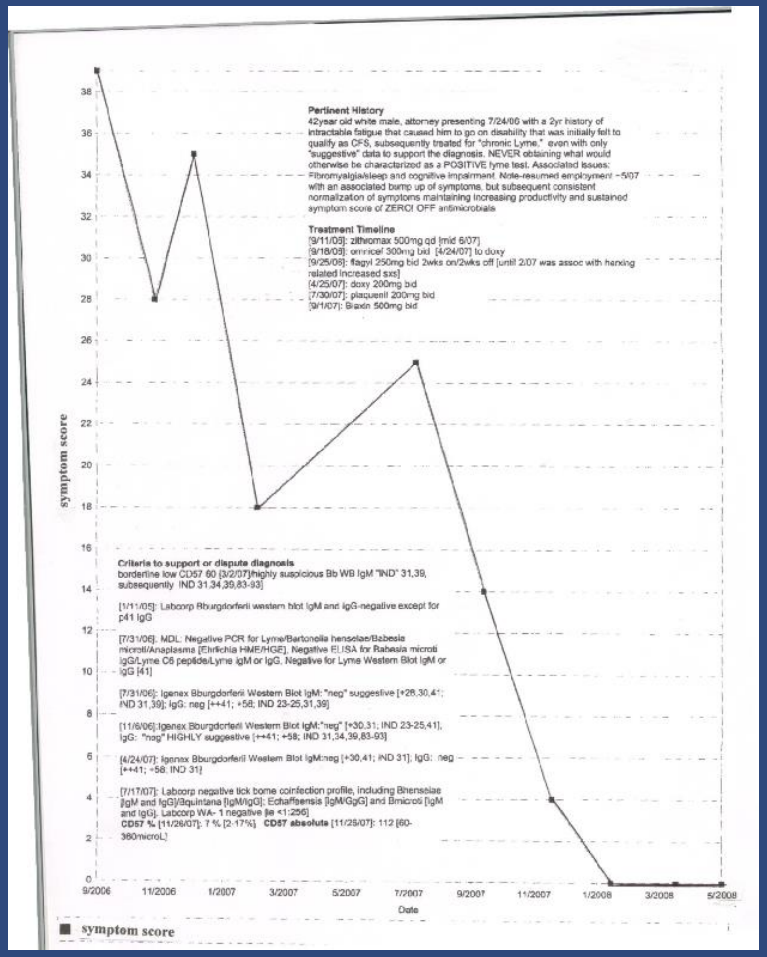
| Symptom Severity Score since your last visit, or at the time of this visit if this is your first visit here: 0-none, 1 mild, 2 moderate, 3 severe | | | | |
|---|---|---|---|---|
| Symptom: | 0 | 1 | 2 | 3 |
| | | | | |
| unexplained fevers, sweats, chills or flushing | | | | |
| unexplained weight change [loss or gain] | | | | |
| fatigue, tiredness, poor stamina | | | | |
| unexplained hair loss | | | | |
| swollen glands | | | | |
| sore throat | | | | |
| testicular or pelvic pain | | | | |
| unexplained menstrual irregularity | | | | |
| irritable bladder or bladder dysfunction | | | | |
| unexplained milk production or breast pain | | | | |
| sexual dysfunction or loss of libido [sex drive] | | | | |
| upset stomach or abdominal pain | | | | |
| changes in bowel function-constipation and/or diarrhea | | | | |
| chest pain or rib soreness | | | | |
| shortness of breath or cough | | | | |
| heart palpitations or skipping heart | | | | |
| stiffness of the back | | | | |
| muscle pain or cramps | | | | |
| twitching of face or other muscles | | | | |
| headache | | | | |
| neck stiffness or pain | | | | |
| tingling,numbness,shooting pains and/or skin sensitivities | | | | |
| facial paralysis or Bell's Palsy | | | | |
| joint pain or swelling | | | | |
| vision problems-double, blurry, increased floaters and/or light senitivity | | | | |
| ear or hearing problems-buzzing, ringing, ear pain, sound sensitivity | | | | |
| motion sickness, vertigo and/or poor balance | | | | |
| lightheadedness, wooziness, unavoidable need to sit down | | | | |
| tremor | | | | |
| confusion and/or difficulty thinking | | | | |
| difficulty with concentration and/or reading | | | | |
| forgetfullness,short term memory loss,poor attention and/or problems absorbing information | | | | |
| disorientation, getting lost and/or going to wrong places | | | | |
| difficulty with speech, or writing or name blocking | | | | |
| mood swings, irritability and/or depression | | | | |
| disturbed sleep-too much,too little,frequent awakening and/or early awakening | | | | |
| TOTAL [Score] | | | | |
| present antibiotic regimen: | | | | |
| miscellaneous comments: | | | | |

