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DIAGNOSTIC HINTS AND TREATMENT GUIDELINES FOR LYME AND OTHER TICK BORNE ILLNESSES

JOSEPH J. BURRASCANO JR., M.D.

Fourteenth Edition
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INTRODUCTION

Welcome to the fourteenth edition of the "Guidelines." With the passage of time, our understanding of tick-borne illness has grown, so new information is presented to help us further refine our management techniques.

“Lyme Disease” is not simply an infection with *Borrelia burgdorferi*, but a complex illness potentially complicated by multiple tick-borne co-infections. In later stages, it also includes a very significant degree of immune suppression. This not only serves to perpetuate the infections, but it is probably responsible for the reactivation of latent infections, such as herpes-type viruses. Many collateral conditions result in those who have been chronically ill so it is not surprising that damage to virtually all bodily systems can result. To fully recover, all of these issues must be addressed in a thorough and systematic manner. No single treatment or medication will result in full recovery of the more ill patient. Only by addressing all these smaller issues and engineering treatments and solutions for all of them will we be able to restore full health to our patients.

Once again, the full spectrum of Lyme Borreliosis will be addressed, from the new bite, through early and late disseminated infections, and certainly to chronic Lyme Disease.

A very important issue is the definition of “Chronic Lyme Disease.” Based on my clinical data and the latest published information, I offer the following definition. To be said to have chronic Lyme, these three criteria must be present:

1. Illness present for at least one year
2. Have persistent major neurologic involvement (such as encephalitis/encephalopathy, meningitis, etc.) or active arthritic manifestations (active synovitis).
3. Still have active infection with B. burgdorferi, regardless of prior antibiotic therapy (if any).

It is clear that in the great majority of patients, chronic Lyme is a disease affecting predominantly the nervous system. Thus, careful evaluation often includes neuropsychiatric testing, SPECT and

MRI brain scans, CSF analysis when appropriate, regular input from Lyme-aware neurologists and psychiatrists, pain clinics, and occasionally specialists in psychopharmacology.

As an extension of the effect of chronic Lyme Disease on the central nervous system, new information has demonstrated a deleterious effect on the hypothalamic-pituitary axis. Varying degrees of pituitary insufficiency are being seen in these patients, the correction of which has resulted in restoration of energy, stamina and libido, and resolution of persistent hypotension. Unfortunately, not all specialists recognize pituitary insufficiency, partly because of the difficulty in making the laboratory diagnosis. However, the potential benefits of diagnosing and treating this justify the effort needed for full evaluation.

The concept of a “therapeutic alliance” between the caregiver and patient must again be emphasized. This means that the patient has to work with and become part of the medical team, and must take responsibility for complying with the recommendations given, maintaining the best possible health status, reporting promptly any problems or new symptoms, and especially in realizing that despite all our best efforts, success in diagnosis and treatment is never assured. The medical team must make great efforts to listen carefully to the patient and not be too quick to dismiss seemingly bizarre or illogical complaints.

I once again extend my best wishes to the many patients and caregivers who deal with Lyme, and a sincere thank you to my colleagues whose endless contributions have helped me shape my approach to tick borne illnesses. I hope that my new edition proves to be useful. Happy reading!

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BACKGROUND INFORMATION

SPIROCHETE LOAD AND IMMUNE SUPPRESSION IN LYME DISEASE

The spirochete load has a direct bearing on the severity of Lyme presentation. Low spirochete loads result in mild or even inapparent infections that can be missed and remain present for years. As spirochete load increases, especially from subsequent tick bites, the morbidity of Lyme increases. Symptoms become apparent and more debilitating the larger the load, and testing for Lyme can become more accurate. Studies have shown that higher loads also begin to clinically impact the immune system, with invasion and killing of B- and T-lymphocytes, including Natural Killer Cells, and inhibition of lymphocyte transformation and mitogenesis. A corollary to the issue of spirochete load is the delicate balance between defense efficacy vs. pathogen strength. In other words, more severe illness also results from weakened defenses, such as from severe stress, immunosuppressant medications, and severe intercurrent illnesses.

The longer one is ill with Lyme, the more likely the illness will be more severe and treatment resistant. The same studies that demonstrated lymphocyte inhibition and lysis from high spirochete loads also demonstrated increased negative effects on the immune system the longer the spirochetes were present. We have seen this clinically, with the ultimate result being full blown Chronic Lyme Disease.

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CO-INFECTION

A huge body of research and clinical experience has demonstrated the nearly universal phenomenon in Lyme patients of co-infection with multiple tick-borne pathogens. Significant

numbers of Lyme patients have been shown to also carry Babesia species, Ehrlichias, Anaplasmas, Mycoplasmas, Bartonellas and viruses. Rarely, yeast forms have been seen in peripheral blood. Studies have shown that co-infection results in a more severe clinical presentation, with more organ damage, and the pathogens become more difficult to eradicate. It is known that Babesia infection, like Lyme Borreliosis, is immunosuppressive. There are changes in the clinical presentation compared to when each infection is present individually, with different symptoms, and atypical signs. There may be decreased reliability of standard diagnostic tests, and most importantly, there is recognition that chronic, persistent forms of each of these infections do indeed exist. As time goes by, I am convinced that even more pathogens will be found.

Therefore, real, clinical Lyme as we have come to know it, especially the later and more severe presentations, probably represents a mixed infection. I will leave to the reader the implications of how this may explain the discrepancy between laboratory study of pure Borrelia infections, and what front-line physicians have been seeing for years in real patients.

The evaluation of a Lyme patient must begin with testing for all currently known tick borne pathogens. Serological studies for Borrelia, Babesia Bartonella and Ehrlichia should be combined where appropriate with direct antigen assays. Antigen detection tests (antigen capture and PCR) are especially helpful in evaluating the seronegative patient and those still ill or relapsing after therapy. Unfortunately, over a dozen protozoans other than Babesia microti can be found in ticks, yet commercial tests for only B. microti and WA-1 are available at this time, so as in Borrelia, clinical assessment is the primary diagnostic tool. In Ehrlichiosis, test for both the monocytic and granulocytic forms. Many presently uncharacterized Ehrlichia-like organisms can be found in ticks and may not be picked up by currently available assays, so in this illness too, serologies are only an adjunct in making the diagnosis.

Babesia are parasites, and I suggest that if a coinfection is found involving this organism, treat this first, so that subsequent therapy for the other pathogens will be more effective.

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COLLATERAL CONDITIONS

Experience has shown that collateral conditions exist in those who have been ill a long time. The evaluation should include testing both for differential diagnosis and for uncovering other subtle abnormalities that may coexist.

Test B12 levels, and be prepared to aggressively treat with parenteral formulations.

Pituitary and other endocrine abnormalities are far more common than generally realized. Evaluate fully, including growth hormone levels. When testing the thyroid, measure free T3 and free T4 levels and TSH. Nuclear scanning and testing for autoantibodies may be necessary.

Activation of the inflammatory cascade has been implicated in blockade of cellular hormone receptors. One example of this is insulin resistance, which may partly account for the dyslipidemia and weight gain that is noted in 80% of chronic Lyme patients. Clinical hypothyroidism can result from receptor blockade and thus hypothyroidism can exist despite normal serum hormone levels. In addition to measuring free T3 and T4 levels, check basal A.M. body temperatures. If hypothyroidism is found, you may need to treat with both T3 and T4 preparations until blood levels of both are normalized.

Tilt table testing is another powerful tool which, just as in CFIDS, may demonstrate neurally mediated hypotension (NMH). NMH can result from autonomic neuropathy and endocrine

dyscrasias. If NMH is present, treatment can dramatically lessen fatigue, palpitations and wooziness, and increase stamina. This test should be done by a cardiologist and include Isuprel challenge. This will demonstrate not only if NMH is present, but also the relative contributions of hypovolemia and sympathetic dysfunction. Therapy is based on blood volume expansion (increased sodium and fluid intake and possibly Florinef plus potassium). If not sufficient, beta blockade may be added based on response to the Isuprel challenge.

Magnesium deficiency is very often present and quite severe. Hyperreflexia, muscle twitches, myocardial irritability, poor stamina and recurrent tight muscle spasms are clues to this deficiency. Magnesium is predominantly an intracellular ion, so blood level testing is of little value. Oral preparations are acceptable for maintenance, but most need additional, parenteral dosing: 1 gram IV or IM at least once a week until neuromuscular irritability has cleared.

SPECT scanning of the brain, if done by knowledgeable radiologists using high resolution equipment, will show characteristic abnormalities in Lyme encephalopathy. What these scans demonstrate is cerebral vasculitis, which is the underlying mechanism for much of the symptoms of Lyme. This not only helps with the differential diagnosis, but if done before and after acetazolamide, it will guide in the use of vasodilators, which may clear some cognitive symptoms. Therapy can include acetazolamide, serotonin agonists and even Ginkgo biloba. Therapeutic trials of these may be needed.

Two different researchers have provided evidence that B. burgdorferi, like many other pathogenic bacteria, can produce neurotoxins. Early clinical trials aimed at removing these toxins have proven quite promising. I will discuss this in more detail in a later section.

