

Mount Vernon Hospital

Submission to the Institutional Review Board

Clinical Investigation as to the role of Hyperbaric Oxygen in the
Treatment of Refractory Lyme Disease

A Self-Funded Community Service Program

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Each year, The Mount Vernon Hospital Hyperbaric Service receives requests to provide Hyperbaric Oxygen Therapy (HBO) for medical conditions outside the 15 approved CMS indications where there is substantial medical support and where these conditions are already routinely treated with adjunctive HBO. These conditions include Stroke, Traumatic Brain Injury, Psoriasis, and Refractory Lyme Disease which are not presently funded by medical insurance programs despite some positive clinical outcomes and the relatively benign nature of HBO. This self-funded, at cost, program is intended to provide a hospital-based, physician supervised and lower cost option to clinically marginal free standing HBO operations.

Hyperbaric Medical Technologies, Inc. and The MVH Hyperbaric Service have extensive experience with HBO and Lyme Disease treatment and have conducted the only In-Vitro In-Vivo Murine Model research on Lyme Spirochete susceptibility to high Oxygen tensions. (See references)

The treatment protocol is based upon actual clinical experience and research. We consider it to be an optimized treatment procedure which adds hyperbaric oxygen (HBO) to conventional optimized antibiotic therapy, nutrition, neuro-psychiatric support and testing for chronic lyme patients, often with neurological sequela that have not responded well to conventional antibiotic therapies alone.

Spirochetes causing lyme disease are micro-aerophilic bacteria that cannot tolerate high oxygen tension. In vivo and in vitro studies have demonstrated that HBO could be bactericidal and hamper the growth and infectiveness of spirochetes in vivo. Further, these bacteria have flagellates which could be a target for metronidazole. It has been shown that metronidazole could hamper growth and activity of the spirochetes in vitro. Therefore the study includes investigation of therapeutic effects of combination of classical antibiotics and HBO with or without metronidazole.

Chronic Refractory Lyme Disease patients will be referred to the TMVH HBO Lyme Program by their Infectious Disease or Lyme Disease specialist Physician for Hyperbaric Treatment only. All other medical care will be managed by the primary care physician (PCP).

Patients will be followed up clinically by their physician. The combination of antibiotics and determination of progress or an end of infection will be determined by the PCP.

Based on discussions and on a case by case basis, the PCP may add other antibiotics such as metronidazole, and measure Tumor Necrosis Factor (TNF) in addition to Western-Blot and ELISA Titer testing before and after the course of HBO treatment.

Each aspect of the program and protocols utilizes independently FDA approved treatment and testing modalities.

Lyme Disease is a tick-borne disease caused by a *Borrelia* spirochete (*Borrelia burgdorferi*). The disease was discovered in 1975. It began as endemic to the northeastern United States, but is now found throughout the country. Records of the Centers for Disease Control show that between 1982 and 1997 there were more than 100,000 cases of Lyme disease reported nationwide, and that in 1996 there were over 16,000 new cases reported from 45 states.

There has been a 10-fold increase in reported cases during the past 10 years and it is believed that a much higher number of cases remain undiagnosed. Lyme disease has proven to be one of the most invasive, persistent, and intractable worldwide plagues of the 21st century. The application of classical antibiotics has been only been truly successful in cases diagnosed early.

The disease is normally diagnosed by looking for antibodies to the organism that causes Lyme disease in the blood of patients. The primary treatment for Lyme disease is antibiotics, administered either orally or intravenously. Definitive treatment is largely successful if antibiotics are initiated aggressively early in the course of the disease. However, some Lyme patients whose condition has become chronic were not initially diagnosed and have become refractory to traditional Lyme therapies and antibiotics.

Some presently chronic Lyme patients do not respond to antibiotics. Another aspect of Lyme disease therapy is the occurrence of the Jarisch-Herxheimer response. This is observed as the development of symptoms in response to antibiotic treatment. The symptoms are typical of a generalized inflammatory reaction: fever, chills, myalgia, headache, tachycardia, vasodilation, with possible mild hypotension. It is believed that these symptoms may be the result of an inflammatory response to the breakdown products of spirochetes killed by the therapy. These symptoms are prominent at the beginning of antibiotic administration and may persist throughout the course of antibiotic therapy.