# Chronic Fatigue case studies

## No evidence of CDC/IDSA criteria for diagnosis of Lyme disease

Case study #1: 42 year old lawyer on disability for 2 years

- Dx: CFS, subsequently "chronic Lyme"
- NEVER meeting "CDC criteria" for the diagnosis,
- Directed antibiotics for ~15 months: now working full time and OFF all other "supportive" medication:



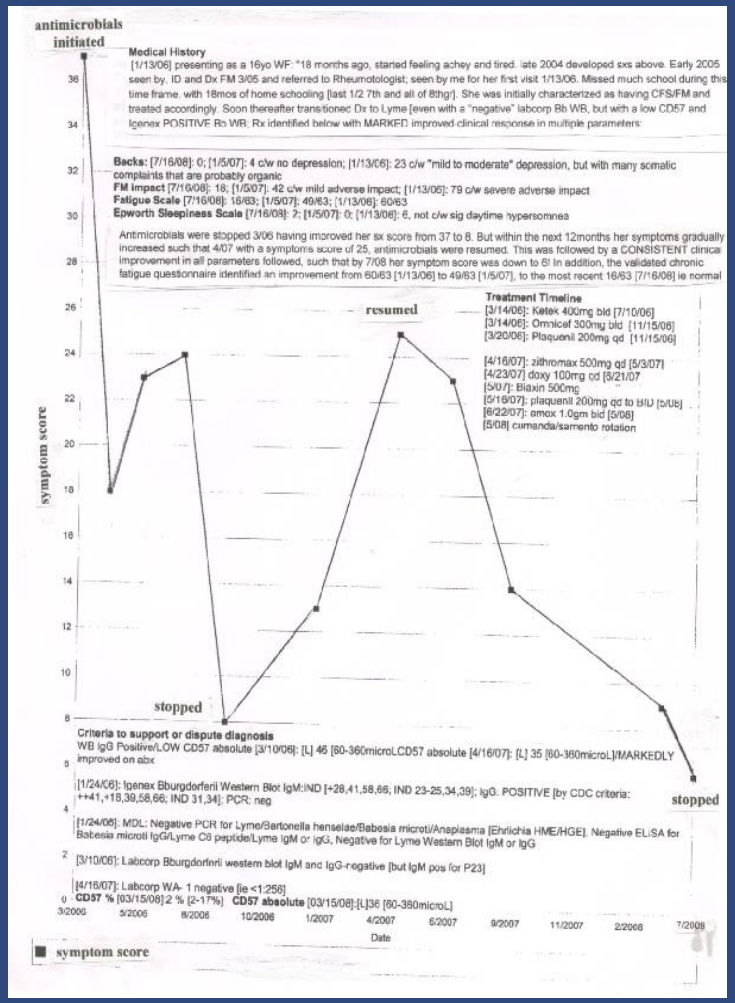
# Chronic Fatigue case studies

## No evidence of CDC/IDSA criteria for diagnosis of Lyme disease

Case study #2

16 year female with Dx of
CFS/FM preliminary studies
"CDC criteria" negative

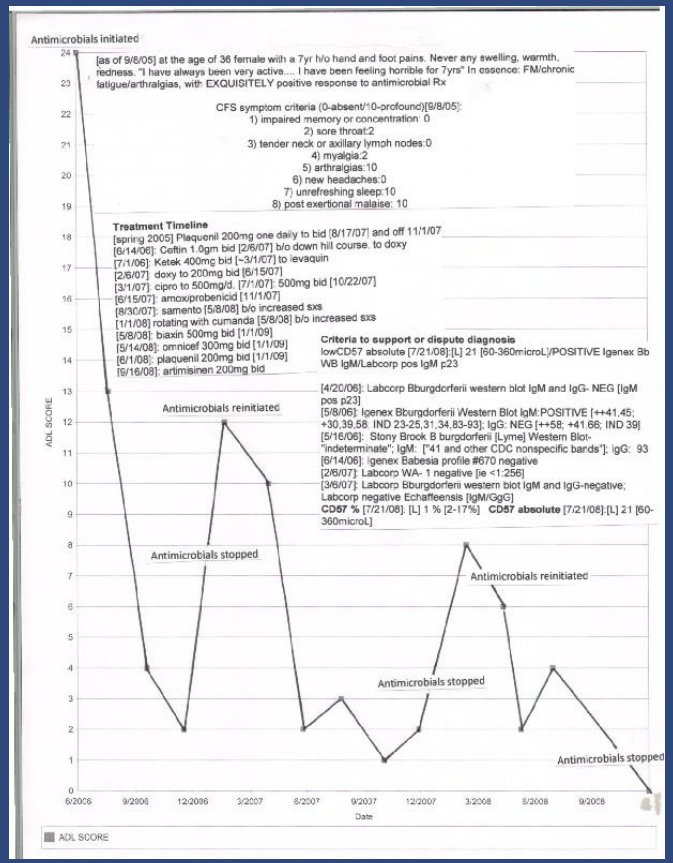
- Subsequently characterized with Lyme disease using "alternative criteria"
- Initial positive response to antimicrobials
- Worsening when antimicrobials were stopped, without known re-exposure.
- Normalization of symptoms when antimicrobials were resumed.



# Chronic Fatigue/Seronegative

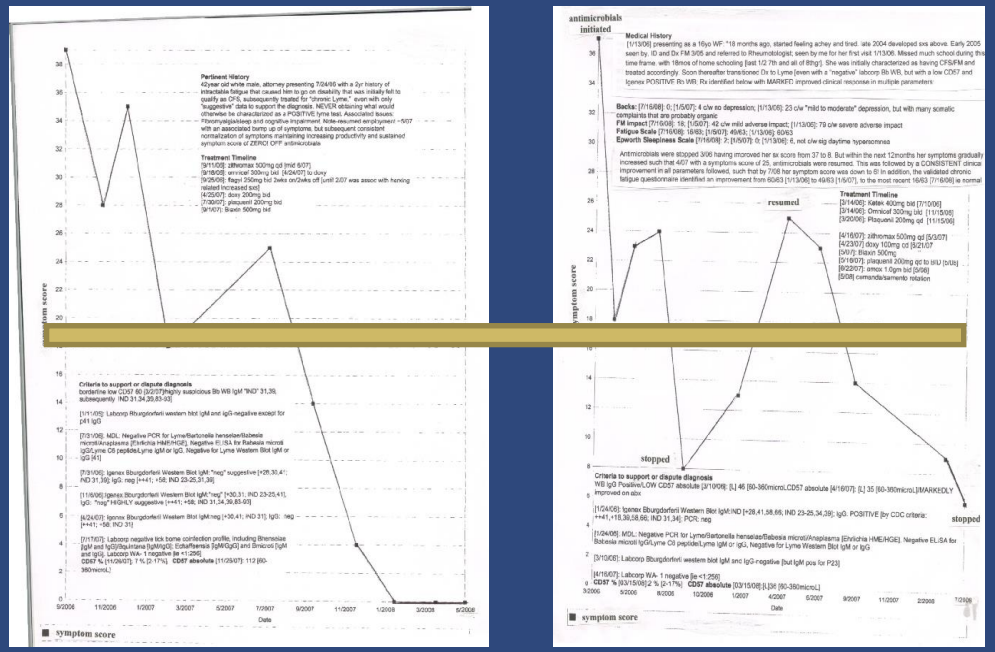
## case studies

- Case study #3: 36 year female with 7yr h/o hand and foot pain
- Responsive to initial course abx
- Recurrence same symptom complex x 2
- each time
  - without new exposure
  - Responsive to re treatment



# “Chronic Fatigue Syndrome”
# Seronegative Lyme
# Response to Antibiotics

Goal>50% improvement in symptom score



# CFS/Lyme

## Original peer review published data

| Analysis of PI patients | N | % total | % seronegative Lyme patients |
|---|---|---|---|
| International Case Defined CFS | 210 | 100% | |
| "seronegative" Bb screen, POSITIVE alternative criteria | 209 | 99% | 100% |
| equal to or > **50% clinical improvement** | 130 | | **62%** |
| <50% improvement but still clinically significant | 55 | | 26% |
| **Total** clinically significant improvement | 185 | | **88%** |

Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123

# Peer Reviewed Original Research

**Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123**

| Analysis of "CFS" patients | N | % seronegative Lyme patients |
|---|---|---|
| equal to or > **50% clinical improvement** | **130*** | **62%** |

*Statistically significant with a p=0.0002

{95% CI} of those subjects with ≥50% improvement (130/209) is 0.62 {0.56, 0.68}, and the p-value testing the null hypothesis that this proportion is equal to 0.50 is rejected at p=0.0002. The statistical method is a binomial test of a single proportion.