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LYME BORRELIOSIS

DIAGNOSTIC HINTS

Lyme is diagnosed clinically, as no currently available test, no matter the source or type, is definitive in ruling in or ruling out infection with these pathogens, or whether these infections are responsible for the patient's symptoms. The entire clinical picture must be taken into account, including a search for concurrent conditions and alternate diagnoses, and other reasons for some of the presenting complaints. Often, much of the diagnostic process in late, disseminated Lyme involves ruling out other illnesses and defining the extent of damage that might require separate evaluation and treatment.

Consideration should be given to tick exposure, rashes (even atypical ones), evolution of typical symptoms in a previously asymptomatic individual, and results of tests for tick-borne pathogens. Another very important factor is response to treatment — presence or absence of Jarisch Herxheimer-like reactions, the classic four-week cycle of waxing and waning of symptoms, and improvement with therapy.

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ERYTHEMA MIGRANS

Erythema migrans (EM) is diagnostic of Bb infection, but is present in fewer than half. Even if present, it may go unnoticed by the patient. It is an erythematous, centrifugally expanding lesion that is raised and warm. Sometimes there is mild stinging or pruritus. The EM rash will begin four days to several weeks after the bite, and may be associated with constitutional symptoms.

Multiple lesions are present less than 10% of the time, but do represent disseminated disease. Some lesions have an atypical appearance and skin biopsy specimens may be helpful. When an ulcerated or vesicular center is seen, this may represent a mixed infection, involving other organisms besides B. burgdorferi.

After a tick bite, serologic tests (ELISA. IFA, western blots, etc.) are not expected to become positive until several weeks have passed. Therefore, if EM is present, treatment must begin immediately, and one should not wait for results of Borrelia tests. You should not miss the chance to treat early disease, for this is when the success rate is the highest. Indeed, many knowledgeable clinicians will not even order a Borrelia test in this circumstance.

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DIAGNOSING LATER DISEASE

When reactive, serologies indicate exposure only and do not directly indicate whether the spirochete is now currently present. Because Bb serologies often give inconsistent results, test at more than one laboratory using, if possible, different methods. The suggestion that two-tiered testing, utilizing an ELISA as a screening tool, followed, if positive, by a confirmatory western blot, is illogical in this illness. The ELISA is not sensitive enough to serve as an adequate screen, and there are many patients with Lyme who test negative by ELISA yet have fully diagnostic western blots. I therefore recommend against using the ELISA. Order IgM and IgG western blots — but be aware that in late disease there may be repeatedly peaking IgM's and therefore a reactive IgM may not differentiate early from late disease, but it does suggest an active infection. When late cases of LB are seronegative, 36% will transiently become seropositive at the completion of successful therapy.

Western blots are reported by showing which bands are reactive. 41KD bands appear the earliest but can cross react with other spirochetes. The 18KD, 23–25KD (Osp C), 31KD (Osp A), 34KD (Osp B), 37KD, 39KD, 83KD and the 93KD bands are the most specific but appear later or may not appear at all. You need to see at least the 41KD and one of the specific bands. 55KD, 60KD, 66KD, and 73KD are nonspecific and nondiagnostic.

PCR tests are now available, and although they are very specific, sensitivity remains poor, possibly less than 30%. This is because Bb causes a deep tissue infection and is only transiently found in body humors. Therefore, just as in routine blood culturing, multiple specimens must be collected to increase yield; a negative result does not rule out infection, but a positive one is significant. You can test whole blood, buffy coat, serum, urine, spinal and other body fluids, and tissue biopsies. Several blood PCRs can be done, or you can run PCRs on whole blood, serum and urine simultaneously at a time of active symptoms. The patient should be antibiotic free for at least six weeks before testing to obtain the highest yield.

Antigen capture is becoming more widely available, and can be done on urine, CSF, and synovial fluid.

Sensitivity is still low, but specificity is high.

Spinal taps are not routinely recommended, as a negative tap does not rule out Lyme. Antibodies to Bb most commonly are found in Lyme meningitis, but are rarely seen in non-meningitic CNS infection, including even advanced encephalopathy. Even in meningitis, antibodies are detected in the CSF in less than 20% of patients with late disease. Therefore, spinal taps are only performed on patients with pronounced neurological manifestations in whom the diagnosis is uncertain, if they are seronegative, or are still significantly symptomatic after completion of treatment. When done, the goal is to rule out other conditions, and to determine if Bb antigens or

nucleic acids are present. It is especially important to look for elevated protein and mononuclear cells, which would dictate the need for more aggressive therapy, as well as the opening pressure, which can be elevated and add to headaches, especially in children.

I strongly urge you to biopsy all unexplained skin lesions/rashes and perform PCR and careful histology. You will need to alert the pathologist to look for spirochetes.

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DIAGNOSTIC CHECKLIST

To aid the clinician, a workable set of diagnostic criteria was developed with the input of dozens of front line physicians. The resultant document has proven to be extremely useful not only to the clinician, but it also can help clarify the diagnosis for third party payers and utilization review committees. **It is important to note that the CDC's published reporting criteria are for surveillance only, not for diagnosis**.

LYME BORRELIOSIS DIAGNOSTIC CRITERIA	RELATIVE VALUE
	1
Tick exposure in an endemic region	2
Historical facts and evolution of symptoms consistent with Lyme	
Systemic signs & symptoms consistent with Bb infection (other potential diagnoses excluded):	
Single system, e.g., monoarthritis	1
Two or more systems, e.g., monoarthritis and facial palsy	2
Erythema migrans, physician confirmed	7
Acrodermatitis Chronica Atrophicans, biopsy confirmed	7
Seropositivity	3
Seroconversion on paired sera	4
Tissue microscopy, silver stain	3
Tissue microscopy, monoclonal immunofluorescence	4
Culture positivity	4
B. burgdorferi antigen recovery	4
B. burgdorferi DNA/RNA recovery	4

DIAGNOSIS	
Lyme Borreliosis Highly Likely	7 or above
Lyme Borreliosis Possible	5–6
Lyme Borreliosis Unlikely	4 or below

I suggest that when using these criteria, you state Lyme Borreliosis is “unlikely,” “possible,” or “highly likely” based upon the following criteria—then list the criteria.

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SYMPTOM CHECKLIST

This is not meant to be used as a diagnostic scheme, but is provided to streamline the office interview. Note the format — complaints referable to specific organ systems are clustered to better display multisystem involvement.

NAME_____DATE_____

RISK PROFILE (PLEASE CHECK)

Tick infested area ___ Frequent outdoor activities ___ Hiking ___ Fishing ___ Camping ___ Gardening ___
Hunting ___ Ticks noted on pets ___ Other household members with Lyme ___
Do you remember being bitten by a tick? No ___ Yes ___ when _____
Do you remember having the “bull's eye rash?” No ___ Yes ___
Any other rash? No ___ Yes ___

Have you had any of the following? CIRCLE ALL YES ANSWERS

1. Unexplained fevers, sweats, chills, or flushing
2. Unexplained weight change (loss or gain — circle one)
3. Fatigue, tiredness, poor stamina
4. Unexplained hair loss
5. Swollen glands: list areas _____
6. Sore throat
7. Testicular pain/pelvic pain
8. Unexplained menstrual irregularity
9. Unexplained milk production; breast pain
10. Irritable bladder or bladder dysfunction
11. Sexual dysfunction or loss of libido
12. Upset stomach or abdominal pain
13. Change in bowel function (constipation, diarrhea)
14. Chest pain or rib soreness
15. Shortness of breath, cough
16. Heart palpitations, pulse skips, heart block
17. Any history of a heart murmur or valve prolapse?
18. Joint pain or swelling: list joints
    _____
19. Stiffness of the joints or back
20. Muscle pain or cramps
21. Twitching of the face or other muscles
22. Headache
23. Neck creaks and cracks, neck stiffness, neck pain
24. Tingling, numbness, burning or stabbing sensations, shooting pains, skin hypersensitivity
25. Facial paralysis (Bell's Palsy)
26. Eyes/Vision: double, blurry, increased floaters, light sensitivity
27. Ears/Hearing: buzzing, ringing, ear pain, sound sensitivity
28. Increased motion sickness, vertigo, poor balance
29. Lightheadedness, wooziness, unavoidable need to sit or lie down
30. Tremor
31. Confusion, difficulty in thinking
32. Difficulty with concentration, reading
33. Forgetfulness, poor short term memory, poor attention, problem absorbing new information
34. Disorientation: getting lost, going to wrong places

35. Difficulty with speech or writing; word or name block
36. Mood swings, irritability, depression
37. Disturbed sleep — too much, too little, fractionated, early awakening
38. Exaggerated symptoms or worse hangover from alcohol

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LYME DISEASE TREATMENT GUIDELINES

LYME BORRELIOSIS

GENERAL INFORMATION

After a tick bite, Bb undergoes rapid hematogenous dissemination, and, for example, can be found within the central nervous system as soon as twelve hours after entering the bloodstream. This is why even early infections require full dose antibiotic therapy with an agent able to penetrate all tissues in concentrations known to be bactericidal to the organism.

It has been shown that the longer a patient had been ill with Bb prior to first definitive therapy, the longer the duration of treatment must be, and the need for more aggressive treatment increases.

