



Lyme Disease
Short vs. Long Term
Treatment Debate

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Disclosure Statement:

None

Outline of Today's Talk

Spectrum of Infection: Health – Disease

Asymptomatic, rapidly fatal, & chronic

Size of the Problem

ILADS vs. IDSA

Chronic Lyme vs. PTLDS

Outcomes: Standard vs Longer Antibiotics

Review of IDSA's own published data

Case reports , case series, & open trials

Randomized controlled trials

Persisters

Lyme, Bartonella, Cousins, & Neighbors—A Growing Family

'Lyme' Being Thought of as Collectively

Borrelia burgdorferi, miyamotoi, lonestari, bissettii, mayonii... & Borrelia du Jour

Other Zoonoses – Overlapping Symptoms

Bartonella species, Brucella species
Babesia microti, Babesia duncani (WA1),
Anaplasma phagocytophilum, Ehrlichia

Health—Disease Spectrum

Asymptomatic Infection

Asymptomatic Borrelioses New England, US

Lyme — 9.4-11%

Borrelia miyamotoi — 3.9%

Krause PJ, Narasimhan S, Wormser GP, et al, 2014

Steere AC, Sikand VK, Meurice F, et al, 1998

Asymptomatic Bartonella in Italy

— 11% of healthy adult blood donors

— 25% of children with “various diseases”

Mansueto P, Pepe I, Cillari E, et al, 2012

Health—Disease Spectrum

Asymptomatic Infection

Asymptomatic Infection in Poland

B. burgdorferi

12.5%
Forestry workers — 48% City folk —

Bartonella

37.5%
Forestry workers — 23% City folk —

Lyme—Rapidly Fatal

Fatal Lyme Carditis – 17 yr old died within 3 weeks

Yoon EC, Vail E, Kleinman G, et al 2015

Sudden Death 5 Patients – Non-specific symptoms

Muehlenbachs A, Bollweg BC, Schulz TJ, et al.,
2016

Fatal Lyme Carditis – Despite antibiotics

Jensen TB, Dalsgaard D, Johansen JB, 2014

Fatal Lyme Neuroborreliosis – Early recurrence

Galiukov IA, Vasilenko FI, Lapidus MS, et al,
2010

Fatal Lyme Pulmonary Failure – Despite

Bartonella—Fatalities

Fatal Bartonella Endocarditis – 70 year old man

Alozie A, Yerebakan C, Westphal B, et al., 2012

Fatal Bartonella Myocarditis – 60 year old man

Holmberg M, McGill S, Ehrenborg C, et al., 1999

Fatal Bartonella Encephalitis – 4 & 6 yr old boys

Fouch B, Coventry S, 2007

Gerber JE, Johnson JE, Scott MA, et al., 2002

Fatal Bartonella Myocarditis

ARVC/D Presentation – 16 Young Swedish
Adult Male Elite Athletes (Orienteers)

Wesslen L, Ehrenborg C, Holmberg M, et al.,

Lyme—Chronic & Disabling

**SF-36 worse than DM, heart disease,
depression, osteoarthritis, or RA**

Cameron, D. 2008

**“physical dysfunction comparable to
patients with congestive heart failure,
and fatigue comparable to patients with
multiple sclerosis”**

Fallon BA, Keilp JG, Corbera KM, et al,

2008

Chronic & Life Threatening

Bartonella ab + Heart Transplant Patients

38 patients vs. 50 healthy controls

21% patients positive vs 0% controls (p.0002)

Picascia A, Pagliuca C, Sommese L, et al, 2015

110 Dilated Cardiomyopathy Patients

- Heart muscle biopsies – 20% Bb PCR positive
- Ceftriaxone treatment resolved heart failure
- 64% were Lyme seronegative
- Only 1 had AV block

None had typical Lyme symptoms

Kuchynka P, Palecek T, Havranek S, et al,

Size of the Problem

CDC Estimates for the USA:
329,000 New Cases Lyme Per Year

More than New Diagnoses of
Invasive Breast Cancer Plus
New HIV Infections in USA
Combined

CDC Case Definition—Not to Be Used for Clinical Diagnosis

“This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis.”

