



Lyme Disease  
Short vs. Long Term  
Treatment Debate

By

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# Lyme

## The Basics

### Caused by Borrelia Burgdorferi

- Spirochete, cousin to the bacteria which causes syphilis, can invade any body part
- Nicknamed 'The Great Imitator'

### Symptoms

- Huge spectrum of illness/health
- Asymptomatic infection to severe illness
- Spontaneously waxing and waning

# Lyme—The Basics

## How Common is the Rash?

“before the onset of arthritis, 13 patients (25%) noted an erythematous papule that developed into an expanding, red, annular lesion”

Steere AC, Malawista SE, Snyderman DR, et al., 1977.

# Lyme—The Basics

## Symptoms

Neurologic—Headaches, stiff neck, problems thinking, insomnia, numbness

Cardiac—Abnormal heart rhythms, heart failure

Musculoskeletal—Muscle & joint pain

Constitutional—Fatigue, flu-like symptoms, sweats, fevers

# Lyme—The Basics

## Herxheimer, Blebs, Allergies

Herxheimer—worsening of symptoms during initiation of antibiotics

Blebs—membrane bound surface vesicles

Occur in Lyme, bartonella, & brucella

Allergy vs herxheimer—cutaneous herxheimers occur, tough to differentiate

# 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

Chronic diseases possibly caused by infection

# 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*, *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

Forestry workers—48%      City folk—12.5%

#### Bartonella

Forestry workers—23%      City folk—37.5%

Chmielewska-Badora J, Moniuszko A,  
Żukiewicz-Sobczak W, et al 2012

# 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  
'appropriate antimicrobial therapy'

Nguyen H, Le C, Nguyen H, 2010

# 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., 2001

# 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, 2015

# 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

Hook SA, Nelson CA, Mead PS, 2015

# 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.

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

# 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

Oksi J, Marjamaki M, Nikoskelainen J, et al. 1999

# 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 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**

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

Confirmed by culture, and/or PCR & Immunoelectron microscopy

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 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**

Rudenko N, Golovchenko M, Vancova M, et al., 2016

# 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 Doxy, 140 Cefuroxime x 2 weeks

5% still had symptoms at last evaluable visit

-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**, 2010

# 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

Lobraico J, Butler A, Petrini J, et al, 2014

# 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, 2008

# 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

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

# Short Term Antibiotics Late Lyme Outcomes

46 Patients Chronic Untreated Late Lyme  
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—Mixed Treatment History

30—Cefixime/prob x 100 days

30—Ceftriaxone 2 wks + amox/prob x 100 days

-No statistical difference between groups

-Relapse, failure, & PCR + more in po group

“90% showed excellent or good treatment response”

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

Oksi J, Nikoskelainen J, Viljanen MK, 1998

# Longer Term Antibiotics

## Disseminated Lyme–Mixed Group

### 145 Mixed Lyme Pts—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., 2007

# 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

Berende A, ter Hofstede HJ, Vos FJ, et al, 2016

# 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

# NIH Sponsored Chronic Lyme Antibiotic 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.

**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

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

**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,  
Cefoperazone, & Doxycycline Eradicate  
Lyme Persisters**

Feng J, Auwaerter PG, Zhang Y, 2015

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

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

# Juvenile Rheumatoid Arthritis: Bartonella & Lyme

## **Bartonella causing/mimicking JRA**

Tsukahara M, Tsuneoka H, Tateishi H, et al., 2001  
Hayem F, Chacar S, Hayem G, 1996

## **Lyme causing/mimicking JRA**

Laxer RM, Artsob H. 1988  
Lipnick RN, Sait T, White PH, et al., 1986  
Eichenfield AH, Goldsmith DP, Benach JL, et al.,  
1986

**Antibiotic Trials for JRA?—Not Done**

# Hydroxychloroquine aka Plaquenil

**Hydroxychloroquine—An anti-malarial that has been used to treat RA for decades**

**Hydroxychloroquine kills Bb in vitro & has been used to treat Lyme patients**

Brorson O, Brorson SH, 2002

Donta ST, 2003

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

# Randomized Controlled Trials Showing Benefits to Antibiotics in Adult Rheumatoid Arthritis

## **Minocycline vs. Placebo**

Kloppenborg M, Breedveld FC, Terwiel JP, 1994  
Tilley BC, Alarcón GS, Heyse SP, et al., 1995  
O'Dell JR, Haire CE, Palmer W, 1997

## **Minocycline vs. Hydroxychloroquine**

**-Minocycline was more effective**

O'Dell JR, Blakely KW, Mallek JA, 2001

# Randomized Controlled Trials Showing Benefits to Antibiotics in Adult Rheumatoid Arthritis

## **Clarithromycin vs. Placebo**

Ogrendik M, 2007

## **Clarithromycin + MTX + MP vs. Placebo + MTX + MP**

Saviola G, Abdi-Ali L, Campostrini L, 2013

## **Roxithromycin vs. Placebo**

Ogrendik M, 2009

Ogrendik M, Karagoz N, 2011

# Randomized Controlled Trials Showing Benefits to Antibiotics in Adult Rheumatoid Arthritis

**Levofloxacin + MTX vs. Placebo + MTX**

Ogrendik M, 2007.