More evidence has accumulated indicating the severe detrimental effects of immunosuppressants including steroids in the patient with active B. burgdorferi infection. Never give steroids or any other immunosuppressant to any patient who may even remotely be suffering from Lyme, or serious, permanent damage may result, especially if given for anything greater than a short course. If immunosuppressive therapy is absolutely necessary, then potent antibiotic treatment should begin at least 48 hours prior to the immunosuppressants.

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TREATMENT RESISTANCE

Bb contains beta lactamases, which, with some strains, may confer resistance to cephalosporins and penicillins. This is apparently a slowly acting enzyme system, and may be overcome by higher or more continuous drug levels especially when maintained by continuous infusions (cefotaxime) and by depot preparations (benzathine penicillin). Nevertheless, some penicillin and cephalosporin treatment failures do occur and have responded to sulbactam/ampicillin, imipenim, and vancomycin, which act through different cell wall mechanisms than penicillin and the cephalosporins.

There is evidence that B. burgdorferi can remain viable within cells, such as macrophages, lymphocytes, endothelial cells, neurons, and fibroblasts. Bb has been shown to evade the effects of beta lactam antibiotics in vitro by sequestering in these intracellular niches. In addition, Bb can coat itself with host cell membranes, and it secretes a glycoprotein that can encapsulate the organism (an “S-layer”). Because this glycoprotein binds host IgM, it is possible that host protein as well as cell membrane hide Borrelial antigens. In theory at least, these coatings interfere with immune recognition, thus affecting the clearing of Bb, and also cause seronegativity.

There are multiple strains of Borrelia burgdorferi and they vary in their antigen profile and antibiotic susceptibilities. It has also been recognized that B. burgdorferi can exist in at least three different morphologic forms: spirochetal, spheroplast (or l-form), and the recently discovered cystic form.

L-forms and cystic forms do not contain cell walls, and thus beta lactam antibiotics will not affect them. Spheroplasts seem to be susceptible to tetracyclines and some erythromycins, yet the cyst has so far only been proven to be susceptible to metronidazole. Apparently, Bb can shift among the three forms during the course of the infection and cause the varying serologic responses seen over time, including seronegativity. Because of this, it may be necessary to change antibiotic or even prescribe a combination of agents.

Vegetative endocarditis has been associated with Borrelia burgdorferi, but the vegetations may be too small to detect with echocardiography. Keep this in mind when evaluating patients with murmurs, as this may explain why some patients seem to continually relapse after even long courses of antibiotics.

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COURSE DURING THERAPY

As the spirochete has a very long generation time (12 to 24 hours in vitro and possibly much longer in living systems) and may have periods of dormancy, during which time antibiotics will not kill the organism, treatment has to be continued for a long period of time to eradicate all the active symptoms and prevent a relapse, especially in late infections. If treatment is discontinued before all symptoms of active infection have cleared, the patient will remain ill and possibly relapse further. In general, early disseminated LB is treated for four to six weeks, and late LB usually requires a minimum of four to six months of continuous treatment. All patients respond differently and therapy must be individualized. It is not uncommon for a patient who has been ill for many years to require open ended treatment regimens; indeed, some patients will require ongoing maintenance therapy to remain well.

Several days after the onset of appropriate antibiotic therapy, symptoms often flare due to lysis of the spirochetes with release of increased amount of antigenic material and possibly bacterial toxins. This is referred to as a Jarish Herxheimer-like reaction. Because it takes 48 to 72 hours of therapy to initiate bacterial killing, the Herxheimer reaction is therefore delayed. This is unlike syphilis, in which these reactions can occur within hours.

It has been observed that symptoms will flare in cycles every four weeks. It is thought that this reflects the organism's cell cycle, with the growth phase occurring once per month (intermittent growth is common in Borrelia species). As antibiotics will only kill bacteria during their growth phase, therapy is designed to bracket at least one whole generation cycle. This is why the minimum treatment duration should be at least four weeks. If the antibiotics are working, over time these flares will lessen in severity and duration. The very occurrence of ongoing monthly cycles indicates that living organisms are still present and that antibiotics should be continued.

With treatment, these monthly symptom flares are exaggerated and presumably represent recurrent Herxheimer-like reactions as Bb enters its vulnerable growth phase then are lysed. For unknown reasons, the worst occurs at the fourth week of treatment. Observation suggest that the more severe this reaction, the higher the germ load, and the more ill the patient. In those with long-standing highly symptomatic disease who are on IV therapy, the week-four flare can be very severe, similar to a serum sickness reaction, and be associated with transient leucopenia and/or elevations in liver enzymes. If this happens, decrease the dose temporarily, or interrupt treatment for several days, then resume with a lower dose. If you are able to continue or resume therapy, then patients continue to improve. Those whose treatment is stopped and not restarted at this point usually will need retreatment in the future due to ongoing or recurrent symptoms because the infection was not eradicated. Patients on IV therapy who have a strong reaction at the fourth week will need to continue parenteral antibiotics for several months, for when this monthly reaction finally lessens in severity, then oral or IM medications can be substituted. Indeed, it is

just this observation that guides the clinician in determining the endpoint of IV treatment. In general, IV therapy is given until there is a clear positive response, then treatment is changed to IM or po until free of signs of active infection for 4 to 8 weeks. Some patients, however, will not respond to IM or po treatment and IV therapy will have to be used throughout. As mentioned earlier, leucopenia may be a sign of persistent Ehrlichiosis, so be sure to look into this.

Repeated treatment failures should alert the clinician to the possibility of an otherwise inapparent immune deficiency, and a workup for this may be advised. Obviously, evaluation for co-infection should be performed, and a search for other or concurrent diagnoses needs to be entertained.

There are three things that will predict treatment failure regardless of which regimen is chosen: Non-compliance, alcohol use on a regular basis, and failure of the patient to obtain proper rest. Advise them to take a break when (or ideally before) the inevitable mid afternoon fatigue sets in.

All patients must keep a carefully detailed daily diary of their symptoms to help us judge the effects of treatment, the presence of the classic four week cycle, and treatment endpoint. One must follow such diaries, temperature readings in late afternoon, physical findings, notes from physical therapists, and cognitive testing to best judge when to change or end antibiotics.

Remember — there currently is no test for cure, so this clinical follow-up assumes a major role in Lyme Disease care.

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BORRELIA NEUROTOXIN (With thanks to Dr. Shoemaker)

Two groups have reported evidence that Borrelia, like several other bacteria, produce neurotoxins. These compounds reportedly can cause many of the symptoms of encephalopathy, cause an ongoing inflammatory reaction manifested as some of the virus-like symptoms common in late Lyme, and also potentially interfere with hormone action by blocking hormone receptors. At this time, there is no assay available to detect whether this compound is present, nor can the amount of toxin be quantified. Indirect measures are currently employed, such as measures of cytokine activation and hormone resistance. A visual contrast sensitivity test (VCS test) reportedly is quite useful in documenting CNS effects of the neurotoxin, and to follow effects of treatment. This test is available at some centers and on the internet.

It has been said that the longer one is ill with Lyme, the more neurotoxin is present in the body. It probably is stored in fatty tissues, and once present, persists for a very long time. This may be because of enterohepatic circulation, where the toxin is excreted via the bile into the intestinal tract, but then is reabsorbed from the intestinal tract back into the blood stream. This forms the basis for treatment.

Synthetic fiber agents, available by prescription for the treatment of high cholesterol, have the ability to bind some bacterial toxins. When take orally in generous amounts, the neurotoxin, present in the intestinal tract, binds to the resin, is trapped, and then excreted. Thus, over several weeks, the level of neurotoxin is depleted and clinical improvement can be seen. Current experience is that improvement is first seen in three weeks, and treatment continues for two to four months. Retreatment is always possible.

Two prescription medications that can bind these toxins include cholestyramine resin (Questran), and Welchol pills. These medications may bind not only toxins but also many drugs and vitamin supplements. Therefore no other oral medications or supplements should be taken from one hour before, to three hours after a dose of one of these fiber agents.

Cholestyramine must be taken four times daily, and Welchol is prescribed at three pills twice daily. While the latter is obviously much simpler to use, it is less effective than cholestyramine. The main side effects are bloating and constipation, best handled with increased fluid intake and gentle laxatives.

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LYME DISEASE TREATMENT INFORMATION

There is no universally effective antibiotic for treating LB. The choice of medication used and the dosage prescribed will vary for different people based on multiple factors. These include duration and severity of illness, presence of co-infections, immune deficiencies, prior significant immunosuppressant use while infected, age, weight, gastrointestinal function, blood levels achieved, and patient tolerance. Doses found to be effective clinically are often higher than those recommended in older texts. This is due to deep tissue penetration by Bb, it's presence in the CNS including the eye, within cells, within tendons, and because very few of the many strains of this organism now known to exist have been studied for antibiotic susceptibility. In addition, all animal studies of susceptibility to date have only addressed early disease in models that behave differently than human hosts. Therefore, begin with a regimen appropriate to the setting, and if necessary, modify it over time based upon response.

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ANTIBIOTICS

There are several types of antibiotics in general use for Bb treatment. The tetracyclines, including doxycycline and minocycline, are bacteriostatic unless given in high doses. If high blood levels are not attained, treatment failures in early and late disease are common. However, these high doses can be difficult to tolerate. For example, doxycycline can be very effective but only if adequate blood levels are achieved either by high oral doses (300 to 600 mg daily) or by parenteral administration.