Michael J. Sheridan, ScD, FACE
Consulting Epidemiologist & Biostatistician, INOVA Health System
Chair, INOVA Institutional Review Boards A & B
Clinical Professor of Epidemiology, Johns Hopkins University School of Medicine

# LYME DISEASE
## MANAGEMENT

### RISKS of Not Treating

- Currently laboratory tests are unable to confirm or deny persistent infection on a routine basis
- Persistence of infection after courses of treatment can occur
- Withholding therapy runs the risk of allowing ongoing infection to adversely impact outcomes

Cameron DJ Consequences of treatment delay in Lyme disease
Journal of Evaluation in Clinical Practice 13 (2007) 470–472

# LYME DISEASE
## MANAGEMENT

- Clinical Judgment
- Short term antibiotics in late stage disease
- Evidence of persistent infection
- Treatment
  - Prophylaxis
  - Acute Lyme-with or without a rash
- Long term treatment
  - "No Benefit" -analysis of the retreatment trials
  - Positive outcomes of retreatment
- Antimicrobials
  - Options
  - Pulsing
- Clinical oversight

# LYME DISEASE
## ILADS 2014 GUIDELINES
## TREATMENT OF CHRONIC LYME DISEASE

Intracellular agents

**Macrolides**
- Azithromycin
- Clarithromycin

**Tetracyclines**
- Doxycycline
- Minocycline

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

# LYME DISEASE
## ILADS 2014 GUIDELINES
## TREATMENT OF CHRONIC LYME DISEASE

### Planktonic/Extracellular

**Cephalosporins**

- Cefdinir
- Cefuroxime
- Ceftibuten
- Cefotaxime

**Penicillins**

- Amoxicillin w or wo Clavulenic Acid
- Benzathine PCN

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

# LYME DISEASE
## ILADS 2014 GUIDELINES
## TREATMENT OF CHRONIC LYME DISEASE
## DOSING

# DOXYCYCLINE

- Bacteriorstatic
  - 100mg BID
- Bacteriocidal
  - 200mg BID

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

# LYME DISEASE
## ILADS 2014 GUIDELINES
## TREATMENT OF CHRONIC LYME DISEASE
## DOSING

**Amoxicillin**

- 1500-2000mg in divided doses
- Consider Probenicid 500mg with each dose to augment serum levels

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

# LYME DISEASE
## ILADS 2014 GUIDELINES
## TREATMENT OF CHRONIC LYME DISEASE
## DOSING

**Cefuroxime**

- 500-1000mg twice daily with food

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

# MANAGEMENT OF CHRONIC LYME DISEASE

## Hydrochloroquine

- Consider if have arthralgia/arthritis as a dominant feature [1]
- May be augmented by Macrolides [2]
- May have impact on the "cyst" "spheroplast" "L-forms" of *Borrelia burgdorferi* [3]


1. Steere AC, Angelis SM. Therapy for Lyme arthritis: strategies for the treatment of antibiotic-refractory arthritis. Arthritis Rheum. 2006 Oct;54(10):3079-86. Review.
2. Donta ST Macrolide therapy of chronic Lyme Disease Med Sci Monit, 2003;9(11):P136-142
3. Brorson O, Brorson SH An in vitro study of the susceptibility of mobile and cystic forms of Borrelia burgdorferi to hydroxychloroquine. Int Microbiol. 2002 Mar;5(1):25-31.

