New Dapsone Study: Breaking Biofilm

Dr. Richard Horowitz, lead-author: Effect of dapsone alone and in combination with intracellular antibiotics against the biofilm form of *B. burgdorferi*

New in vitro study on dapsone (diaminodiphenyl sulfone), and dapsone combination therapy (DDS CT) was just published by Dr. Richard Horowitz et al. and provides hope of effective treatment for patients with persistent Lyme disease.

The study is suggestive that dapsone combination therapy may well characterize both a novel and successful option to treat *Borrelia burgdorferi* persister cells in the form of biofilm. There are several hypotheses causing great controversy regarding the persistent symptoms that greater than 10-20% of patients are experiencing after infection with *B. burgdorferi*. The study evaluated the effectiveness of dapsone against *B. burgdorferi* biofilm forms of the bacteria by testing in individual as well as in combination therapy with several
drugs including cefuroxime, doxycycline, rifampin, and azithromycin \textit{in vitro}.

The results were robust, showing that using dapsone alone or in various combinations with the above stated drugs significantly reduced the mass and protective glycosaminoglycan layer affecting the capability of the biofilm form of \textit{B. burdorferi}. DDS CT efficacy on the \textit{B. burgdorferi} biofilms was also determined by ascertaining the biofilm polysaccharide matrix content, glycosaminoglycans (GAG).

Study results showed the most efficient single use antibiotic at reducing biofilm was dapsone at both 10 µM and 50 µM concentrations, showing 69% and 58% residual viability respectively. Used individually, other antibiotic treatments (doxycycline, cefuroxime, and azithromycin) proved to be less efficient and, in some cases, even caused an increase biofilm mass. In contrast, triple and quadruple combination antibiotic therapies showed greater efficacy. The most significant finding was that dapsone used individually or in combination therapy with rifampin, and a tetracycline and/or a macrolide and/or a cephalosporin showed great promise in the treatment of persistent Lyme patients, with prior clinical studies demonstrating improvement in many of the debilitating symptoms that patients suffer including fatigue, pain, neuropathy, sleep disturbances, cognitive dysfunction, sweats and flushing. It is urgent that randomized trials are launched to evaluate the clinical effectiveness of DDS CT as the spread of Lyme disease continues to increase on a global scale.

Read the full journal article: Effect of dapsone alone and in combination with intracellular antibiotics against the biofilm form of \textit{B. burgdorferi}

Read the 2016 article: The Use of Dapsone as a Novel “Persister” Drug in the Treatment of Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome
NIH Grants 1.9 Million for Vaccine to Prevent Lyme

West Virginia University researchers received a $1.9 million grant from the National Institute of Allergy and Infectious Diseases, an institution of the National Institute of Health (NIH), for a vaccine to prevent humans from contracting Lyme disease.

Mariette Barbier, assistant professor in the School of Medicine’s Department of Microbiology, Immunology and Cell Biology, is leading the five-year project, along with Timothy Driscoll, assistant professor of biology in the Eberly College of Arts and Sciences, and Heath Damron, assistant professor and director of the WVU Vaccine Development Center.

Barbier and her team will try to develop a vaccine effective against the various species of Borrelia (the Lyme disease bacteria). They will be using RNA sequencing to examine how pathogens respond in both infected ticks and mice, and identify relevant antigens during infection.

Driscoll will be studying the proteins made by Borrelia during the black-legged ticks life cycle. “In vaccine development, what we try to do is identify those proteins and target them in hopes of clearing the pathogen out, killing it, essentially. If a protein is essential for survival, it makes it harder for the pathogen to change it and evade the immune
system,” says Driscoll.

Barbier has studied bacterial pathogens, including *Pseudomonas aeruginosa*, which requires iron to grow and infect their host. “We figured out which antigens could be used to formulate a vaccine, and found the Achilles heel to the bacteria to use against it,” Barbier said. “We focused on one system, which is the iron acquisition system of *Pseudomonas.*” Since *Borrelia* does not require iron, she is driven to find what would be required of *Borrelia*.

Barbier said. “If it doesn’t use iron, what else can we use against it? By bringing in the expertise of others, we’re going to crack the problem.”