Penicillins are bactericidal. As would be expected in managing an infection with a gram negative organism such as Bb, amoxicillin has been shown to be more effective than oral penicillin V. Because of its short half-life and need for high levels, amoxicillin is usually administered along with probenecid. Since blood levels are extremely variable they should be measured.

Cephalosporins must be of advanced generation: first generation drugs are rarely effective, and second generation drugs are comparable to amoxicillin and doxycycline both in-vitro and in-vivo. Third generation agents are currently the most effective of the cephalosporins because of their very low MBC's (0.06 for ceftriaxone) and they have been shown to be effective in penicillin and tetracycline failures. Cefuroxime axetil (Ceftin), a second generation agent, is also effective against staph and thus is useful in treating atypical erythema migrans that may represent a mixed infection, containing some of the more common skin pathogens in addition to Bb.

When choosing a third generation cephalosporin, there are several points to remember: Ceftriaxone has 95% biliary excretion and can crystallize in the biliary tree with resultant colic and possible cholecystitis. GI excretion results in a large impact on gut flora. Biliary and superinfection problems with ceftriaxone can be lessened if this drug is given in interrupted courses, such as three to five days in a row each week. More recently, chenodeoxycholic acid, used to dissolve gallstones, is being prescribed along with ceftriaxone as prophylaxis. Cefotaxime is less convenient to administer because of the need for either multiple daily doses or continuous infusions, but as it has only 5% biliary excretion, it never causes biliary concretions, and may

have less impact on gut flora. It is the experience of some clinicians that cefotaxime can be even more efficacious if given as a continuous infusion, rather than in interrupted doses.

Erythromycin has been shown to be almost ineffective as monotherapy. The advanced macrolides and azalides such as azithromycin and clarithromycin can be difficult to tolerate orally due to their tendency to promote yeast overgrowth and poor GI tolerance at the high doses needed. As they have impressively low MBCs and do concentrate in tissues and penetrate cells, they theoretically should be ideal agents. However, initial clinical results were disappointing, especially with oral azithromycin. It has been suggested that when Bb is within a cell, it is held within a vacuole and bathed in fluid of low pH, and this acidity may inactivate this class of antibiotics. Therefore, they are administered concurrently with hydroxychloroquine or amantadine, which raise vacuolar pH, rendering these antibiotics more effective. It is not known whether this same technique will make erythromycin a more effective antibiotic in LB. Another alternative is to administer azithromycin parenterally. Results are excellent, but expect to see abrupt Jarisch-Herxheimer reactions.

Metronidazole (Flagyl) is commonly used in select patients with treatment resistant, chronic Lyme. When present in a hostile environment, such as growth medium lacking some nutrients, or spinal fluid, or serum with certain antibiotics added, Bb will change into a cystic form. This cyst seems to be able to remain dormant, but when placed into an environment more favorable to its growth, the cyst can open, and an intact spirochete emerges. The conventional antibiotics used for Lyme, such as the penicillins, cephalosporins, etc. do not kill the cystic form of Bb. Furthermore, the cyst lacks the usual surface antigens found on the spirochete (these are the markers detected by ELISAs and western blots). This may be another reason for the chronically sick Lyme patient remaining seronegative.

There is evidence that metronidazole will kill the cystic form. This fits with the now well known clinical observations that metronidazole can be remarkably effective for many chronic Lyme patients. However, this medication apparently has no effect on intact spirochetes. Therefore, the trend now is to treat the chronically infected patient who has resistant disease by combining metronidazole with one or two other antibiotics to target all forms of Bb. Because there is laboratory evidence that tetracyclines may inhibit the effect of metronidazole, this class of medication may not be as useful as others in these two- and three-drug regimens. There have been some recent reports that Bb does not contain genes that would confer susceptibility to metronidazole. However, this clearly does not fit with in vitro and a large body of clinical data, which have demonstrated the usefulness of this agent in the Lyme patient. Perhaps we do not have all the genetic information needed to dismiss the use of this agent. Once again, real world experience is one step ahead of bench research.

Important precautions:

1. Pregnancy while on metronidazole is not advised, as there is a risk of birth defects.
2. No alcohol consumption! A severe, “antabuse” reaction will occur, consisting of severe nausea, flushing, headache, and other unpleasant symptoms.
3. Metronidazole is potentially neurotoxic. Peripheral neuropathy may result. Therefore, breaks in treatment are commonly prescribed, such as using this agent every other week.
4. Yeast overgrowth is especially common. A strict anti-yeast regimen must be followed.
5. VERY severe Herxheimer-like reactions are seen in the more ill patient during the first week of therapy, and again four weeks later.

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COMBINATION THERAPY

This consists of using two or more dissimilar antibiotics simultaneously. There are several reasons for this. Combinations should utilize dissimilar antibiotics for antibiotic synergism, to better compensate for differing killing profiles and sites of action of the individual medications, and to cover the three known morphologic forms of Bb. The idea is to work in body fluids and in deep tissues, outside and within cells, and effect killing by different mechanisms for synergism. An example is a combination of amoxicillin and clarithromycin. Note how complimentary these two are for treating infection with Bb. GI intolerance and yeast superinfections are the biggest drawbacks to this type of treatment. However, these complications can often be prevented or easily treated, and the clinically observed benefits of this type of regimen clearly have outweighed these problems in selected patients.

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PULSE THERAPY

This consists of administering antibiotics (usually parenteral ones) two to three days in a row per week. The efficacy of this regimen is based on the fact that it takes 48 to 72 hours of continuous bactericidal antibiotic levels to kill the spirochete, yet it will take longer than the four to five days between pulses for the spirochetes to recover. This allows for several advantages:

- Dosages are doubled (ie: cefotaxime, 12 g daily), increasing efficacy
- More toxic medications can be used with increased safety (ie: vancomycin)
- May be effective when conventional, daily regimens have failed.
- IV access may be easier or more tolerable
- More agreeable lifestyle for the patient
- Often less costly than daily regimens

Note that this type of treatment is expected to continue for a minimum of ten weeks, and often must continue beyond twenty weeks. As with all Lyme treatments, specific dosing and scheduling must be tailored to the individual patient's clinical picture based upon the treating physician's best clinical judgment.

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MONITORING THERAPY

Drug levels are measured, where possible, to confirm adequate dosing. The regimen may have to be modified to optimize the dose, and again at any time major changes in the treatment regimen occur. With parenteral therapy, CBC and chem/liver panels are done at least twice each month, especially during symptom flares, with urinalysis and protime monitored monthly.

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INDICATORS FOR PARENTERAL THERAPY

The following are guidelines only and are not meant to be absolute. It is based on retrospective study of over 600 patients with late Lyme disease.

- Illness for greater than one year
- Prior immunosuppressive therapy
- Major neurological involvement
- Active synovitis with high sedimentation rate
- Elevated protein or cells in the CSF

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ANTIBIOTIC CHOICES

ORAL THERAPY

Always check blood levels when using agents marked with an *, and adjust dose to achieve a peak level in the mid- teens and a trough greater than five. Because of this, the doses listed below may have to be raised. Consider Doxycycline first due to concern for Ehrlichia.

*Amoxicillin	Adults: 1g q8h plus probenecid 500mg q8h; doses up to 6 grams daily are often needed
	Pregnancy: 1g q6h and adjust
	Children: 50 mg/kg/day divided into q8h doses
*Doxycycline	Adults: 100 mg qid with food; doses of up to 600 mg daily are often needed, as doxycycline is only effective at high blood levels.
	Not for children or in pregnancy.
	If levels are too low at tolerated doses, give parenterally.
*Cefuroxime axetil	Oral alternative that may be effective in amoxicillin and doxycycline failures. Useful in EM rashes co-infected with common skin pathogens.
	Adults and pregnancy: 1g q12h and adjust.
	Children: 125 to 500 mg q12h based on weight.
Tetracycline	Adults only, and not in pregnancy. 500 mg tid to qid
Erythromycin	Poor response and not recommended.
Clarithromycin	Adults: 500 to 1000 mg q12h. Add hydroxychloroquine, 200–400 mg/d or amantadine 100–200 mg/d.
	Cannot be used in pregnancy or in younger children
Azithromycin	Adults: 500 to 1200 mg/d.
	Adolescents: 250 to 500 mg/d.
	Add hydroxychloroquine, 200–400 mg/d, or amantadine 100–200 mg/d
	Cannot be used in pregnancy.
	Oral azithromycin is not as effective as clarithromycin.
Augmentin	Cannot exceed three tablets daily due to the clavulanate, thus is given with amoxicillin.
	This combination can be effective when Bb beta lactamase is felt to be present.
Chloramphenicol	Not recommended as not proven and potentially toxic.
Metronidazole (see text)	500 to 1500 mg daily in divided doses. Adults only.