This reaction has also been reported to follow HBO exposure of patients to hyperbaric oxygen as well (W. Fife, personal communication, 1988). Tumor Necrosis Factor is a proinflammatory cytokine produced largely by activated macrophages and detectable in the blood. It along with Interleukin One (IL-1), IL-6, and IL-8 are thought to be responsible for the Jarisch-Herxheimer reaction (fever, chills, myalgia, headache, tachycardia, vasodilatation with possible mild hypotension) that is often seen in patients being treated for Lyme Disease, and other spirochetal diseases (i.e. syphilis). Negussie et al, and Griffen have both recently shown that plasma TNF levels and the Jarisch-Herxheimer response are closely associated

Hyperbaric Oxygen Therapy (HBO) involves exposing the patient's whole body to levels of oxygen not possible at normal atmospheric pressure. This is done in monoplace hyperbaric pressure chambers in sessions normally lasting about one and one-half hours (90 minutes). In traditional and accepted medical use, HBO is normally used as adjunctive therapy in concert with traditional treatment methods for a number of medical conditions.

A rationale for the use of Hyperbaric Oxygen in Lyme disease treatment is largely credited to Dr. William Fife. Fife observed a reduction of joint pain and other symptoms in Lyme patients given HBO exposures. He also saw what he considered to be a Jarisch-Herxheimer response that suggested the *Borrelia burgdorferi* (*Bb*) organisms were being killed by the high oxygen concentrations.

The effect of oxygen on this micro-aerophilic organism was demonstrated by the work of Austin (1993), who showed that *in vitro* cultures of *Bb* in which the oxygen and carbon dioxide had ambient sea level values ($PO_2 = 160$ mm Hg.) showed a loss in the ability to infect and spread the infection, while if cultured in 4% O_2 , 5% CO_2 , ($PO_2 = 30$ mm Hg), the infectiveness of the organism remained viable. This study suggests that this organism is sensitive to elevated levels of oxygen, and should be inhibited by a normal hyperbaric oxygen exposure such as a chamber pressure of 2.4 atmospheres absolute (atm abs).

At this pressure the inspired PO_2 is 1,824 mm Hg with distal tissue oxygen tensions of approximately 200-300 mm Hg or higher. This was the level used by Fife. This study suggests that this organism is sensitive to elevated levels of oxygen, and should be inhibited by a normal HBO exposure such as a chamber pressure of 2.4 atmospheres absolute (atm abs). At this pressure the inspired PO_2 is 1,824 mm Hg with distal tissue oxygen tensions of approximately 200-300 mm Hg or higher. This was the level used by Fife.

In an effort to scientifically quantitate the Austin and Fife observations and establish a therapeutic oxygen dosage, a landmark *in-vitro* / *in-vivo* research protocol was developed and conducted at the Infectious Diseases Immunodiagnostic Laboratory of The New York Medical College, Valhalla, NY. (Pavia, et al) The study protocol exposed *Bb* cultures and chronically infected mice using temperature controlled Hyperbaric pure oxygen pressures up to 3 atmospheres absolute (atm abs). Study results showed that 14 of 17 different strains of *Bb* had their growth inhibited by 33 to 94%, while there was little or no growth inhibition of 3 *Bb* strains.

In the *in-vivo* portion of the study, separate groups of C3H or CD1 mice were infected intradermally with 100,000 *Borrelia* spirochetes. Two to four weeks later, one group of infected mice received 1.0 to 1.5 hour exposures at pressures ranging from 2.0 to 3.0 atmospheres for two consecutive or alternating days. The treated would appear to support these previous studies and this specific protocol. The New York Medical College Study (totally funded by Lyme disease associations and individuals) and future work by the NYMC / TMVH team and this IRB proposed program will further help to define the primary pathogenic processes which occur during the exposure of *Bb* to hyperbaric oxygen tensions.

Refractory Lyme-We propose that in a very limited number of cases, even the most optimal antibiotic and adjunctive (diet, etc.) conventional therapies only appear to eradicate *Borrelia burgdorferi* (*Bb*) from patients diagnosed with Chronic Refractory Lyme Disease, when in fact these spirochetes are actually “sequestered” by fibroblasts and other specific tissues. These are normal defenses of the body that also seem to protect the *Bb* spirochetes from the combined effects of antibiotics and the immune system. We consider that tolerable doses of antibiotics are not able to eradicate these sequestered *Bb* spirochetes. Such *Bb* spirochetes remain dormant, and when the antibiotic is terminated and/or other demands are placed on the host’s immune system, these patients often become symptomatic and must be treated again.

As another factor, it is well known that the antibiotics prescribed for Lyme disease often do not cross the blood-brain barrier effectively. This effect may contribute to the apparent sequestering of *Bb* spirochetes in such tissues, which permits them to resist antibiotics, the host immune system, and for symptomatic re-infection to occur. Whereas antibiotics might be restricted in their action by *Bb* spirochete sequestering and the blood-brain barrier, Hyperbaric Oxygen will not be subject to either of these limitations. High oxygen tensions will diffuse easily across the blood-brain barrier, and will penetrate any conceivable fibroblast or *Bb* tissue sequestration.