# LYME DISEASE
## ILADS 2014 GUIDELINES
## TREATMENT OF CHRONIC LYME DISEASE
## PEDIATRIC DOSING

- **Doxycycline**
  - 4mg/kg/day twice daily
  - Use with caution in children < 18years old
- **Amoxicillin**
  - 50mg/kkg/day in three divided doses

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

# LYME DISEASE
## ILADS 2014 GUIDELINES
## TREATMENT OF CHRONIC LYME DISEASE
## PEDIATRIC DOSING

- **Cefuroxime**
  - 30mg/kg/day in two divided doses

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

# LYME DISEASE
## ILADS 2014 GUIDELINES
## TREATMENT OF CHRONIC LYME DISEASE
## PARENTERALS

**Indications:**

- Severe presentation
  - Eg. Meningitis
- Intolerance to orals
- Inadequate response to orals

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

# LYME DISEASE
## TREATMENT OF CHRONIC LYME DISEASE
## RISKS

- FIRST DOSING of ANY parenterals: under supervision
- Consider anaphylaxis kit

ILADS BASICS Workgroup

# LYME DISEASE
## TREATMENT OF CHRONIC LYME DISEASE

### Evidence Based Antibiotic Combination

- Feng Jie et al : Drug Combinations against *Borrelia burgdorferi* in vitro: Eradication achieved by using Daptomycin, Cefoperazone and Doxycycline PLOS One March 25th 2015
- Found it was more effective to kill *B. burgdorferi* persisters by drug combination than single antibiotic, but bacteriocidal activity depended on the particular antibiotics

ILADS BASICS Workgroup

# LYME DISEASE
## TREATMENT OF CHRONIC LYME DISEASE

### Examples of IV Combination Agents

- **Combination of two parenteral**
- **IV Cephalosporin**
- IV **Azithromycin**
- **IV Doxycycline**
- Option to add (metronidazole IV/PO, tinidazole PO) to any of the above

ILADS BASICS Workgroup

# LYME DISEASE
## TREATMENT OF CHRONIC LYME DISEASE

### Examples of IM/IV plus Oral Antibiotic Combinations

- Regimen using IM penicillin
  - Benzathine penicillin, 1.2 million units IM
  - Oral Macrolide
  - (Option to add (metronidazole, tinidazole) to any of the above
- Regimen using IV cephalosporin
  - Ceftriaxone 2 grams
  - Oral Macrolide
  - Option to add (metronidazole, tinidazole) to any of the above

Slide courtesy of Joseph Burrascano, Jr, MD

ILADS BASICS Workgroup

# LYME DISEASE
## MANAGEMENT

- Clinical Judgement
- Short term antibiotics in late stage disease
- Evidence of persistent infection
- Treatment
  - Prophylaxis
  - EM Rash
- Long term treatment
  - "No Benefit" -analysis of the retreatment trials
  - Positive outcomes of retreatment
- Antimicrobials
  - Options
  - Pulsing
- Clinical Oversight

# MANAGEMENT OF CHRONIC LYME DISEASE

## Pulsing

| DAY: | SUNDAY | MONDAY | TUESDAY | WEDNESDAY | THURSDAY | FRIDAY | SATURDAY |
|---|---|---|---|---|---|---|---|
| Week 1 | | antibiotic | | antibiotic | | antibiotic | |
| Week 2 | | antibiotic | | antibiotic | | antibiotic | |
| Week 3 | | antibiotic | | antibiotic | | antibiotic | |
| Week 4 | | | | | | | |

Potential value:

1. Higher more likely "cidal" doses on "active" days
2. Theoretically "fooling" *Bb* on "off days" since *Bb* has been shown to adapt to a toxic environment
3. Often better tolerated given "wash out" days and week "off"

Hassler D, Riedel K, Zorn J, Preac-Mursic V. Pulsed high-dose cefotaxime therapy in refractory Lyme borreliosis. Lancet 1991 Jul 20;338(8760):193

# MANAGEMENT OF CHRONIC LYME DISEASE

## Pulsing

| DAY: | SUNDAY | MONDAY | TUESDAY | WEDNESDAY | THURSDAY | FRIDAY | SATURDAY |
|---|---|---|---|---|---|---|---|
| Week 1 | | antibiotic | | antibiotic | | antibiotic | |
| Week 2 | | antibiotic | | antibiotic | | antibiotic | |
| Week 3 | | antibiotic | | antibiotic | | antibiotic | |
| Week 4 | | | | | | | |

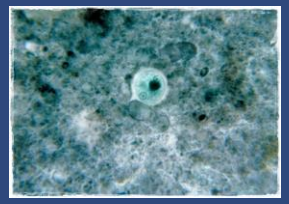
Potential value:

Prognosticate response on "week off":

a) Often feeling better, less "toxic" from herxing and/or side effects of drugs
b) When feeling worse on "off weeks" suggestive of inadequate control of the underlying infectious process

# LYME DISEASE
## ILADS 2014 GUIDELINES
## TREATMENT OF CHRONIC LYME DISEASE

# L-form/spheroplast/cell wall deficient



Replicating spiral form

Cell wall deficient "L" or cyst form

- **Metronidazole**
- **Tinidazole**
- **Hydroxychloroquine**
- **Tigecycline**


1. Brorson O et al, Transformation of cystic forms of Borrelia burgdorferi to normal, mobile spirochetes, *Infection* 25 (1997); 4:240-45.
2. Brorson O et al, A rapid method for generating cystic forms of Borrelia burgdorferi, and their reversal to mobile spirochetes, *APMIS*, 106 (1998):1131-41

# MANAGEMENT OF CHRONIC LYME DISEASE

## Antibiotic Pulsing [1] to Rx "L-form" "spheroplast" or "cyst forms"

### Flagyl (Metronidazole) or Tindamax (Tinidazole) [2]

| DAY: | SUNDAY | MONDAY | TUESDAY | WEDNESDAY | THURSDAY | FRIDAY | SATURDAY |
|---|---|---|---|---|---|---|---|
| Week 1 | | antibiotic | | antibiotic | | antibiotic | |
| Week 2 | | antibiotic | | antibiotic | | antibiotic | |
| Week 3 | | antibiotic | | antibiotic Flagyl or Tindamax | Flagyl or Tindamax | antibiotic Flagyl or Tindamax | |
| Week 4 | | OFF | | OFF | | OFF | |


1. Sharma B, Brown AV, Matluck NE, Hu LT, Lewis K. Borrelia burgdorferi, the Causative Agent of Lyme Disease, Forms Drug-Tolerant Persister Cells. Antimicrob Agents Chemother. 2015 Aug;59(8):4616-24. doi: 10.1128/AAC.00864-15. Epub 2015 May 26
2. Sapi E, Kaur N, Anyanwu S, Luecke DF, Datar A, Patel S, Rossi M, Stricker RB. Evaluation of in-vitro antibiotic susceptibility of different morphological forms of Borrelia burgdorferi. Infect Drug Resist. 2011;4:97-113. doi: 10.2147/IDR.S19201. Epub 2011 May 3.

# LYME DISEASE
## MANAGEMENT

- Clinical Judgment
- Short term antibiotics in late stage disease
- Evidence of persistent infection
- Treatment
  - Prophylaxis
  - EM Rash
- Long term treatment
  - "No Benefit" -analysis of these studies
  - Positive outcomes of retreatment
- Antimicrobials
- Clinical Oversight

# MANAGEMENT OF CHRONIC LYME DISEASE
## PROACTIVE SUPPORTIVE ISSUES

1. Consents
2. Additional Clinical Oversight
   a. Tracking clinical responses
   b. Differential diagnosis
   c. Risk Management

# CONSENTING
# RISKS/BENEFITS

- To treat
  - Acute
  - persistent Lyme
  - tick exposure

**I realize that the choice of treatment approach to use in treating my condition is mine to make in consultation with my physician. After weighing the risks and benefits of the two treatment approaches, I have decided: (CHECK ONE)**

| | | | | |
|---|---|---|---|---|
| ☐ | To treat my Lyme disease through a treatment approach that relies heavily on clinical judgment and may use antibiotics until my clinical symptoms resolve. I recognize that this treatment approach does not conform to IDSA guidelines and that insurance companies may not cover the cost of some or all of my treatment. | | ☐ | Not to pursue antibiotic therapy |
| ☐ | Only to treat my Lyme disease with antibiotics for thirty days, even if I still have symptoms. | | | I may obtain a copy of IDSA guidelines by going to: http://www.cdc.gov/ncidod/dvbid/lyme/IDSA_2000.pdf<br>ILADS guidelines by going to: http://www.ilads.org/files/ILADS_Guidelines.pdf |

- versus NO or limited intervention

# QUALITY ASSURANCE-CONSENTING

CAVEATS:

- Maintain a SIGNED copy in the chart
- Document patient given/declined accepting copy of signed agreement , and all questions answered before consent signed.
  - For minors (<18yo)-MAKE SURE to have BOTH parents sign

I understand the benefits and risks of the proposed course of treatment, and of the alternatives to it, including the risks and benefits of foregoing treatment altogether. My questions have all been answered in terms I understand. All blanks on this document have been filled in as of the time of my signature.

