

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

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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 seroconversion(+ 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 and 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* Persists 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 supplements- including L-methylfolate(up to 45 mg/day)NAC and Alpha lipoid acid, with plaquenil and biofilm therapy
- Severe flares(Jarish-herxheimer reactions), macrocytic 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
- Its 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.