Read more about the project here (eurekalert.org)

Click here for Project Info on NIH site

Read about another recent NIH-funded Lyme Vaccine study here

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**NIH awards $3.5 Million for Novel Lyme Disease Vaccine Study**

With a new $3.5 million grant from the National Institutes of Health (NIH), Utpal Pal, PhD, professor in Veterinary Medicine at the University of Maryland (UMD) will be partnering with Matthias Schnell, director of the Jefferson Vaccine Center at
Thomas Jefferson University to develop a novel “next-generation” Lyme disease vaccine.

Pal, a tick immunobiologist, and Schnell, whose lab studies rabies virus as a platform for vaccination, will adapt the rabies virus platform to fight Lyme disease. The inactivated rabies virus, which helps the body produce antibodies to fight rabies, will be repurposed to produce other types of proteins that can fight Borrelia burgdorferi, the Lyme disease bacteria, a technique found effective for other viral vaccinations.

This study will test the four already identified vaccine candidate proteins, as well as the three major types of rabies vaccine platforms—using live attenuated virus, inactivated virus, and the shell of a virus with viral proteins on the outside but no virus inside to trick the body. Pal is also studying both Borrelia proteins and the tick proteins that keep the Borrelia alive so it can be transmitted to humans.

Read more about this project here — (prweb.com)

Click here for Project Info on NIH site

Utpal Pal, PhD lectured at LDA’s 2018 Annual Scientific Conference – Immune Evasion of Lyme Disease Agents

Read about Pal’s previous research – UMD Research Isolates Bb Protein that Disables Immune System
About Lyme Disease Symptoms

Lyme Disease Symptoms & Signs

Lyme disease symptoms can affect any system in the body and can mimic symptoms of many different diseases.

Lyme Disease Symptoms Compiled by the LDA

As listed in the LDA LymeR Primer Available for online ordering

As listed in the LDA Spanish LymeR Primer Available for Downloading

Click dropdown arrows for symptoms
Internal anatomy of the heart

- Aorta
- Superior vena cava
- Right pulmonary artery
- Right pulmonary veins
- Right atrium
- Right AV valve
- Inferior vena cava
- Pulmonary valve
- Aortic valve
- Left pulmonary artery
- Left pulmonary veins
- Left atrium
- Left AV valve
- Left ventricle
- Right ventricle
Cardiac/Pulmonary

- Click for Symptoms
  - chest pain or rib soreness, shortness of breath, heart palpitations, pulse skips, heart block, heart murmur

Lyme Rash

Photo by Edwin J. Masters, MD
Only about 9% get the classic bull’s eye rash. Others may get another type of Erythema Migrans (EM) rash or may get no rash at all. Rash at other than bite site may be disseminated disease. Symptoms may occur days or months after a tick bite.

According to the Centers for Disease Control & Prevention (CDC) surveillance criteria, an erythema migrans (EM) rash in an endemic area, means Lyme disease. In a non-endemic area, a rash requires a positive test. *The CDC criteria are for surveillance purposes, not diagnosis.*
Gastrointestinal

- Click for Symptoms

nausea or vomiting, GERD, change in bowel function (constipation, diarrhea), gastritis, abdominal cramping, cystitis, irritable bladder or bladder dysfunction, newly diagnosed irritable bowel syndrome (IBS)
Musculoskeletal

- Click for Symptoms

  joint/muscle pain in feet, ankle pain, shin splints, joint pain or swelling, stiffness of the joints, neck or back, muscle pain or cramps that migrate, Temporomandibular joint dysfunction (TMJ/TMJD jaw pain), neck creaks & cracks, neck stiffness.
Neurological

- **Click for Symptoms**

  muscle twitching, headache, tingling, numbness, burning or stabbing sensations, facial paralysis (Bell’s palsy), dizziness, poor balance, increased motion sickness, light-headedness, wooziness, difficulty walking, tremor, confusion, difficulty thinking/concentrating/ reading, forgetfulness, poor short-term memory, disorientation (getting lost, going to wrong place), difficulty with
speech, double or blurry vision, eye pain, blindness, increased floaters, increased sensitivity to light or sound, buzzing or ringing in ears, ear pain, decreased hearing, seizure activity, white matter lesions, low blood pressure.