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PARENTERAL THERAPY

Ceftriaxone	Risk of biliary sludging can be minimized with intermittent breaks in therapy (ie: infuse five or less days in a row per week).
	Adults and pregnancy: 2g q12h, four days in a row each week.
	Children: 75 mg/kg/day up to 2g/day
Cefotaxime	Comparable efficacy to ceftriaxone; no biliary complications.
	Adults and pregnancy: 2g q8h; may dose as high as 12g daily. Suggest a continuous infusion.
	Children: 90 to 180 mg/kg/day dosed q6h (preferred) or q8h, not to exceed 12 g daily.
*Doxycycline	Requires central line as is caustic. Surprisingly effective, probably because higher overall, and spiked blood levels when given parenterally.
	Always measure blood levels.
	Adults: 400 mg q24h and adjust based on levels.
	Cannot be used in pregnancy or in younger children.
Azithromycin	Requires central line as is caustic.
	Dose: 500 to 1000 mg daily in adolescents and adults.
Penicillin G	IV penicillin G is minimally effective and not recommended.
Benzathine penicillin	Surprisingly effective IM alternative to oral therapy.
	May need to begin at lower doses as strong, prolonged (6 or more week) Herxheimer-like reactions have been observed.
	Adults: 1.2 million U three times per week (higher doses with large body habitus)
	Adolescents: 300,000 to 2.4 million U weekly.
	May be used in pregnancy.
Poorly studied but anecdotally effective	
Vancomycin	Observed to be one of the best drugs in treating Lyme, but potential toxicity limits its use. It is a perfect candidate for pulse therapy to minimize these concerns.
	Use standard doses and confirm levels.
Imipenim and Unisyn	Similar in efficacy to cefotaxime, but often works when cephalosporins have failed.
	Must be given q6 to q8 hours.
Cefuroxime	Useful but not demonstrably better than ceftriaxone or cefotaxime.
Ampicillin IV	More effective than penicillin G. Must be given q6 hours.

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TREATMENT CATEGORIES

PROPHYLAXIS of high risk groups — education and preventive measures. Antibiotics are not given.

TICK BITES — Embedded Deer Tick With No Signs or Symptoms of Lyme (see appendix)

Decide to treat based on the type of tick, whether it came from an endemic area and percent infected, how it was removed, and length of attachment (nymphs: at least one day; adults: anecdotally, as little as four hours). The risk of transmission is greater if the tick is engorged, or of it was removed improperly allowing the tick's contents to spill into the bite wound. High risk bites are treated as follows (remember the possibility of coinfection!):

1. Adults: Oral therapy for 21 days.
2. Pregnancy: Amoxicillin 1000 mg q6h for 6 weeks. Test for Babesia, Bartonella and Ehrlichia.
   Alternative: Cefuroxime axetil 1000 mg q12h for 6 weeks.
3. Young Children: Oral therapy for 21 days.

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EARLY LOCALIZED — Single erythema migrans with no constitutional symptoms:

1. Adults: oral therapy for 6 weeks.
2. Pregnancy: 1st and 2nd trimesters: IV X 21 days then oral X 6 weeks
   3rd trimester: Oral therapy X 6 weeks.
   Any trimester — test for Babesia, Bartonella, and Ehrlichia
3. Children: oral therapy for 6 weeks.

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DISSEMINATED DISEASE — Multiple lesions, constitutional symptoms, lymphadenopathy, or any other manifestations of dissemination.

EARLY DISSEMINATED — Milder symptoms present for less than one year and not complicated by immune deficiency or prior immunosuppressive treatment:

1. Adults: Oral therapy until no active disease for 4 weeks (4–6 months typical)
2. Pregnancy: As in localized disease, but duration as above. Treat throughout pregnancy, and do not breast feed.
3. Children: Oral therapy with duration based upon clinical response.

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PARENTERAL ALTERNATIVES for more ill patients and those unresponsive to or intolerant of oral medications:

1. Adults and children: IV therapy for at least 6 weeks (until clearly improved).
   Follow with oral therapy or IM benzathine penicillin until no active disease for 6–8 weeks.
   IV may have to be resumed if oral or IM therapy fails.
2. Pregnancy: IV then oral therapy as above.

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LATE DISSEMINATED — Present greater than one year, more severely ill patients, and those with prior significant steroid therapy or any other cause of impaired immunity:

1. Adults and pregnancy: Extended IV therapy (10 or more weeks), then oral or IM, if effective, to same endpoint.
2. Children: IV therapy for 6 or more weeks, then oral or IM follow up as above.

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CHRONIC LYME DISEASE

By definition, this category consists of patients with active infection, of a more prolonged duration, and most likely have higher spirochete loads, weaker defense mechanisms, possibly more virulent or resistant strains, and probably are significantly co-infected. Neurotoxins may also be significant in these patients. Search for and treat concurrent illnesses including viruses, chlamydias, and mycoplasmas. These patients require a full evaluation for all of these problems, and each abnormality must be addressed.

This group will most likely need parenteral therapy, especially high dose, pulsed therapy, and antibiotic combinations, including metronidazole. Antibiotic therapy will need to continue for many months, and the antibiotics may have to be changed periodically to break plateaus in recovery. Be vigilant for treatment-related problems such as antibiotic-associated colitis, yeast overgrowth, intravenous catheter complications, and abnormalities in blood counts and chemistries.

If treatment can be continued long term, then a remarkable degree of recovery is possible. However, attention must be paid to all treatment modalities for such a recovery — not only antibiotics, but rehab programs, nutritional supplements, enforced rest, low carbohydrate, high fiber diets, attention to food sensitivities, avoidance of stress, abstinence from caffeine and alcohol, and absolutely no immunosuppressants, even local doses of steroids (intra articular injections, for example).

Unfortunately, not all patients with chronic Lyme disease will fully recover and treatment may not eradicate the active Borrelia infection. Such individuals may have to be maintained on open-ended, ongoing antibiotic therapy, for they repeatedly relapse after antibiotics are stopped. Maintenance antibiotic therapy is thus mandatory.

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SAFETY

Nearly two decades of experience in treating thousands of patients with Lyme has proven that therapy as described above, although intense, is generally well tolerated. The most common adverse reaction seen is allergy to probenecid. In addition, yeast superinfections are seen, but these are generally easily recognized and managed. The induction of Clostridium difficile toxin production is seen most commonly with ceftriaxone, but can occur with any of the antibiotic regimens mentioned in this document. However, pulsed dose therapy and regular use of the lactobacillus preparations seems to be helpful in controlling yeast and antibiotic related colitis, as the number of cases of C. difficile in Lyme patients is low when these guidelines are followed.

When using central intravenous lines including PICC lines (peripherally inserted central catheters), if ANY line problems arise, it is recommended that the line be pulled for patient safety. Salvage attempts (urokinase, repairing holes) are often ineffective and may not be safe.

Please advise all patients who take the tetracyclines of skin and eye sensitivity to sunlight and the proper precautions, and advise birth control if appropriate. When doxycycline is given parenterally, do not refreeze the solution prior to use!

Remember, years of experience with chronic antibiotic therapy in other conditions, including rheumatic fever, acne, gingivitis, recurrent otitis, recurrent cystitis, COPD, bronchiectasis, and others have not revealed any consistent dire consequences as a result of such medication use. Indeed, the very real consequences of untreated, chronic persistent infection by B. burgdorferi can be far worse than the potential consequences of this treatment.

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CO-INFECTIONS IN LYME

PIROPLASMOSIS (Babesiosis)

GENERAL INFORMATION

Piroplasms are not bacteria, they are protozoans. Therefore, they will not be eradicated by any of the currently used Lyme treatment regimens. Therein lies the significance of co-infections — if a Lyme patient has been extensively treated yet is still ill, suspect a co-infection.

Babesia infection is becoming more commonly recognized, especially in patients who already have Lyme Disease. It has been published that as many as 66% of Lyme patients show evidence of co-infection with Babesia. It has also been reported that Babesial infections can range in severity from mild, subclinical infection, to fulminant, potentially life-threatening illness. The more severe presentations are more likely to be seen in immunocompromised and elderly patients. Milder infections are often missed because the symptoms are incorrectly ascribed to Lyme. Babesial infections, even mild ones, may recrudesce and cause severe illness. This phenomenon has been reported to occur at any time, even up to several years after the initial infection. Furthermore, asymptomatic carriers pose risks: to the blood supply as this infection has been reported to be passed on by blood transfusion, and to the unborn child from an infected mother as it can be transmitted *in utero*. Some quotes from the literature:

Krause, PJ. Spielman, A, Telford, SR et.al. *Persistent parasitemia after acute Babesiosis* N Engl J Med 1998. 339:160

“The clinical spectrum of human Babesiosis ranges from an apparently silent infection to a fulminant malaria-like disease.”
“When left untreated, silent Babesial infection may persist for months to years."
“Silent infections, which occur in about a third of infected people, may recrudesce."
“Babesial infection may recrudesce after many months of asymptomatic parasitemia.”
“Although parasites were initially detected microscopically in the blood of two of the untreated subjects, and all of the treated subjects, none could be found a week after the onset of illness.”
“Persistent symptoms of Babesiosis accompanied persistent blood-borne Babesial DNA.”
“The persistence of seroreactivity increasingly correlated with the persistence of Babesial DNA.”
“In those with only subtle symptoms, Babesiosis often remains undiagnosed.”
“Furthermore, physicians tend not to recognize Babesial infection in those who are co-infected with the agent of Lyme Disease, because Babesial symptoms tend to be ascribed to Lyme Disease.”