Signature of Patient/Parent or Guardian  Signature of second Parent or Guardian {PATIENT.LABELNAME}

[Please note that **minors i.e. under age of 18 years of age, require signature of BOTH parents PRIOR to initiation of treatment**]

# LYME DISEASE
## MANAGEMENT
## ILADS 2014 GUIDELINES
## TREATMENT OF CHRONIC LYME DISEASE

- Treat based upon Clinical Judgment
- Short term antibiotics fail in large percentage of patients-previously discussed
- Need to minimally cover:
  - Spirochetal form
  - May need to cover L-form/spheroplast/cell wall deficient form

Cameron DJ, Johnson LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Rev. Anti Infect. Ther. 12(9), 1103-1135(2014)

# MANAGEMENT OF CHRONIC LYME DISEASE
## PROACTIVE SUPPORTIVE ISSUES

1. Consents
2. Additional Clinical Oversight
   a. Tracking clinical responses
   b. Differential diagnosis
   c. Risk management

# Chronic Lyme disease DOCUMENTATION

EACH VISIT

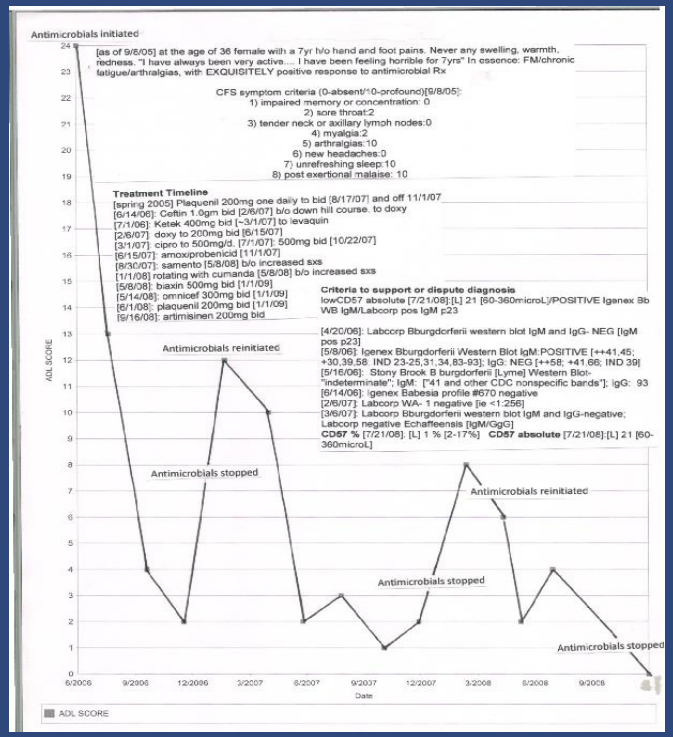
1. Symptoms- Quantitative metric with which to track clinical activity
2. Helping to gauge how aggressive to be with intervention

| Symptom Severity Score since your last visit, or at the time of this visit if this is your first visit here: 0-none, 1 mild, 2 moderate, 3 severe | | | | |
|---|---|---|---|---|
| Symptom: | 0 | 1 | 2 | 3 |
| | | | | |
| unexplained fevers, sweats, chills or flushing | | | | |
| unexplained weight change [loss or gain] | | | | |
| fatigue, tiredness, poor stamina | | | | |
| unexplained hair loss | | | | |
| swollen glands | | | | |
| sore throat | | | | |
| testicular or pelvic pain | | | | |
| unexplained menstrual irregularity | | | | |
| irritable bladder or bladder dysfunction | | | | |
| unexplained milk production or breast pain | | | | |
| sexual dysfunction or loss of libido [sex drive] | | | | |
| upset stomach or abdominal pain | | | | |
| changes in bowel function-constipation and/or diarrhea | | | | |
| chest pain or rib soreness | | | | |
| shortness of breath or cough | | | | |
| heart palpitations or skipping heart | | | | |
| stiffness of the back | | | | |
| muscle pain or cramps | | | | |
| twitching of face or other muscles | | | | |
| headache | | | | |
| neck stiffness or pain | | | | |
| tingling,numbness,shooting pains and/or skin sensitivities | | | | |
| facial paralysis or Bell's Palsy | | | | |
| joint pain or swelling | | | | |
| vision problems-double, blurry, increased floaters and/or light senitivity | | | | |
| ear or hearing problems-buzzing, ringing, ear pain, sound sensitivity | | | | |
| motion sickness, vertigo and/or poor balance | | | | |
| lightheadedness, wooziness, unavoidable need to sit down | | | | |
| tremor | | | | |
| confusion and/or difficulty thinking | | | | |
| difficulty with concentration and/or reading | | | | |
| forgetfullness,short term memory loss,poor attention and/or problems absorbing information | | | | |
| disorientation, getting lost and/or going to wrong places | | | | |
| difficulty with speech, or writing or name blocking | | | | |
| mood swings, irritability and/or depression | | | | |
| disturbed sleep-too much,too little,frequent awakening and/or early awakening | | | | |
| TOTAL [Score] | | | | |

