




LDA
Lyme Disease Action


The issue of persistence?

Dr Sandra Pearson, Medical Director, LDA
@PearsLDA

LDA Patient Helpdesk


- June 2012: confidential email ticket system via secure server
- 2 volunteers: establishing facts, giving information, refining questions
- Input from Medical Director
- 3676 #tickets
- 15 – 25 open tickets daily
- Patient Advocacy: Pragmatic approach towards uncertainty
- Spectrum: Possible.....Probable.....Definite



Possible causes of persistent symptoms after treatment of LB

- Persistent active infection with Borrelia?
- Immune dysfunction? Autoimmunity?
- Tissue damage. Damage to neural networks?

- Re-infection with LD?
- Other illness?



14th International Conference on Lyme Borreliosis and other Tick-Borne diseases

Vienna, Austria

27-30 September 2015

www.iclb2015.com



Poster 161



"Isolation of live Borrelia from post-treatment Lyme disease syndrome patients"

Rudenko et al 2015



Rudenko et al, Clinical Microbiology and Infection 2015

Isolation of live *Borrelia burgdorferi sensu lato* spirochaetes from patients with undefined disorders and symptoms not typical for Lyme borreliosis

Southeast USA, Jul-Aug 2013

n= 24 patients, 34 samples (serum/plasma)

n= 17 patients (71%) recalled a tick bite
n= 12 patients (50%) recalled an EM rash

Tests: ELISA, IgM/IgG WB, Babesia, Ehrlichia and Rickettsia

"patients had undergone antibiotic treatment due to a suspicion of having Lyme disease even though they were seronegative"

Doxycycline 100mg bd – some had extended treatment eg 9 months



Rudenko et al, Clinical Microbiology and Infection 2015

Reported symptoms:

- severe headache
- nausea
- muscle and joint pain
- numbness and tingling sensations in extremities
- neck pain
- back pain
- panic attacks
- depression
- dizziness
- vision problems
- sleep problems
- shortness of breath



Rudenko et al, Clinical Microbiology and Infection 2015

- DNA purification, PCR, multi-locus sequence testing (MLST)
- Transmission and scanning electron microscopy

Results:

- Culture of **live *Borrelia*** using modified Kelly-Pettenkofer(MKP) medium
- Isolation of *B. burgdorferi sensu stricto* strain (2 patients) and *B. bissettii*-like strain (1 patient) from total of 3 patients



Study would not have happened if all the samples had been evaluated according to CDC guidelines

"All samples were 'inappropriate' because:

- a) the region of sample origin, the south-eastern USA, is considered by the CDC as a non-endemic LB area
- b) all patients included in this study were seronegative according to the current CDC surveillance definition of LB;
- c) all patients underwent extended treatment with doxycycline before the sample collection
- d) patient samples were not taken specifically for the purpose of cultivation

However, taking into consideration the high value of any sample of human origin we decided to analyse them, especially because the tick bite was recalled in most cases."



Preac-Mursic et al, Infection 1989

Survival of *Borrelia burgdorferi* in Antibiotically treated patients with Lyme borreliosis

- n=6 (CSF and skin biopsies)
- "B. burgdorferi may persist as shown by positive culture in MKP-medium; patients may have sub-clinical or clinical disease without diagnostic antibody titres to B. burgdorferi. We conclude that early stage of the disease as well as chronic Lyme disease with persistence of B. burgdorferi after antibiotic therapy cannot be excluded when the serum is negative for antibodies against B. burgdorferi."



Oksi et al, Annals of Medicine 1999

***Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis**

n=165. All seropositive, one culture positive

32 defined treatment failures (>3 months Tx), 0-30 month follow-up

"the treatment, and 12 of these patients had a clinical relapse. In addition, *Borrelia burgdorferi* was cultured from the blood of three patients during the follow-up. All three patients belonged to the group with relapse, and two of them were also PCR positive.

"We conclude that the treatment of Lyme borreliosis with appropriate antibiotics for even more than 3 months may not always eradicate the spirochete."

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Studies on Re-treatment

- Klemmner et al, NEJM 2001 "Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease"
- Krupp et al, Neurology 1993 "Study and treatment of post Lyme disease (STOP-LD): A randomized double masked clinical trial"
- Fallon et al, Neurology 2008 "A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy"

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Borrelia: Enzootic life-cycle 'Job description'

Radolf JD, et al 'Of Ticks, Mice and Men'. *Nature reviews. 2012 Microbiology, 10(2), 87-99*

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Borrelia: "Genomic complexity and metabolic parsimony"
(Radolf et al, Nature reviews, Microbiology 2012)

- Binds to tick salivary proteins.
- Virulence: Variation outer surface proteins/antigenic expression. VisE protein → "immune chaos".
- Protein binding → Immune evasion, dissemination, tissue tropism, binding to extra-cellular matrix via adhesins.
- Sequestration in immune privileged sites: ECM, CNS.
- "Sacrificing virulence for persistence" → Slowing the rate of replication → Dormancy.
- Persister cells: Antibiotic tolerance. Feng et al, PLOS One 2014. Sharma et al, Antimicrobial Agents and Chemotherapy 2015
- Immune dysfunction: Dissociation of T & B cell responses. Hastey et al, Infection and Immunity 2014
- Immune suppression. Eisner et al, PLOS Pathogens 2015

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Borrelia: Genetic aspects

1. Caimano et al, Infection and Immunity 2011
2. Bugrysheva et al, Infection and Immunity 2005
3. Stevenson et al, Infection and Immunity 2002
4. Sapi et al, PLOS One 2012

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Thank you for listening!

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