“Physicians caring for patients with moderate to severe Lyme disease should consider obtaining diagnostic tests for Babesiosis and possibly other tick-borne pathogens... especially in patients experiencing "atypical Lyme disease” or patients in whom the response to antibiotic treatment is delayed or absent.”

Krause, PJ, Telford, SR, Spielman, A, et.al. *Concurrent Lyme disease and Babesiosis*. JAMA 1996. 275 (21):1657

“Subjects with evidence of both infections reported a greater array of symptoms than those infected by the spirochete or piroplasm alone.”
“Co-infection generally results in more intense acute illness and a more prolonged convalescence than accompany either infection alone.”
“Spirochete DNA was evident more often and remained in the circulation longer in co-infected subjects than in those experiencing either infection alone.”
“Co-infection might also synergize spirochete-induced lesions in human joints, heart and nerves.”
“Babesial infections may impair human host defense mechanisms”
“The possibility of concomitant Babesial infection should be considered when moderate to severe Lyme Disease has been diagnosed.”

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SYMPTOMS

In milder forms, symptoms may include a vague sense of imbalance without true vertigo, headache, mild encephalopathy, fatigue, sweats, air hunger and occasionally cough. When present as a co-infection with Lyme, initial symptoms of the illness are often more acute and severe. Suggestions of co-infection include the above symptoms, but the headaches are more severe, and encephalopathy is out of proportion to the other Borrelia symptoms. The fulminant presentations include high fevers, shaking chills and hemolysis, and can be fatal.

DIAGNOSTIC TESTS

Diagnostic tests are insensitive and problematic. There are at least thirteen Babesial forms found in ticks, yet we can currently only test for B. microti and WA-1 with our serologic and nuclear tests. Standard blood smears reportedly are reliable for only the first two weeks of infection, thus are not useful for diagnosing later infections and milder ones including carrier states where the germ load is too low to be detected.

Krause, PJ, Telford, SR, Spielman, A, et.al. *Concurrent Lyme disease and Babesiosis*. JAMA 1996. 275 (21):1660

“As is common in the case of Babesial infections, parasites frequently cannot be seen in blood films.”

Therefore, multiple diagnostic test methods are available and each have their own benefits and limitations and often several tests must be done. Be prepared to treat based on clinical presentation, even with negative tests.

SEROLOGY

Unlike Lyme, Babesia titers can reflect infection status. Thus, persistently positive titers or western blots suggest persistent infection.

PCR

This is more sensitive than smears for B. microti, but will not detect other species.

ENHANCED SMEAR

This utilizes buffy coat, prolonged scanning (up to three hours per sample!) and digital photography through custom-made microscopes. Although more sensitive than standard smears, infections can still be missed. The big advantage is that it will display multiple species, not just B. microti.

FLUORESCENT IN-SITU HYBRIDIZATION ASSAY (FISH)

This technique is also a form of blood smear. It is said to be 100-fold more sensitive than standard smears for B. microti, because instead of utilizing standard, ink-based stains, it uses a fluorescent-linked RNA probe and ultraviolet light. The Babesial organisms are then much easier to spot when the slides are scanned. The disadvantage is that currently only B. microti is detected.

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TREATMENT

Treating Babesia infections had always been difficult, because the therapy that had been recommended until 1998 consisted of a combination of clindamycin plus quinine. Published reports and clinical experience have shown this regimen to be unacceptable, as nearly half of patients so treated have had to abandon treatment due to serious side effects, many of which were disabling. Furthermore, even in patients who could tolerate these drugs, there was a failure rate approaching 50%.

Krause, PJ. Spielman, A, Telford, SR et.al.. *Persistent parasitemia after acute Babesiosis* N Engl J Med 1998. 339:162

“Of the treated subjects, almost half had symptoms that were consistent with reactions to quinine, including hearing loss, tinnitus, hypotension, and such gastrointestinal symptoms as anorexia, vomiting, and diarrhea.”
“Although treatment with clindamycin and quinine reduces the duration of parasitemia, infection may persist and recrudesce and side effects are common.”

Because of these dismal statistics, the current regimen of choice for Babesiosis is the combination of atovaquone plus azithromycin. This combination was initially studied in animals, and then applied to Humans with good success, because when atovaquone was used alone, resistance developed in 20% of cases, but reportedly did not occur when azithromycin was added. Fewer than 5% of patients have to halt treatment due to side effects, and the success rate is clearly better than that of clindamycin plus quinine.

The duration of treatment with atovaquone plus azithromycin for Babesiosis varies depending on the degree of infection, duration of illness before diagnosis, the health and immune status of the patient, and whether the patient is co-infected with Borrelia burgdorferi. Typically, a three-week course is prescribed for acute cases, while chronic, longstanding infections with significant morbidity and co-infection will require several months of therapy. Relapses have occurred, and retreatment is occasionally needed.

Problems during therapy include diarrhea, mild nausea, the expense of atovaquone (over $600.00 per bottle — enough for three weeks of treatment), and rarely, a temporary yellowish discoloration of the vision. Regular blood counts, liver panels and amylase levels are recommended during any prolonged course of therapy. Patients who are not cured with this regimen can be retreated but with higher doses, as this has proven effective in many of my patients. Artemesia (a non-prescription herb) may be added, but is not effective when used alone. Metronidazole can also be added to increase efficacy, but there is minimal clinical data on how much more effective this regimen is.

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EHRLICHIOSIS

GENERAL INFORMATION

While it is true that this illness can have a fulminant presentation, and may even become fatal if not treated, milder forms do exist, as does chronic low-grade infection, especially when other tick-borne organisms are present. The potential transmission of Ehrlichia during tick bites is the main reason why doxycycline is now the first choice in treating tick bites and early Lyme, before serologies can become positive. When present alone or co-infecting with B. burgdorferi, persistent leukopenia is an important clue. Thrombocytopenia and elevated liver enzymes are less common, but likewise should not be ignored. Headaches, myalgias, and ongoing fatigue seem to relate to this illness, but are extremely difficult to separate from symptoms caused by Bb.

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DIAGNOSTIC TESTING

Testing is problematic with Ehrlichia, similar to the situation with Babesiosis. More species are known to be present in ticks than can be tested for with clinically available serologies and PCRs. In addition, serologies and PCRs are of unknown sensitivity and specificity. Standard blood smears for direct visualization of organisms in leukocytes are of low yield. Enhanced smears using buffy coats significantly raises sensitivity and will indicate a wider variety of species. Despite this, infection can be missed, so clinical diagnosis remains the primary diagnostic tool. Again, consider this diagnosis in a Lyme Borreliosis (LB) patient not responding well to therapy.

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TREATMENT

Standard treatment consists of Doxycycline, 200 mg daily for two to four weeks. Higher doses, parenteral therapy, and longer treatment durations may be needed based on the duration and severity of illness, and whether immune defects or extreme age is present. However, there are reports of treatment failure even when higher doses and long duration treatment with doxycycline is given. In such cases, consideration may be given for adding rifampin, 600 mg daily, to the regimen.

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BARTONELLA

Bartonella henselae, the agent of cat scratch disease, has been found in Ixodid ticks and as a co-infection in patients with Lyme Disease. With co-infection, symptoms of Bartonella are almost

impossible to distinguish from Lyme, but may include lymphadenopathy, splenomegaly, hepatomegaly, headache, encephalopathy, somnolence, flu-like malaise, weight loss, sore throat, and a papular or angiomatous rash. In acute cases, there can be hemolysis with anemia, high fever, weakened immune response, jaundice, abnormal liver enzymes, and myalgias. Endocarditis and myocarditis have been reported. More severe infections are associated with immune deficiency and possibly occurrence of opportunistic infections. As in Lyme Disease and Babesiosis, Bartonella may be transmitted to the fetus in the infected pregnant patient.

Diagnostic tests include serology, blood and CSF PCR, and biopsy of skin lesions and lymph nodes.

In the co-infected Lyme patient, eradication may be difficult. Many antibiotic agents have been reported to be effective, including cephalosporins, fluoroquinolones, erythromycins, gentamicin, rifampin and streptomycin. In practice, these patients seem to do best with a combination regimen that utilizes agents that can penetrate cells. Typical combinations include an erythromycin, plus a fluoroquinolone or rifampin. Treatment progress is most commonly assessed by PCR post treatment and serial titers.

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NUTRITIONAL SUPPLEMENTS IN DISSEMINATED LYME DISEASE

Studies on patients with chronic illnesses such as Lyme and Chronic Fatigue have demonstrated that some of the late symptoms are related to cellular damage and deficiencies in certain essential nutrients. Double blinded, placebo controlled studies, and in one case direct assay of biopsy specimens have proven the value of some of the supplements listed. Some are required, while others are optional — see below. They are listed in order of importance.

The quality of supplements used is often more important than the dose. In fact, “mega doses” are not recommended. Instead, seek out, if possible, pharmaceutical grade products, especially if USP certified. Pharmanex brand products are recommended because they fit these criteria. In the list below, it is indicated whether the product should be gotten from Pharmanex, or whether a different source or generic substitute is OK. To order Pharmanex brand products, call 1-800-487-1000 and give the following US reference # 9256681.