Neuropsychiatric

- Click for Symptoms
  mood swings, violent outbursts, irritability,
depression, disturbed sleep (too much, too little, early awakening), personality changes, obsessive—compulsive disorder (OCD), paranoia, panic/anxiety attacks, hallucinations.

Reproductive

- Click for Symptoms

testicular pain/pelvic pain, menstrual irregularity, milk production (lactation), sexual dysfunction or loss
of libido.

Other Symptoms

- Click for Symptoms
  
  fever, sweats, or chills, weight change (loss or gain), fatigue, tiredness, hair loss, swollen glands, sore throat, difficulty swallowing, swelling around the eyes, burning in feet, swelling
Lyme Transmission

Click for Info

Not all patients recall a tick bite. Studies vary as to how long the tick must be attached in order to transmit Lyme disease. The longer an infected tick is attached, the greater the chance of contracting Lyme disease. Lyme can be transmitted through the placenta.
Lyme from *Borrelia mayonii*
Another strain of Borrelia that causes Lyme

Early symptoms: fever, headaches, rash, neck pain Later: arthritis. Difference from *Borrelia burgdorferi* may include nausea & vomiting, diffuse rashes, higher concentration of bacteria in blood

*Symptoms reviewed by Elizabeth Maloney, MD; President, Partnership for Tick-Borne Diseases Education*
Other Tick-Borne Diseases & Conditions:

Patients may also contract other tick-borne diseases (coinfections) from a tick bite along with Lyme disease.

Visit LDA website Other Tick-Borne Diseases page

Other Resources for Lyme Disease Symptoms:

Columbia Lyme Rash Poster

Dr. Joseph Burrascano’s 2005 Lyme Disease Symptom List Chart

“En Español Enfermedad De Lyme” Spanish Patient Intake, Printable PDF

LDA Cardiac (Heart) Poster

LDA Lyme Disease Medical Photos Including Rashes

LDA LymeLiteracy LDA President’s Blog

LDA “LymeR Primer™” Detailed LDA Printable Brochure

En Española – “LymeR Primer™” Folleto de Sensibilización

ILADS Treatment Guidelines International Lyme & Associated Diseases Society

Columbia Lyme & Tick-Borne Diseases Research Center – Treatment Page Columbia University, Irving Medical Center

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Clinical practice treatment guidelines are often used as reference by physicians for Lyme disease treatment and treatment of other tick-borne diseases. The LDA provides some links here for informational purposes only, as LDA does not make specific treatment recommendations.

The only Lyme disease treatment guidelines that were
posted on the National Guidelines Clearinghouse (NGC), under the auspices of the US Department of Health & Human Services, are those adhering to newly revised National Academy of Medicine (NAM), formerly the Institute of Medicine (IOM), standards for guidelines: the International Lyme & Associated Diseases Society (ILADS) Lyme Guidelines, which address usefulness of antibiotic prophylaxis for tick bite, effectiveness of EM treatment, and antibiotics’ role in treatment of persistent Lyme disease symptoms.  

Note: Funding to support AHRQ’s NGC contract ended on July 16, 2018. View update here.

You can also checkout our handy infographic for treatment guidelines.

ILADS Guidelines for the Management of Lyme Disease

ILADS press release on the new guidelines

You can also review Chronic Lyme Disease: An Evidence-Based Definition by the ILADS Working Group

Other Lyme treatment guidelines of note are those developed by one of the most recognized pioneers in Lyme treatment, Dr. Joseph Burrascano, now retired as a treating physician.

Link: Burrascano Diagnostic Hints & Guidelines* (16th edition, 10/2008)

Primary care physicians and other healthcare providers seeking continuing medical education (CME) credits for Lyme disease diagnosis and treatment can now approach the non-profit Partnership for Tick-Borne Diseases Education (PTDE) led by Elizabeth Maloney, MD, a physician with longstanding experience in speaking about tick-borne diseases, organizing Lyme disease conferences, and co-authoring treatment guidelines on Lyme and other tick-borne diseases.