**Pulsed Tetracycline + Clinda vs. Placebo**

Gompels LL, Smith A, Charles PJ, 2006,

**Doxycycline + MTX vs. Placebo + MTX**

O'Dell JR, Elliott JR, Mallek JA, 2006

# Neuropsychiatric Presentations

## Bartonella

**“acute onset personality changes and agitation, depression, and panic attacks”**

Schaller JL, Burkland GA, Langhoff PJ, 2007.

**Depression and psychosis**

**“psychiatric symptoms did not resolve until antibiotic treatment was given”**

Baker J, Ruiz-Rodriguez R, Whitfeld M, 1995.

# Neuropsychiatric Presentations

## Lyme

“A broad range of psychiatric reactions have been associated with Lyme disease including paranoia, dementia, schizophrenia, bipolar disorder, panic attacks, major depression, anorexia nervosa, and obsessive-compulsive disorder.”

Depression in late Lyme—26-66%

Fallon BA, Nields JA, 1994

# Neuropsychiatric Presentations

## Lyme

**33% psychiatric patients Lyme seropositive**  
**19% healthy subjects Lyme seropositive**

Hájek T, Pasková B, Janovská D, 2002

### Case series of 3 patients—

**Patient #1 Depression and panic disorder**

**Patient #2 Depression and mania**

**Patient #3 Panic disorder**

**These disorders remitted after antibiotics.**

Fallon BA, Niels JA, Parsons B, et al., 1993

# Lyme or MS? Both?

## Does Lyme Cause MS?

**Lyme can be clinically indistinguishable from multiple sclerosis (MS)**

Garcia-Monco JC, Miro Jornet J, Fernandez Villar B, et al., 1990

Kohler J, Kern U, Kasper J, et al., 1988

Pohl-Koppe A, Logigian EL, Steere AC, et al., 1999

Halperin JJ, Luft BJ, Anand AK, 1989

Triulzi F1, Scotti G, 1998

# Bb Cysts in Spinal Fluid of All MS Patients Studied

*B. burgdorferi* cysts isolated from the CSF of all MS patients, but not from healthy controls, except 1 without symptoms but with a history of Lyme

Brorson O, Brorson SH, Henriksen TH, et al, 2001

Authors concluded that MS is likely caused by *B. burgdorferi*

Zajkowska JM, Hermanowska-Szpakowicz T, 2002

# Randomized Controlled Trial Antibiotics—MS

## 28 Patients

11 of them (39%) with Progressive MS

## Roxithromycin vs. Placebo

Treatment group—3 six wk cycles over 1 yr

-No significant difference

-Design Flaws—Heterogeneous patient population re: progressive forms of MS

-Unusual antibiotic treatment regimen

Woessner R, Grauer MT, Frese A, 2006

# Open Label Trial Antibiotics—MS

10 Patients—3 mos Run-in Before Treatment, then Given Mino x 3 years

“proportion of active scans was lower during the first six months of treatment (5.6%,  $p < 0.001$ ) and during the extension (8.7%,  $p = 0.002$ ) than during the run-in (47.5%)”

Zhang Y, Metz LM, Yong VW, 2008

# Open Label Trial Antibiotics—MS

**10 Patients—3 mo Run-in Before Treatment, then Given Mino x 2 years**

**-High relapse rates before mino, no relapses on mino at 6-24 months: 1.2/yr to zero**

**-High rates of MRI activity before mino;**

**Only 1 patient had active brain lesions on mino (was on reduced dose due to nausea)**

Zabad RK, Metz LM, Todoruk TR, et al., 2007

# Open Label Trial Antibiotics—MS

15 Patients on IF- $\beta$  with Breakthrough  
-Doxycycline was added for 4 months

“reductions in contrast-enhancing lesion numbers and posttreatment Expanded Disability Status Scale values ( $P < .001$  for both)”

Minagar A, Alexander JS, Schwendimann RN, 2008

# Randomized Controlled Trial

## Antibiotics—MS

8 Patients—40 Needed to Meet Statistics

Azithro + Rifampin vs Placebo x 9 mos

-3 of 4 who got antibiotics showed decrease in brain lesions, 1 of 4 without decrease didn't get follow up MRI due to pregnancy

-2 of 4 who got placebo showed an increase

-Change not statistically significant, but study was underpowered to reach statistical significance

Less brain atrophy in those who received antibiotics—Was statistically significant

Sriram S, Yao SY, Stratton C, et al., 2005

# Randomized Controlled Trial Antibiotics—MS

## 40 Patients

Copaxone + Mino vs. Copaxone + Pbo x 9 mo

Mino group: “Relapse tended to be lower” & “endpoints showed a consistent trend favoring combination treatment”

- Reduced enhancing lesions by 63%
- Reduced new or enlarging lesions by 65%
- Not statistically significant

Metz LM, Li D, Traboulsee A, Myles ML, et al., 2009



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

**Albert Einstein**