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BASIC DAILY REGIMEN

ACIDOPHILUS (required when on antibiotics)

Essential daily supplement to maintain the normal balance of bowel flora, especially if on antibiotics, or if gastrointestinal disturbances are present. Always try to get enteric coated, milk-free acidophilus. The best kinds are frozen or refrigerated to ensure potency. Take two with each meal.

MULTI-VITAMIN (required)

I recommend the Life Pack family of multivitamins. These are unique supplements — Pharmaceutical grade and USP certified, they are the only products clinically proven in double-blinded, placebo controlled crossover studies to quench free radicals and raise antioxidant levels in the blood and lipids. Choose LifePak for males under 40, LifePak Women for hormonally active

women, and LifePak Prime for postmenopausal women and for men over 40. They are available through Pharmanex. Continue long term.

CO-Q10 (ubiquinone) — **required if not taking the prescription drug atovaquone (Mepron)**

Deficiencies have been related to poor function of the heart, limitations of stamina, gum disease, and poor resistance to infections. Heart biopsy studies in Lyme patients indicated that they should take between 200 and 300mg daily of standard CoQ 10, or 90 mg of the well absorbed, highly purified, crystalline CoQ 10 product sold by Pharmanex, (surprisingly, the Pharmanex brand is far less expensive than the generic). The body will manufacture its own C0Q 10 when the original illness is controlled, but only if stimulated by aggressive exercise. Therefore, use this supplement until the patient is feeling well and exercising regularly.

VITAMIN B (required)

Clinical studies demonstrated the need for supplement vitamin B in infections with Borrelia, to help clear neurological symptoms. Take one 50 mg B-complex capsule daily. If neuropathy is severe, an additional 50 to 100 mg of B6 daily may be helpful. Generics are OK.

MAGNESIUM (required)

Magnesium supplementation is very helpful for the tremors, twitches, cramps, muscle soreness, heart skips and weakness. It may also help in energy level and cognition. The best source is magnesium L-lactate dehydrate ("Mag-tab SR," sold by Niche Pharmaceuticals [1-800-677-0355], and available at Wal-Mart). DO NOT rely on "cal-mag," calcium plus magnesium combination tablets, as they are not well absorbed. Take at least one to two tablet twice daily. Higher doses may cause diarrhea, and you should check with your physician before using more than this. In some cases, injections or intravenous doses may be necessary. Continue long term.

ESSENTIAL FATTY ACIDS (required)

Studies show that when EFAs are taken regularly, statistically significant improvements in fatigue, aches weakness, vertigo, dizziness, memory, concentration and depression are likely. There are two broad classes: GLA (omega-6 oils) and EPA (omega-3 oils), derived respectively from plant and fish oils. This is what to take:

Plant Oils: borage oil, evening primrose oil, or black currant seed oil (choose one). Do NOT use Flax seed oil!

Fish Oil: Omega-3 (Fish Oil) capsules, 1000 mg per capsule. Use "Optimum Omega" by Pharmanex, if a higher quality product is desired, or to minimize the "fishy" aftertaste.

RECOMMENDATION: four plant oil capsules and four fish oil capsules daily, taken with meals. Continue for three to four months then try to taper down the dose.

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OPTIONAL SUPPLEMENTS FOR SPECIAL CIRCUMSTANCES

CORDYMAX (optional)

Cordyceps is a well-known herb from Tibet and has been shown in clinical studies to improve stamina, fatigue, and enhance lung and antioxidant function. It increases mitochondrial ATP

levels and also raises superoxide dismutase levels. The positive effects can be so dramatic, I strongly urge all people with fatigue to try this. Available only from Pharmanex as “CordyMax.”

METHYLCOBALAMIN (Methyl B12) (optional)

This is a prescription drug available only from compounding pharmacies. It is related to vitamin B12 and has several documented benefits: it helps to heal damage to the nervous system, enhances diminished T-cell function, can restore the normal diurnal cycle, and can help with memory and cognition. Methyl B12 must injected into the muscle as it will not be absorbed if swallowed or used sublingually. Dose ranges from 25 to 50 mg daily, based on weight.

REISHI MAX (optional)

This enhanced extract from cracked spores of the reishi mushroom has been shown in clinical studies to augment function of the Natural Killer Cells and macrophages. Take two a day for maintenance, and four a day in disease states. Available only from Pharmanex.

ECHINACEA (optional)

May be helpful in fighting acute and chronic viral illnesses. Choose a pharmaceutical grade brand (“Immune Formula” by Pharmanex), and do not use the liquid form as this contains alcohol. Do not take daily on a long-term basis, as the benefit may wear off. For a chronic illness, double the usual daily dose but take in cycles — use daily three weeks on, one week off each month.

BIO-GINKGO (optional)

The most effective ginkgo brand in my experience — pharmaceutical grade, and very high potency to assure full bioavailability. Available only from Pharmanex. Ginkgo has been shown to increase blood flow to many organs, including the brain. Patients report clearer thinking and better memory. Be aware that this brand is strong — start with a low dose, then increase every few days or a pressure-type, vascular headache may result from all the increased circulation.

GLUCOSAMINE (optional)

Can be of long term benefit to the joints. Do not be misled into buying a product that also contains chondroitin, as this chemical does not add anything, but it can make the product more expensive. Look for a product that contains the herb Boswellia serrata — this is a non-irritative anti-inflammatory. Although many generics exist, the Pharmanex product, “Cartilage Formula,” has the right ingredients and is of proven efficacy. Expect improvement only over time (several weeks), but plan to use this indefinitely to maintain joint health.

CREATINE (optional)

Creatine has been shown to be of benefit in neuromuscular degenerative diseases such as Lou Gherig's Disease (ALS) and can be very helpful in supporting low blood pressure, as in NMH. Important: To use this safely, you must have an adequate fluid intake. The creatine product should contain taurine, an amino acid needed to enhance creatine absorption, plus some carbohydrate to aid creatine entry into muscle. You will need a 20 gram loading dose for the first five days, then 4 to 10 grams daily maintenance. Try “Cell Tech” from the Vitamin Shop, and follow label directions.

MILK THISTLE (optional)

Useful to support liver function. Take 175 mg three times daily — use an 80% Silymarin extract.

MUSCLE FIX (optional)

This blend of nutrients from Pharmanex really helps sore, tight muscles. Must be taken on an empty stomach — either two, twice daily between meals, or four at bedtime. Can be used intermittently as needed, or daily.

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LYME DISEASE REHABILITATION

Those with long-standing tick borne illnesses end up in poor physical condition. **Even with successful treatment of the infections, chronic Lyme patients will not return to normal unless they pursue a formal program of therapeutic exercise, as outlined below**.

In late stage disease, many negative effects to the body are occurring: muscles atrophy, and to some degree, the heart muscle also suffers, as do the joints, tendons, nerves, etc. The percent fat content of the body as a whole rises, the cholesterol rises, and the balance between HDL and LDL becomes less favorable. In at least 80% of the patients, significant weight gain occurs.

Because of the extreme fatigue and body pain, many Lyme sufferers end up spending inordinate amounts of time in bed, and get far less exercise than they did before they became ill. This begins a debilitating downward spiral that can be very difficult to reverse.

As a result, Lyme patients are stiff, weak, tired, have poor stamina, and are at increased risk for cardiovascular disease and diabetes. Antibiotic treatment alone cannot correct these effects. Therefore, it is necessary to prescribe physical therapy, the extent of which depends on an individual patients' condition, followed by a graded exercise program.

The earliest phase involves multiple modalities (massage, heat, TENS, MENS, ultrasound, etc.) and aggressive range of motion exercises supervised by a physical therapist, to relieve discomfort and to promote better sleep and flexibility. The goal of physical therapy is to prepare the patient for the required, gym-based exercise program. This starts with stretching and mild muscular toning. Then, the program must expand to include muscular conditioning and strengthening, ideally under the supervision of a credentialed exercise physiologist. “Body sculpture” classes are ideal. Aerobics are **not** recommended until the patient has fully recovered.

This is the time for the very best of health habits. I recommend light, low fat food, high in fiber, with high quality nutritional value, minimal amounts of starch and other simple carbohydrates, absolute abstention from alcohol, elimination of caffeine, and if applicable, a serious commitment to weight loss. Consider testing for food hypersensitivities and recommending books that outline “arthritis diets,” as they can help some patients.

Cessation of smoking is extremely important and must be addressed immediately.

As written orders for physical therapy are required to initiate the program, an example of the format of a typical prescription for Lyme rehabilitation follows.

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LYME REHAB — PHYSICAL THERAPY PRESCRIPTION

NAME _____

D.O.B. _____ DATE _____

Please enroll this patient in a program of therapy to rehabilitate him/her from the effects of Lyme Disease. If necessary, begin with classic physical therapy, then progress when appropriate to a **whole body** conditioning program. Such therapy must **be graded, carefully individualized, and be performed on a one-on-one basis**, at least initially, to ensure the maximal amount of supervision and guidance.

THERAPEUTIC GOALS (to be achieved in order as the patient's ability allows):

PHYSICAL THERAPY (if needed):

1. Relieve pain and muscle spasms utilizing multiple modalities as available and as indicated: massage, heat, ultrasound, TENS, "micro amp", etc.
2. Increase mobility while protecting damaged and weakened joints, tendons, and ligaments, to increase range of motion and relieve stiffness.
3. **Physical therapy alone is not enough. The role of physical therapy here is to prepare the patient for the required, preferably gym-based, exercise program outlined below**.

