Recent Lyme Disease Research-The Good, The Bad, And The Ugly

Hope McIntyre MD
Dr John Aucott’s Research

- Researcher in Lyme for many years - Last year opened a new research center at John’s Hopkins University through the rheumatology department

- Much of his research corroborates what we in ILADS always knew about Lyme but did not have proof - his research gives us proof
• Characteristics of seroconversion and implications for diagnosis of post-treatment Lyme disease syndrome: acute and convalescent serology among a cohort of early Lyme disease patients

• Published in Rheumatology June 13, 2014 (Alison Rebman-lead author)

• 39% of patients were seronegative both before and after treatment

• The majority of seropositive patients had only IgM WB +, IgG WB seroconversion was infrequent.
• Patients with multiple lesions, who had longer duration of illness and higher number of reported symptoms were more likely to have a positive test.

• The lack of serconversion (+ antibody test) in a subset of patients highlights the limitations of serology alone in identifying Lyme disease.

• “Furthermore these findings underline the difficulty in identifying a prior exposure to Lyme disease in caring for patients with medically unexplained symptoms or fibromyalgia-like syndromes.”
• So what does this study show? What we already knew—antibody tests alone are not good enough. 39% tested negative. Very few converted to IgG(late antibody) WB.

• So the Dr who tells patients that their IgG(late antibody) WB is negative therefore they never had Lyme—WRONG! Dr Aucott’s group proved that people with the classic rash almost never developed late antibody WB if they get early treatment.
• Atypical erythema migrans in patients with PCR + Lyme disease

• Published in Emerging Infectious Disease May 2013

• The bull’s eye (ring-within-a-ring) appearance is infrequent, 25-30% have no rash, 60% of the time the rash just looks like a huge red circle or oval. Other atypical variants are a blue-red appearance and occasionally a vesicular (blistered) central lesion.

• For this reason Lyme is frequently misdiagnosed as a “spider bite”. This is one of the first things I noticed while still in Family practice in Mt Airy—other Dr’s frequently misdiagnosed patients as having a spider bite.

• THE RASH USUALLY DOESN’T LOOK THE WAY ITS SUPPOSED TO LOOK!
• Misdiagnosis of Lyme disease as the summer flu.

• Orthop Rev(Pavia) June 29, 2011

• Fever, joint pain, body ache that is unexplained (not a respiratory illness) in Spring-Fall think about Lyme disease and test for it.
• Post-treatment Lyme disease syndrome symptomatology and the impact on life functioning: is there something here?

• Qual Life Res February 2013

• Extremely elegant study-proved that 36% of patients treated with standard therapy were still significantly ill at 6 months. They also used depression rating scales to prove the symptoms were not caused by depression
• Direct molecular detection and genotyping of Borrelia Burgdorferi from whole blood of patients with early Lyme disease

• PLoS One May 8, 2012

• Aucott’s group investigated whether adding blood PCR would help in early detection. Only detected Lyme in 62% of patients at the first visit, and combining it with standard serology on increased detection to 90% at the first visit. NOT GOOD ENOUGH. SO HE STARTED LOOKING FOR OTHER MARKERS/OTHER WAYS TO DETECT LYME
Clin Vaccine Immunol June 29, 2016

CCL19 as a Chemokine Risk Factor for Post-treatment Lyme Disease Syndrome: A Prospective Clinical Cohort

If this marker was > 111.67 pg/ml this was 82% sensitive ad 83% specific for later PTLDS. 1st potential biomarker for PTLDS(chronic Lyme)
• Longitudinal Transcriptome Analysis Reveals a Sustained Differential Gene Expression Signature in Patients Treated for Acute Lyme Disease

• MBio Jan-Feb 2016

• The changes in Gene expression persisted with or without chronic symptoms (so not a good marker for persistence unless no one is cured)
• Dr Eva Sapi’s group at the University of New Haven (CT)

• Improved Culture Conditions for the Growth and Detection of Borrelia from Human Serum

• International Journal of Medical Sciences 10/2013

• In patients with acute Lyme disease Lyme bacteria grew in 47% at 6 days, 83% at 8 weeks and 94% at week 16.

• This is our new test the Advanced Lab culture
• Problems with Advanced lab culture

• Cost $595 for the 8 week test, $695 for the 16 week test.

• Still missed Lyme in 6% of patients with acute Lyme

• Still-+ culture proves active infection

• + antibody titer just proves you had it in the past

• May be less accurate in patients with chronic Lyme-less likely to be in the blood than with acute infection-could just be in the tissues not in the blood.