The *Borrelia (Bb)* spirochete is a micro-aerophilic organism. Previous studies seem to indicate that *Bb* loses infectiousness and might even be killed by some direct free-radical biochemical effects of HBO₂ or in some synergistic effect through macrophages and the normal immunological defense mechanisms.

Interaction of *B. burgdorferi* organisms with mouse bone marrow-derived macrophages leads to phagocytosis of microorganisms, induction of nitric oxide and superoxide radicals (O₂⁻) by macrophages and killing of spirochetes ([Immunol Lett.](#) 1994 May;40(2):139-46). None of the Lyme disease spirochetes possessed catalase or peroxidase activities. The borreliac superoxide dismutase was not inducible by growth with increased oxygen concentrations and thus appeared to be produced constitutively ([Infect Immun.](#) 1997 Nov;65(11):4865-8). Therefore, HBO might help to kill the microorganism by increasing free radicals generation.

Another unusual structural feature in the spirochetes is a single flagella, attached to each end of the spirochete, running the length of the organism and surrounded by it. This feature is significant in relation to immune protection, since most bacterial flagella are highly antigenic. Because *B. burgdorferi* is a micro-aerophilic bacterium like *Helicobacter pylori*, metronidazole was chosen in the susceptibility test ([APMIS.](#) 1999 Jun;107(6):566-76). High doses of metronidazole were found to destroy the cyst form of the organism, and it was suggested to treat resistant infections caused by *B. burgdorferi* with a combination of metronidazole and other antibiotics in order to eradicate both cystic and mobile forms of *B. burgdorferi*.

Objective

The objective of this Community Service Program is to provide hospital-based, physician supervised Hyperbaric Oxygen Therapy (HBO) to Physician Lyme specialists wishing to provide HBO in addition to antibiotics to their chronic Lyme patients. We fully intend to document and work with the Lyme PCP to document and optimize Chronic Lyme Patient outcomes and to determine if a course of adjunctive HBO exposures in addition to optimized antibiotic therapy will make a demonstrable change in the condition of disabled patients suffering from the chronic neurological phase of Lyme disease, chronic neuroborreliosis.

The ultimate objectives of this Program are to identify a specific optimal combination of chronic Lyme treatments and to develop an optimum treatment research protocol towards a cure and eventual medical insurance reimbursement.

Patients

The patients which will be accepted in the program have requested to participate and are formally referred to the Study by physicians in the area who treat Lyme disease. Participating physicians agree to remain the patient's primary care physician (PCP) and make referral to the TMVH program ONLY to add HBO therapy to optimized antibiotic, nutritional and other medical care. The PCP will only make patient referrals based on acceptance criteria. Patient candidates will receive an on-site interview, orientation and a informed consent. Acceptance by a TMVH HBO Supervising Patient is based on his/her sole decision.

Inclusion criteria

1-The MVH Chronic Refractory Lyme Disease Community Service Program will consider patient referrals of chronic Lyme disease patients who have **developed significant joint disease and/or neurological sequelae and who have exhausted their conventional clinical options without significant improvement in their medical condition.**

2-Patients must be referred by their PCP whom agrees to continue to provide on-going medical supervision and patient medical history

3-Patients must be interviewed and pass the HBO Medical Clearance Exam. All potential HBO patients must be able to follow direction and complete all pre-HBO medical testing as determined by the TMVH HBO Physician.

4-Patients or their appropriate representative will sign informed consent prior to testing or HBO exposure.

5-All Patient participation is solely at the discretion of the study / HBO supervising physician's.

6-Such patient acceptance criteria are expected to provide patients having a detailed medical history, lab reports, and course of Lyme therapy to date. All patients are expected to be on an optimized antibiotic regimens as prescribed by their primary Lyme physician, and will be maintained on the same antibiotics through the HBO program as possible, always considering the patients clinical response first. Patients that are no longer able to tolerate OR are allergic to antibiotics will be considered.

Exclusion criteria

The study group patient/subjects will be screened for absolute and relative contraindications to the mechanical and neurological effects of HBO. No severe reactions specific to patients with Lyme disease are anticipated from the administration of pure oxygen at the pressures and exposure times to be used. However, the Jarisch-Herxheimer reaction is expected to appear in subjects after HBO exposures as the destruction of *Bb* spirochetes takes place. Patients with a history of seizure disorder or ear problems will be excluded from study Patients with other debilitating diseases like cancer will be excluded

Each accepted Lyme patient will be evaluated as to testing results, clinical evaluation and program compliance at the end of each block of 10 treatments. Any patient that develops relative contraindications to continued HBO therapy, such as ENT problems, which result in more than 2 therapy cancellations might be dropped from the study at our sole discretion.