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5623a1.htm>

“...the total number of people diagnosed with Lyme disease is roughly 10 times higher than the yearly reported number.”

<http://www.cdc.gov/media/releases/2013/p0819-lyme-disease.html>

Advocates for Short Term Antibiotics

IDSA Guidelines

“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...”

Advocates for Long Term Antibiotics

ILADS Guidelines

“Clinicians should retreat patients who were successfully treated initially but subsequently relapse or have evidence of disease progression.”

“Clinicians should discuss antibiotic retreatment with all patients who have persistent manifestations of Lyme disease. These discussions should provide patient-specific risk–benefit assessments for each treatment option”

Lyme Disease – Standard of Care

Disseminated Lyme

-43% treat > 3 months

Chronic Lyme

-57% treat > 3 months

Ziska MH, Donta ST, Demarest FC, 1996

Two divergent but equally legitimate standards
of care for the treatment of Lyme disease

Johnson L, Stricker RB, 2004

Lyme Disease – Standard of Care Majority Not Following IDSA

CDC Study Shows:

39% Lyme Cases Treated for < 4 weeks

20% Lyme Cases Treated for 5-8 weeks

36% Lyme Cases Treated for > 8 weeks

5% Lyme cases not treated

56% Not Following IDSA

Human Studies Documenting Persistent *Bb* Infection, **NOT Cited by IDSA Guidelines**

12 patients failed standard antibiotics
Spirochetes in synovium of 50%

Steere AC, Duray PH, Butcher EC. 1988

67 yr old died – ARDS due to Lyme

Failed 2 wks tetracycline, 10 d IV penicillin,
2nd course IV penicillin, duration unspecified

Autopsy: Spirochetes in lymph nodes

Kirsch M, Ruben FL, **Steere AC**, et al., 1988

Human Persistent *Bb* Infection Cited by IDSA Guidelines, **Pertinent Findings Omitted**

38 Treated Patients – Long Term Outcomes

26% relapsed by 1 year & required re-treatment

34% had long term morbidity despite treatment

Patient #12 – Got 2 wks IV penicillin

Despite treatment, severe neurologic illness

Re-treated – 2 wks IV ceftriaxone, no change

Patient died

-Spirochetes demonstrated in brain

Shadick NA, Phillips CB, Logigian EL, **Steere AC**, et al., 1994

Human Studies Documenting Persistent *Bb* Infection, **NOT Cited by IDSA Guidelines**

7 Lyme Patients – ceftriaxone 3 wks mean

- Most (57%) relapsed, re-treated ceftriaxone
- Antibiotics helped all patients, but most (71%) remained symptomatic

Patient #2 – After 3 wks ceftriaxone:

- Bb* demonstrated in bladder, confirmed with monoclonal antibodies

Chancellor MB, McGinnis DE, Shenot PJ, et al., 1993

Human Persistent *Bb* Infection Cited by IDSA Guidelines, **Pertinent Findings Omitted**

“the detection of Osp A DNA in joint fluid indicates the presence of viable spirochetes”

<u>Patients</u>	<u>Treatment Received</u>	<u>SF PCR + After Treatment</u>
<u>12</u>	<u><1 month oral antibiotics</u>	<u>12 out of 12 (100%)</u>
<u>19</u>	<u>1-2 months oral antibiotics and/or 3 wks IV antibiotics</u>	<u>7 out of 19 (37%)</u>
<u>10</u>	<u>“multiple courses of antibiotic therapy”</u>	<u>3 out of 10 (30%)</u>

Nocton J J; Dressler F; Rutledge B J; Rys P N; Persing D H; **Steere A C**, 1994

Human Studies Documenting Persistent *Bb* Infection, **NOT Cited by IDSA Guidelines**

58 year old woman, no tick bite or EM; but multiple neurologic manifestations

-Seronegative, CSF Lyme ab negative

-7 LP's: CSF was intermittently positive by PCR, Osp A antigen capture, & Bb immune complexes

-7 rounds of IV antibiotics & 3 years continuous oral

-Severe Herxheimers upon re-initiation of each antibiotic therapy, followed by improvements

Lawrence C, Lipton RB, Lowy FD, **Coyle PK**. 1995

Human Studies Documenting Persistent *Bb* Infection, **NOT Cited by IDSA Guidelines**

3 CNS Lyme patients – brain biopsy proven persistent infection after antibiotics

Patient #1

**Seronegative, CSF ab neg, no pleocytosis
Positive *Bb* CSF culture**

3 wks ceftriaxone, partial improvement

8 months doxy – Relapse – Lyme PCR positive in both plasma & bone marrow

Ceftriaxone re-started, but patient died.