• Positive test proves you have Lyme NOW, negative test does not exclude Lyme(you could have negative test and still have it.)
• CDC case statistics for lyme disease 2014

• PA wins with 7,484 reported cases! Could be 10 times this many as disease under-reported and under-diagnosed. Or PA could just be doing a better job reporting than other states. MA second with 5,304 cases, my home state of MD 1,346.

• Still with 36% of patients remaining ill (Dr Aucott’s data) at least 2,695 new chronic Lyme disease patients in PA in 2014
Treatment Studies-Jie Feng’s group at Hopkins

• Drug combinations against Borrelia Burgdorferi Persisters in Vitro: Eradication Achieved by Using Daptomycin, Cefoperazone and Doxycycline

• March 25, 2015

• A “test tube” study. These antibiotics killed Lyme in the test tube

• Proved existence of complex forms in the “test tube”

• Multiple in vitro (test tube) forms- Spirochetal, Spheroplast(L-form), and microcolony(biofilm) forms
• BB developed increasing tolerance to antibiotics as spirochete form changed into variant forms

• 3 day old culture-96% spirochetes, 4% round body forms

• 7 day old culture-38% spirochetes, 23% round body forms, 39% microcolony(biofilm)

• 10 day old culture 64% biofilm, 20% round body, 16% spirochetes
• Problems with this:

• In the test tube only- not in people

• Daptomycin very expensive IV antibiotic which no one can afford. Only worked with doxycycline PLUS Cefoperazone or carbenecillin or clofazimine.

• Cefoperazone, carbenecillin and clofazimine are not available and would also be very expensive and IV. Combining the first 2 with ceftin or cipro or another cephalosporin antibiotic- didn’t seem to work
• Identification of Additional Anti-Persister activity against Borrelia burgdorferi from an FDA Drug Library

• Antibiotics(Basel) Sept 16, 2015

• Nystatin and fluconazole seemed helpful. But really the majority of compounds in this study are topical only or are more stuff we can’t get. Multiple quinolone (Cipro-like) antibiotics tested that are not available. They didn’t look at mepron, malarone or coartem-antimalarials that have some activity in my experience

• But again, someone is looking at what kills Lyme and a lot of the stuff we commonly use doesn't kill these persisters well-which is what ILADS has been teaching for years-Lyme persists because it changes to these hard to kill forms

• Still no proof that these forms develop in people-just in test tube
• Identification of new compounds with high activity against stationary phase BB from the NCI compound collection

• Emerg Microbes Infect June 2015

• Cancer compounds that kill Lyme-used for CA so very toxic and very expensive-can’t get these yet as new experimental compounds -still adds to knowledge base about what kills Lyme
The heat is on: killing backlegged ticks in residential washers and dryers to prevent tick borne illness

Nelson et al. Ticks and Tick Borne Diseases 5/10/16

Wash water had to >130 degrees F to kill ticks (so they really are not killed by washing)

Putting clothes dry into the dryer killed ticks after only 6 minutes on high heat

If clothes are soiled and need to be washed before drying it took at least 50min on high to kill ticks-Drying out- not the heat itself-killed the ticks
• The Lyme disease pathogen has no effect on the survival of its rodent reservoir host

• PLoSOne February 17, 2015 Voordouw, MJ et al

• This study showed that BB infection or tick burden had no effect on the survival of the white-footed mouse (no surprise that it didn’t affect the mice but they proved it!) This is why the mice are such a great reservoir for Lyme disease.

• Deer are not the reservoir but are necessary for survival of the deer tick - the adults meet and mate on the deer
The Use of Dapsone as a Novel “Persister” Drug in the Treatment of Chronic Lyme Disease/PTLDS

Clinical & Experimental Dermatology Research July 2016

Dr Richard Horowitz et al

dapsone 25-100mg with or without rifampin, with either a tetracycline or a macrolide (azithromycin) and a cephalosporin, with or without Malarone (an antimalarial) improved patients symptoms significantly who had either Lyme alone or with babesiosis
• Preliminary study- no clear protocol as only 100 patients studied and many combinations used in the study.

• Dapsone itself inexpensive but requires administration of multiple suplements- including L-methylfolate(up to 45 mg/day)NAC and Alpha lipoid acid, with plaquenil and biofilm therapy

• Severe flares(Jarish-herxheimer reactions), macrocyctic anemia and Methemoglobinemia.