Approved study participants receive base-line testing which include clinical examination, scoring of the symptoms, a PCR, TNF and Titer assay. If possible, Polymerase Chain PCR and plasma levels of TNF will be measured bi-monthly in order to help quantify the effectiveness of the HBO therapy and to track the Jarisch-Herxheimer reaction.

The investigators consider that the HBO dosages used in this study, especially in conjunction with continued and optimized antibiotic therapy, should be carried out within a hospital setting in order to afford any medical support that might be required by Lyme study patient/subjects. If any subjects have reactions at home that might require hospital care they are to contact MVH and if necessary, their travel be facilitated to MVH by appropriate transportation in order to effect treatment.

A full clinical assessment will be given at the end of each block of twenty (20) HBO exposures. Patients determined to continue in the study will continue for a possible total of sixty (60) HBO exposures.

All HBO exposures will be nominal 100% oxygen at 2.5 atmospheres absolute for sixty to ninety minutes. The first three days of the study will be spent on administrative matters, briefings, and baseline testing. HBO₂ exposures begin the second week for each patient.

Chronic Lyme disease patients tend to have Jarish-Herxheimer responses following both antibiotics and exposure to HBO. This is believed to be due to an immunological reaction to the antigens released into the Lyme patient from killed organisms. It presents with the characteristics of a generalized immune reaction. As an immune reaction, the intensity of the response varies significantly between different individuals, and with the “dosage” of the pathogen. (Antibiotics or HBO-especially in combination).

For a given individual, the intensity of the J-H response seems to be an indication of the pathogenic process of the specific therapy. It is also known that there can also be a positive “synergistic” interaction between some antibiotics and HBO such that a more intense J-H response may occur if HBO and antibiotics are given in close proximity.

Because the J-H response can range from mild “flu like” symptoms to severe if it induces anaphylactic shock or migraine headaches in the Lyme patient, it is best that it be induced in a controlled manner. Accordingly, we propose the following protocol to manage the “phasing” of the antibiotic and HBO₂ therapies.

As our preliminary in-vitro and in-vivo studies have indicated, the replication and/or pathogenic effect of HBO on the Bb Spirochete appear to be dose responsive.

The clinical investigation “Phased” concept is to schedule the HBO therapies as a gradual increase in dosage to control / monitor the J-H response and also coordinate the timing of the HBO exposure

is as follows.

First treatment	2.0 atm for 60 min
Second treatment	2.0 atm for 90 min
Third treatment	2.5 atm for 60 min

with an optimized antibiotic regime. The sequence of HBO exposures

Fourth and further treatments 2.5 atm for 90 min

The HBO treatments are to be conducted on alternating days in order to allow the JH response to manifest itself, be “scored” by the patient, and allowed to subside. Any patient that has not returned to a near “0” JH score by the morning of the next HBO exposure, will repeat the exposure and antibiotic “phasing” or be suspended from HBO exposure for an additional day or until the JHR subsides.

Timing of antibiotic administration.

While the dosage and frequency of an optimized antibiotic regime will vary from patient to patient, we will generate a specific “Dosage Phasing” protocol for each patient. Our preliminary results indicate that the conservative approach requires that the first four incremental HBO treatments there be at least 8 hours between the last dose of antibiotics and the HBO exposure. The fifth and sixth HBO exposures that there be at least 6 hours separation. Given the JHR “scoring” and clinical presentation criteria presented above, subsequent treatments will have at least a 2 hour interval between the antibiotic administration and the HBO exposure. Patients that do not substantially resolve their JHR prior to their next HBO exposure will repeat the same HBO exposure, or be suspended an additional day and the antibiotic “phasing” decreased.

Informed consent

All potential Program patients be interviewed and receive both an oral and written informed consent regarding the potential hazards of HBO therapy and J-H reaction. The patient acceptance criteria are expected to provide us with subject patients having a detailed medical history, lab reports, and course of Lyme therapy to date.

All patients are expected to be on antibiotic regimens as prescribed by their primary Lyme physician, and will be maintained on the same pre-study antibiotics, or change antibiotic therapy, and maintain dosages through the study as possible, always considering the patients clinical response first.

This study has been approved by The Mount Vernon Hospital Institutional Review Board (IRB) and meets the requirements of the Declaration of Helsinki on the Use of Human Subjects in Research.

Place of study

The study is to be conducted at and under the direction of The Mount Vernon Hospital Chronic Wound Treatment and Hyperbaric Center. This hospital-based multi-disciplinary medical facility is uniquely staffed and equipped to conduct this study.

We must acknowledge that this study would not be possible without the essential participation of the MVH administration, clinical investigators, leading Lyme disease research and clinical specialists that have contributed to the development of this protocol and ongoing data analysis.