Autopsy: Brain tissue Lyme PCR positive

Human Studies Documenting Persistent *Bb* Infection, **NOT Cited by IDSA Guidelines**

Patient #2

Initially IgM+, IgG-, seronegative thereafter
CSF repeatedly neg for Lyme antibodies & PCR
Brain Lyme PCR positive in 3 separate samples

Failure 7 wks ceftriaxone & 9 mos po antibiotics
-Multiple relapses, recurrent brain lesions &
positive plasma Lyme PCR

Then Re-treated: 100 days ceftriaxone – Brain
lesions resolved, MRI & PCR's neg on long
term follow up.

Human Studies Documenting Persistent *Bb* Infection, **NOT Cited by IDSA Guidelines**

165 Patients Met CDC Case Definition

Avg 16 wks antibiotics – 85% got ceftriaxone

32/165 (19%) relapsed

13/32 (41%) positive by culture, PCR, or both;
– 3/32 (9%) patients were culture positive

All 13 re-treated – 4 to 6 wks IV ceftriaxone
69% improved

Human Studies Documenting Persistent *Bb* Infection, **NOT Cited by IDSA Guidelines**

24 yr old – EM followed by Lyme arthritis

-Arthritis was antibiotic responsive, but kept relapsing when antibiotics were stopped

Despite Years of Oral and IV Antibiotics

-Joint tissue & fluid revealed *Bb*

-Joint fluid was Lyme PCR positive

Battafarano DF, Combs JA, Enzenauer RJ, et al, 1993

Human Persistent *Bb* Infection Despite Long Term Antibiotics

“This study would not have happened if all the samples had been evaluated by the authors according to CDC guidelines.”

5 Patients – Culture Positive for *Borrelia*

- Seronegative

- From Southeast USA (non-Lyme endemic)

- Received long term antibiotic treatments

Borrelia burgdorferi and *Borrelia bissettii*
isolated, despite 9 months doxy

Human Studies Documenting Persistent *Bb* Infection, **NOT Cited by IDSA Guidelines**

Persistent *Bb* infection despite recommended and/or long term antibiotic therapy

Confirmed by culture, and/or PCR & Immunoelectron microscopy

Aberer E, Breier F, Schmidt. 1996

Maraspin V, Ruzic-Sabljić E, **Strle F**, et al. 1995

Preac-Mursic V, Wilske B, Schierz G, et al. 1984

Pícha D, Moravcová L, Holecková D, et al. 2008

Hulinska D, Votypka J, Valesova M. 1999

Schmidli J, Hunziker T, Moesli P, et al. 1988

Cimmino MA, Azzolini A, Tobia F, et al. 1989

Pfister HW, Preac-Mursic V, Wilske B, et al. 1991

Human Studies Documenting Persistent *Bb* Infection, **NOT Cited by IDSA Guidelines**

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Svecová D, Gavornik P. 2008

Hulinska D, Krausova M, Janovska D, et al. 1993

Hudson BJ, Stewart M, Lennox VA, et al. 1998

Preac Mursic V, Marget W, Busch U. 1996

Liegner KB, Shapiro JR, Ramsay D et al. 1993

Priem S, Burmester GR, Kamradt T, et al. 1998

Haupt T, Hahn G, Rittig M, et al. 1993

Honegr K, Hulínská D, Beran J, et al., 2004

Human Xenodiagnosis—NIH Study

Laboratory-reared ticks, free of infection, fed on volunteers with 'post treatment Lyme disease syndrome'