• This is where the body makes the wrong kind of hemoglobin and the blood cannot effectively carry oxygen-people can turn cyanotic(blue) as not getting enough oxygen even though not anemic

• Pancreatitis also listed as a common side effect and liver problems
• Cost of the drug is thus increased by need for more frequent blood tests (at least every 3 weeks) and specialty tests—methemoglobin levels

• This is going to be a 3rd or 4th or even 5th line option for some time, data just too preliminary and drug too toxic—may know more when Dr Horowitz’s new book is published in the fall.
• New research on babesiosis as looking at screening the blood supply due to the risk of babesiosis from infected blood

• Money guides research—if someone develops a new, more accurate test for babesiosis they stand to make big bucks as their test will be used to check the blood supply

• No good new test yet, but multiple studies done in the last year
Bad News

- Identification of a novel pathogenic Borrelia species causing Lyme borreliosis with unusually high spirochetemia
- 6 patients identified from WI, Minnesota, ND
- High fevers, more generalized rash, only shows up with C6 peptide antibody, many spirochetes in blood
• Neoplasms misdiagnosed as chronic Lyme disease

• Nelson et al

• JAMA intern med January 2015

• report of 3 cases where patients with unusual cancers were misdiagnosed and treated for chronic Lyme disease

• Need to be thorough and make sure we are not missing something else
• Diagnosis, Treatment and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis and Babesiosis: A Review

• Wormser et al (Lyme denialist)

• JAMA April 26, 2016

• Treat with only 10 days doxy for Erythema Migrans

• 7-10 days of atovaquone + proguanil for babesiosis
• 7-10 days of clindamycin + quinine for those severely ill with babesiosis

• But- a minimum of 6 weeks of therapy for immunocompromised patients with babesiosis with no parasites on smear for at least 2 weeks

• 14 days of doxycycline for patients with neurologic Lyme disease

• Really frightening that this is what’s being published in JAMA-a mainstream medical journal that many Drs read. As if we weren’t already under-treating, now he recommends shorter courses
• Randomized Trial of longer-Term Therapy for Symptoms Attributed to Lyme Disease

• New Eng Journal of Med 3/31/16 Berende/kullberg

• 280 patients got 2 weeks of IV Ceftraixone(open label- they knew they got this) followed by either placebo, clarithromycin 500mg twice a day with plaquenil(hydroxychloroquine 200mg twice a day, or Doxycycline 100mg twice a day for 12 weeks

• SF 36 function scale was the same in all 3 groups
• Problems with the study- this was a mixed group of patients-some had had Lyme only a short time, others had had it for years

• They used a standard dose of doxycycline and clarithromycin NOT the double dose recommended by ILADS physicians. Also we would use all 3 drugs together.

• If I wanted to do a trial to prove chronic antibiotics didn’t work- this is how I would do it. Use the same dose of antibiotic we know leaves 36% of patients ill, and guess what 36% of patients will still remain ill. Yet this study will be used to deny patients treatment.
• Unorthodox Alternative Therapies Marketed to Treat Lyme Disease

• Lantos et al Clinical Infect Disease July 15, 2015

• This article talks about the multiple unusual treatments used to treat Lyme disease -of which only Hyperbaric Oxygen has any evidence it kills Lyme and that study was in mice

• It’s true that there are many websites where patients can buy remedies for Lyme and they are all unproven. Some may be just trying to make a buck off suffering people, some may actually believe their treatment helps
• Much as I hate to agree with these infectious disease Doctors, I think it is important for patients to be skeptical of cure-all remedies

• It's important to look at the evidence, cost and risk of various therapies.

• I don’t believe that ozone therapy, light or magnet therapy or laser therapy (Rife) are proven to help and may cause harm

• Steam rooms and infrared saunas may help and are not harmful (unless you overdo it and get heat illness or dehydration) but can be expensive.
• I have had some patients have less pain with low dose naltrexone but it doesn’t help everyone

• Heavy metals like bismuth and silver can be harmful. (skin can turn grey permanently with silver) And I have not had much success with removing mercury by chelation- I have not had this be helpful

• I recommend strongly not to take the “miracle mineral supplement” which is actually diluted bleach, and also recommend against combining high dose Vitamin C and Salt- this just causes diarrhea

• I do not think ingesting clay or taking enemas is helpful to “detox”

• Welchol and cholestyramine can rarely help brain symptoms but Welchol is expensive, and cholestyramine a nasty, gritty powder. Both can interfere with absorption of other medications. These are not obviously harmful/are safe to take as they have been used to lower cholesterol

• Detoxing by drinking lemon or lime water or alkaseltzer gold is safe, but not proven to help.