



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

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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,  
2<sup>nd</sup> 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>&lt;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**

Oksi J, Kalimo H, Marttila RJ, et al. 1996

# 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

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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

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## 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

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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**