1/8 (12.5%) feedings resulted in tick infection

This was repeated 8 months later and was found to be positive again

Marques A, Telford SR 3rd, Turk SP, et al, 2014

Short Term Antibiotics

Early Lyme Outcomes

285 with Solitary EM vs 259 Controls

No Symptoms – Rash Present < 1 Week

145 Received Doxy x 2 weeks

140 Received Cefuroxime x 2 weeks

5% incomplete response last evaluable visit

3% incomplete response at 12 months

-2.2% developed new symptoms at 12 mos

-Frequency of new symptoms < control

-Severity of new symptoms > control

Cerar D, Cerar T, Ruzić-Sabljić E, Wormser GP, Strle F,

Short Term Antibiotics

Early Lyme Outcomes

107 EM Patients

52 Received Doxy x 2 weeks

55 Received Azithromycin x 5 days

Development of New Symptoms

17% of azithromycin group

35% of doxy group

Strle F, Preac-Mursic V, Cimperman J, et al., 1993

Short Term Antibiotics

Early Lyme Outcomes

100 EM Patients

42 Received Doxy x 2 weeks

58 Received Azithromycin x 5 days

Development of New Symptoms

17% of azithromycin group

26% of doxy group

Strle F, Maraspin V, Lotric-Furlan S, et al., 1996

Short Term Antibiotics

Early Lyme Outcomes

74 EM Lyme Patients – Doxy x 3 Wks

-39% of patients had persistent symptoms and/or functional impact 6 months later

Aucott JN, Crowder LA, Kortte KB,

2013

61 EM Patients After Standard Antibiotics

“symptoms experienced by the group of patients with persistent symptoms had unexpectedly strong overlap with those experienced by acutely infected patients”

-61% had persistent symptoms at 12 months

Short Term Antibiotics

Disseminated Lyme Outcomes

118 CNS Lyme Patients – Neuroborreliosis

Positive LP or presence of ACA

- 2 Weeks Oral Doxycycline Equivalent to 2 Weeks IV Ceftriaxone

Cure Rates 4 Months After Treatment

- Doxy – 52% still had symptoms
- Ceftriaxone – 67% still had symptoms

Ljøstad U1, Skogvoll E, Eikeland R, et al,

Short Term Antibiotics

Late Lyme Outcomes

Chronic Lyme Patients Defined As:

Untreated late stage lyme > 6 months duration

History of EM or positive lyme serologies

No pleocytosis

-26% had abnormal lumbar punctures

-17% had elevated protein

-11% positive Lyme antibody in CSF

-4% were CSF culture positive

-2% was blood culture positive

-2% was EM culture positive

Short Term Antibiotics

Late Lyme Outcomes

Chronic Untreated Late Lyme

46 Patients

4 wks doxy vs. 2 wks ceftriaxone + 2 wks doxy

No statistical difference between groups

12 Month Follow Up

Doxy : 26% Not improved

Ceftriaxone: 30% Not improved

No Cures – Even Among Responders

100% persistently symptomatic

Ogrinc K, Logar M, Lotric-Furlan S, et al., 2006

Longer Term Antibiotics

Disseminated Lyme–Mixed Group

60 Patients –

Heterogeneous Treatment History

- 30 got cefixime/probenecid 100 days
- 30 got ceftriaxone 2 wks, amox/probenecid 100 days
- No statistical difference between groups
- Relapses, failures, & PCR + more in cefixime group

“90% showed excellent or good treatment response”

60% of patients in each treatment group had persistent symptoms at 12 months follow up

Longer Term Antibiotics

Disseminated Lyme–Mixed Group

145 Mixed Lyme Patients – Ceftriaxone 3 wks

-73 got follow up amoxicillin x 100 days

-72 got follow up placebo x 100 days

-No Statistical Difference Between Groups

Outcomes better in amoxicillin group

Design Flaws

Heterogeneous population

Enrollment target not met for statistical power

Oksi J, Nikoskelainen J, Hiekkänen H, et al.,

Review of the PLEASE Study (Persistent Lyme Empiric Antibiotic Europe)

All patients – Rocephin x 2 wks followed by:
3 months of doxy, clarithro/hcq, or placebo