# Chronic Lyme disease

Assessing clinical status/response to intervention

Chronic, waxing and waning, recurrent process:



# MANAGEMENT OF CHRONIC LYME DISEASE
## PROACTIVE SUPPORTIVE ISSUES

1. Consents
2. Additional Clinical Oversight
   a. Tracking clinical responses
   b. Differential diagnosis
   c. Risk management

# LYME DISEASE
## TREATMENT OF CHRONIC LYME DISEASE

**Vigilance re Differential Diagnosis**
**PARTICULARLY when not responding to intervention**

- Other Tick Borne Diseases
  - Parasites/viruses/bacteria
- Malignancy
- Environment
  - Mold
- Endocrine and/or Metabolic issues, etc….

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# MANAGEMENT OF CHRONIC LYME DISEASE
## PROACTIVE SUPPORTIVE ISSUES

1. Consents
2. Additional Clinical Oversight
   a. Tracking clinical responses
   b. Differential diagnosis
   c. Risk management

# LYME DISEASE
## TREATMENT OF CHRONIC LYME DISEASE

### Cardiovascular Risks of Antibiotics

- QT Prolongation
  - Can also be seen with acute administration
  - -Macrolides , Quinolones
  - Consider EKG at baseline

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# LYME DISEASE
## TREATMENT OF CHRONIC LYME DISEASE

**REGULAR Monitoring**

Often every 4-6 weeks, more frequently when on parenterals-weekly until stable

- Assess response to treatment
  - "Herxheimer response"
  - Drug side effects
  - Therapeutic gains
- Progression
- Relapse

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# LYME DISEASE
## TREATMENT OF CHRONIC LYME DISEASE

NEED for sustained use of prophylactic PROBIOTICS:

### GI Risks of Antibiotics

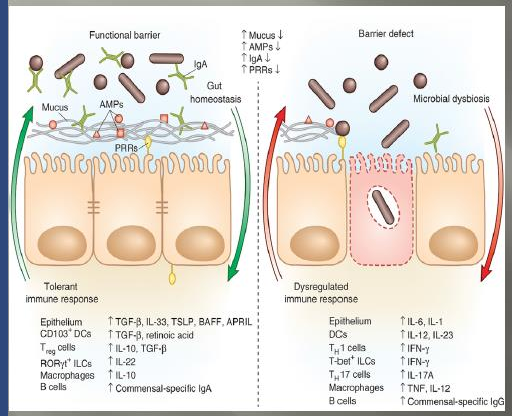


Image: NATURE | VOL489 | 13SEPTEMBER2012

- Opening niches available for pathogenic intrusion
- Induces inflammation
- *C. difficile*
- *Candida* overgrowth

Sheetal 2014

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# LYME DISEASE
## TREATMENT OF CHRONIC LYME DISEASE
## RISKS

- **Comprehensive Metabolic Profile**
  - Liver function
  - Renal function
  - Pancreatic
    - Gall stones

- **Complete Blood Count**
  - Neutropoenia
  - thrombocytopoenia

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# LYME DISEASE
## MANAGEMENT

- Judgment
- Short term antibiotics in late stage disease
- Evidence of persistent infection
- Treatment
  - Prophylaxis
  - Acute Lyme-with or without a rash
- Long term treatment
  - "No Benefit" -analysis of these studies
  - Positive outcomes of retreatment
- Antimicrobials
  - Options
  - Pulsing
- Clinical oversight