Partnership for Tick-Borne Diseases Education, CME for Doctors
How CDC Surveillance Criteria Impact Lyme Treatment

The Centers for Disease Control & Prevention (CDC) has a case definition for Lyme disease which is developed by the Council of State & Territorial Epidemiologists (CSTE). This definition is meant to be used for surveillance purposes only, not for diagnosis. Surveillance is the collection, analysis and interpretation of data for public health, e.g., comparing case numbers in different states: In 2015, PA is number one in Lyme case numbers, NJ is number two, etc. Below, is the current case definition used for surveillance.

Depending upon what state you live in, surveillance reporting of cases might be mandatory. Some states require doctors to report cases that meet this surveillance criteria to the State, and some also require laboratories to report these Lyme cases or maybe only labs who do electronic reporting.

Doctors are not supposed to use the surveillance criteria to diagnose so Lyme treatment should not be based on surveillance criteria. Insurance companies should not base their payment on surveillance criteria.

Click here: Lyme Disease | 2017 Case Definition

DISCLAIMER: The LDA is not a medical organization. The LDA does not make specific recommendations for treatment. Whenever medical advice is needed, the services of a qualified medical provider should be sought. The guidelines on the web sites above are the products of the guidelines’ authors who are solely responsible for their content.
Lyme Vaccine Candidate: Valneva Announces Phase 2 Study Results

Valneva announced that the vaccine candidate against Lyme disease, VLA15-201, showed positive initial results meeting its endpoints in the Phase 2 study. They stated in the July 22, 2020 press release that “compared to Phase 1, the higher doses used in this trial elicited higher antibody responses across all serotypes.” Of particular note was the immunological response found in older adults (50-65 years), one of the main target groups for a Lyme vaccine. The vaccine candidate is described as “generally safe across all dose and age groups tested”, finding no Serious Adverse Events (SAEs) associated with VLA15. This is an important finding given the history of vaccines and serious concerns that have been generated regarding patient safety and vaccines in the Lyme community.

VLA15 is the only active Lyme disease vaccine candidate in clinical development today, covering six serotypes of Lyme disease prevalent in North America and Europe. It was granted Fast Track designation by the U.S. Food and Drug Administration (FDA) in July 2017. In a few months, Valneva expects to report top-line results for the second Phase 2 study, VLA15-202. Valneva and Pfizer are collaborating for development and commercialization of VLA15.

Read full July 22, 2020 press release here

Read Valneva vaccine history and Lyme Disease Association’s concerns here:
Rickettsia Found in New Jersey Ticks

The picture in New Jersey of spotted fever group rickettsiosis (SFGR), which includes Rocky Mountain Spotted fever (RMSF), is complex. In this latest study from the *Am. Journal of Tropical Medicine and Hygiene* (James Occi, Rutgers University, et al, ), the researchers tested American dog ticks and lone star ticks in NJ to determine which *Rickettsia* are found in these two NJ ticks. They did not find the *Rickettsia* for RMSF in either of those ticks; however, they did find other *Rickettsia* in those ticks.


James Occi is a member of the Lyme Disease Association’s Scientific and Professional Advisory Board. Thanks to him for below picture of *Dermacentor variabilis*, American dog ticks: female, male, and engorged female laying eggs.
Elizabeth L. Maloney, MD Publishes on Reducing the Burden of Lyme Disease
Elizabeth L. Maloney, MD, President of the Partnership for Tick-Borne Diseases Education and Family Medicine Physician in Wyoming, MN published a paper titled “Reducing the Burden of Lyme Disease” in *Minnesota Family Physician*. It includes discussion of tick bite management, early treatment, and shared decision-making.

In the article, Dr. Maloney highlights the expensive cost of Lyme disease, stating that, “Nationwide, the annual direct medical costs could reach 1.3 billion dollars” and calls attention to the disadvantages in research the illness has suffered, as well as clinical trial evidence that is “generally scant and/or of low quality”.