All groups improved equally

Design Flaws

-Heterogeneous Treatment Group

90% had prior antibiotics; 10% not yet treated

-No True Placebo Group

All patients were treated with antibiotics

Antibiotic Re-Treatment of Chronic Lyme: Studies Demonstrating Benefits

Open Label Trials

Donta ST. 2003

Donta ST. 1997

Clarissou J, Song A, Bernede C. et al., 2009

Randomized Controlled Trials

Krupp LB, Hyman LG, Grimson R, et al., 2003

Fallon BA, Keilp JG, Corbera KM, et al., 2008

Cameron D: 2008

Review of the Cameron Amoxicillin

Randomized Controlled Trial

Improvements in SF-36 in Treatment Group
Highly Significant (46% vs 18%, P=0.007)."

Cameron D: 2008

Potential Statistical Issues

-Difference in mental component summary score between treatment and placebo groups at baseline

-High drop out rates

Wormser GP, Shapiro ED, Halperin JJ, 2009

Review of the NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials

Klempner MS, Hu LT, Evans J, et al., 2001.
Krupp LB, Hyman LG, Grimson R, et al. 2003.
Fallon BA, Keilp JG, Corbera KM, et al., 2008.

Delong AK, Blossom B, Maloney EL, Phillips SE.

2012

Review of the NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials

Klempner MS, Hu LT, Evans J, et al., 2001

Ceftriaxone x 1 mo then 2 mo doxy vs placebo

-Trials Were Underpowered

Statistics required improvements to a level of health a full standard deviation superior to that of the general population to detect a treatment effect

Delong AK, Blossom B, Maloney EL, Phillips SE.

Review of the NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials

Krupp LB, Hyman LG, Grimson R, et al., 2003

Ceftriaxone x 28 days vs placebo

Trial Underpowered Except for Only One of Three Outcomes: Fatigue

-Demonstrated Benefits to Fatigue After Antibiotics

Delong AK, Blossom B, Maloney EL, Phillips SE.

Review of the NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials

Fallon BA, Keilp JG, Corbera KM, et al., 2008

Ceftriaxone x 10 weeks vs placebo

Design & Analysis Appropriate to Detect Changes in Cognitive Function

___ -Benefits to Cognitive Function with Antibiotics

___ -Cognitive Worsening with Stopping Antibiotics

Subgroup Analysis –

___ 1. Efficacy & Benefit of Antibiotics

CDC Estimates for the USA:

329,000 New Cases Lyme Per Year

Then Why So Few Randomized True
Placebo Controlled Clinical Trials of
Antibiotics in Chronic Lyme?

Only 4 Studies

(Only 3 NIH Funded Studies)

Klempner No Benefits – Design Flaws

Cameron – Showed Benefits, Design Flaws

Krupp & Fallon – Both Showed Benefits

Why Did it Take 35 Years to Realize that We Can't Even Kill Bb in the Test Tube?

Amoxicillin, doxycycline, and ceftriaxone

- None of them effectively kill Bb in vitro with one application – Persisters remain
- Combinations not more effective
- Pulsed therapy with ceftriaxone was effective after 4 pulses

B. Burgdorferi Persisters—How Best to Eradicate Them? Differences of Opinion

- Mitomycin-C Kills Lyme Persisters**
- Daptomycin Kills Stationary Colonies
but Not Persisters**

Sharma B, Brown AV, Matluck NE, et al., 2015.

Daptomycin Better than Mitomycin-C Against Lyme Persisters

Feng J, Weitner M, Shi W, et al., 2016

B. Burgdorferi Persisters—How Best to Eradicate Them?

**Combination of Daptomycin,
Cefoperozone, & Doxycycline Eradicate
Lyme Persisters**

Feng J, Auwaerter PG, Zhang Y, 2015.

**Cefoperozone Replaced with Ceftin:
Combination: Dapto, Ceftin, & Doxy
Eradicate Lyme Persisters**

Feng J, Weitner M, Shi W, et al., 2016



“The only thing that interferes with my learning is my education.”

Albert Einstein