The author advises that, “Blacklegged tick bites acquired in Minnesota carry a significant risk of Lyme disease,” and offers guidance for making decisions regarding antibiotic prophylaxis of asymptomatic bites.
Maloney stresses the importance of early treatment and writes, “Early Lyme disease, when promptly diagnosed and appropriately treated with antibiotics, is curable.” Above all, she states, “the risks and benefits of all options should be discussed with patients in the setting of shared decision-making in order to arrive at a therapeutic plan that fits both the clinical circumstances and the patient’s goals and values.”

Read Elizabeth L. Maloney, MD’s article in *Minnesota Family Physician*.

This article posted with permission from *Minnesota Family Physician*.

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**Lyme Disease Vaccine Collaboration Announced**

Press Release Summary
Specialty vaccine company Valneva SE and Pfizer Inc. announced a collaboration to develop VLA15, Valneva’s Lyme disease vaccine candidate, which is currently in Phase 2 clinical studies.

According to a Pfizer press release, VLA15 is the only active
Lyme disease vaccine program in clinical development today. The program covers six serotypes of Lyme disease that are prevalent in North America and Europe. The vaccine’s mechanism targets the outer surface protein A (OspA) of Borrelia burgdorferi (Bb), the bacteria that causes Lyme disease. OspA is one of the most dominant surface proteins expressed by Bb when present in a tick.

Pfizer states that VLA15 has demonstrated strong immunogenicity and safety data in pre-clinical and Phase 1 studies. In July 2017, the program was granted Fast Track designation by the U.S. Food and Drug Administration (FDA). Valneva expects to report on results from the first Phase 2 studies by mid-2020.

“We look forward to working closely with Valneva to continue advancing the VLA15 program and potentially bring a new solution to patients for this significant unmet need,” said Nanette Cocero, Global President, Pfizer Vaccines.

Comments From the Lyme Disease Association
The Lyme Disease Association President, Pat Smith, had this to say about the announcement: “A safe and effective vaccine for Lyme disease has been a goal for many decades. Unfortunately, many stakeholders, especially some vaccine recipients and providers who were then giving the vaccine, felt there were problems associated with the past Lyme vaccine, perhaps connected to its Osp A base. There are still many unanswered questions about what really happened, and like much that happens with Lyme disease, decades later, we still do not have those answers. The prudent thing for the government and/or vaccine developers to have done would have been to hold public meetings regarding a new Lyme vaccine with all interested stakeholders to hear concerns and answer questions about the development of a new Osp A-based vaccine and what research was done to address the previous concerns and any newly arisen concerns.
In general, much research on Lyme disease has still not been done. In fact, ~46 years into Lyme disease, it ranks below leprosy in the number of clinical trials done in infectious diseases (Goswami et al., 2013). Those who have questioned the safety and efficacy and approval process of the past vaccine have been publicly accused of bringing that vaccine down. When the opportunity for dialogue which engages the Lyme community and all stakeholders has not been offered as part of the approval process, it creates an atmosphere of distrust among those whose trust is necessary to accept a new Lyme disease vaccine.”

Links for You

Read Pfizer’s VLA15 press release.

Read articles on the history of Lyme disease vaccines.

Current Lyme Disease Testing Problems

Elizabeth Maloney, MD, explains current Lyme disease testing issues, including the ELISA and Western Blot, sensitivity and specificity of the testing, and the problems associated with the two-tier testing recommended by the CDC. It begins with the general characteristics of diagnostic testing

The Summary states: “Serologic testing for Lyme is inaccurate. While the inadequate sensitivity of ELISA and Western blot tests is the primary problem, imprecision and the lack of
clinical validity contribute to the poor performance of two-tier testing in clinical settings. Although the high specificity of the CDC two-tier strategy works well for epidemiologic purposes, the testing sequence reduces the overall sensitivity, thereby limiting its clinical effectiveness. While positive results on two-tier testing in an untreated patient who has symptoms of Lyme disease would confirm the clinical diagnosis (and it would be a mistake to label such results as “false positives”), negative results do not rule out Lyme disease.”

See full article by Elizabeth Maloney, MD here: Applying Basic Concepts in Laboratory Testing to Serologic Testing for Lyme Disease

See International Lyme & Associated Diseases (ILADS) Controversy & Challenges Page – Issues with Diagnosis & Diagnostics

ELISA Test: The original whole cell sonicate test