EXERCISE Begin with a private trainer for careful direction and education.

PATIENT EDUCATION AND MANAGEMENT (to be done during the initial one-on-one sessions and reinforced at all visits thereafter):

1. Instruct patients on **correct exercise technique**, including proper warm-up, breathing, joint protection, proper body positioning during the exercise, and how to cool-down and stretch afterwards.
2. Please work one muscle group at a time and perform extensive and extended **stretching** to each muscle group immediately after each one is exercised, before moving on to the next muscle group.
3. A careful interview should be performed at the start of each session to make apparent the effects, both good and bad, from the prior visit's therapy, and adjust therapy accordingly.

PROGRAM

1. **Aerobic exercises are NOT allowed**, not even low impact variety, until stamina improves.
2. **Conditioning**: work to improve strength and reverse the poor conditioning that results from Lyme, through a **whole-body** exercise program, consisting of light calisthenics and weight lifting, using small weights and many repetitions. This can be accomplished in exercise classes called “stretch and tone,” or “body sculpture,” or can be achieved with exercise machines, or carefully with free weights.
3. **Each session should last one hour**. If the patient is unable to continue for the whole hour, then modify the program to decrease the intensity to allow him/her to do so.
4. **Exercise no more often than every other day**. The patient may need to start by exercise every 4th or 5th day initially, and as his/her abilities improve, work out more often, but NEVER two days in a row. The days in between exercise sessions should be spent resting.
5. This **whole-body conditioning program** is what is required to achieve wellness. Simply placing the patient on a treadmill or an exercise bike is not acceptable (except briefly, as part of a warm-up), nor is a simple walking program.

PHYSICIAN'S SIGNATURE _____

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MANAGING YEAST OVERGROWTH

Many patients with chronic illnesses including Lyme Disease develop an overgrowth of yeast. A basic strategy to combat this is to eat a full container of sugar-free, non-fruit flavored yogurt that contains active cultures daily, and take acidophilus, two after each meal. Here are some other suggestions:

MOUTH: Yeast problems usually begin in the mouth, for when thrush is present, organisms may repeatedly pass down into the GI tract where they cause the most problems. A tongue with a beige coating, bad breath, and a bad taste in the mouth are signs of oral yeast. Patients should use a toothpaste that contains surfactants (detergent-like cleaning agents), and antiseptic mouthwashes (Scope, Listerine, etc.), and brush the teeth, tongue, gums, cheeks and the roof of the mouth while holding the mouthwash in the mouth.

The most effective treatment, employed as a last resort, consists of using “Dakin's Solution” as a mouth rinse. This is a mixture of household liquid bleach (Clorox), one teaspoon in four ounces of water. A small amount is held in the mouth while brushing, then spit out, and repeated until the thrush has cleared. This is usually a one-time treatment, but may have to be repeated every few weeks.

After using an antiseptic to clean the mouth, it is necessary to immediately eat yogurt or chew an acidophilus capsule to replenish the beneficial flora in the mouth. Because the germ count after such a cleaning will be artificially reduced, and because yeasts are opportunists, they would be the first to come back. By having the yogurt or acidophilus then, a more normal oral flora will result and thrush will be better controlled.

Since yeast germs feed on sugars and starches, avoid simple carbohydrates including sugars, starches, and some fruits. Refer to the diet outlined below.

Prescription medications may be necessary. Mycelex troches and Nystatin liquid are not the best choice, for they contain large amounts of simple sugars. Instead, Nystatin oral powder is preferred, as it does not contain sugar. It is mixed with water, and swished and swallowed four times daily. Systemic antifungals tablets (Diflucan, Lamisil, Nizoral) may be necessary.

INTESTINAL TRACT: An overgrowth of yeast here will ferment dietary sugars and starches, forming acids, gas, and alcohols. Symptoms include gas, heartburn and/or pain in the stomach area, and because of the alcohol, there can be headaches, dizziness, lightheadedness, wooziness and post-meal fatigue. To clear intestinal yeast, first the oral cavity must be cleared so yeast does not reenter the system with every swallow. Avoid sweets, starches, fruits and juices to starve the germs. Use PLAIN yogurt daily, and acidophilus, 2 capsules three times daily after meals. Systemic antifungal medications may be needed.

VAGINAL: An occasional vaginal yeast infection can be controlled with products such as Monistat cream or suppositories. If it is a recurrent or ongoing problem, then it often reflects a simultaneous intestinal infection, re-infecting the genital area with every bowel movement. Therefore follow the above protocol for intestinal overgrowth, and use topical preparations such as Monistat concurrently for up to two weeks.

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YEAST CONTROL DIET (Restricted carbohydrate regimen)

FOODS ALLOWED

Meat, fish, fowl, cheese, eggs, dairy, tofu

FRUITS

- **Only high fiber fruits are allowed**
- **Fruits are only allowed at the end of a meal, and never on an empty stomach**

ALLOWED
Grapefruit, tomatoes, avocado, lemons, limes

SMALL AMOUNTS ONLY! (The high fiber content in these makes up for the carbohydrates)
Pears, apples, strawberries, etc.

NOT ALLOWED
Oranges, watermelons, bananas, grapes, etc. (too much sugar and not enough fiber)

VEGETABLES

Green vegetables and salads are O.K. Avoid starchy vegetables (potato, rice, beans, etc.)

STARCHES

If it is made from flour, it is not allowed! (No breads, cereals, cake, etc.)

SWEETENERS

NOT ALLOWED
No sugars at all; no fructose or corn syrup, and no honey

ALLOWED (if tolerated)
Aspartame, Nutrasweet, Equal; saccharin products allowed but not recommended

DRINKS

ALLOWED
Vegetable juices, water, seltzer, diet sodas, coffee and tea without sugar or caffeine NOT ALLOWED Fruit juices, regular sodas, any drinks sweetened with sugars, syrups or honey

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PATIENT INSTRUCTIONS ON BITE PREVENTION AND TICK REMOVAL

HOW TO PROTECT YOURSELF FROM TICK BITES

PROPERTY

Remove wood piles, rock walls, and bird feeders as these attract tick-carrying small animals and can increase the risk of acquiring Lyme.

INSECTICIDES: Property should be treated with a product called “Damminix.” This consists of cardboard tubes containing cotton balls that have been dipped in insecticide. These tubes are placed around the property in the wooded areas and below shrubs. Mice, which are a key link in the propagation of Lyme disease, find the cotton and bring it back to their burrows to be used as nesting material, with the result being a big decrease in the number of ticks in the area. Unfortunately, after two years tick populations may rise again as other small animals that do not gather cotton become hosts to the ticks. Therefore, Damminix alone is not sufficient. Use this product in conjunction with liquid or granular insecticides.
LIQUID & GRANULAR PESTICIDES: Products meant for widespread application such as permethrin and its derivatives are preferred. They are available as a liquid concentrate and as granules. If liquid insecticides are used, application should be by fogging, not by coarse sprays. Apply these products in a strip a few feet wide at the perimeter of the lawn at any areas adjacent to woods and underbrush. Also treat any ornamental shrubs near the house that may serve as a habitat for small animals. The best time to apply these products is in late Spring and early Fall.

CLOTHING
When wearing long pants, tuck the cuffs into the socks so any ticks that get on shoes or socks will crawl on the outside of the pants and be less likely to bite. Also, light colored clothing should be worn so the ticks will be easier to spot. Smooth materials such as windbreakers are harder for ticks to grab onto and are preferable to knits, etc.

Tick repellents that contain “permethrin” (Permanone, Permakill) are meant to be sprayed onto clothing. Spray the clothes before they're put on, and let them dry first. Do not apply this chemical directly to the skin.

Ticks are very intolerant of being dried out. After being outdoors in an infested area, place clothes in the dryer for a few minutes to kill any ticks that may still be present.

SKIN
Insect repellents that contain “DEET” are somewhat effective when applied to the arms, legs, and around the neck. Do not use any repellent over wide areas of the body as they can be absorbed causing toxicity. Also, it is inadvisable to use a product that contains more than 50% DEET, and 25% concentrations are preferred. Use repellents cautiously on small children, as they are more susceptible to their toxic effects. Be aware that this repellent evaporates quickly and must be reapplied frequently.

Check carefully for ticks not only when home but frequently while still outside!

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HOW TO REMOVE AN ATTACHED TICK

Using a tweezer (not fingers!), grasp the tick as close to the skin as possible and pull straight out. Then apply an antiseptic. Do not try to irritate them with heat or chemicals, or grasp them by the body, as this may cause the tick to inject **more** germs into your skin. Tape the tick to a card and record the date and location of the bite. Remember, the sooner the tick is removed, the less likely an infection will result.

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APPENDIX

RATIONALE FOR TREATING TICK BITES

Prophylactic antibiotic treatment upon a known tick bite is recommended for those who fit the following categories:

1. People at higher health risk bitten by an unknown type of tick or tick capable of transmitting Borrelia burgdorferi, e.g., pregnant women, babies and young children, people with serious health problems, and those who are immunodeficient.
2. Persons bitten in an area highly endemic for Lyme Borreliosis by an unidentified tick or tick capable of transmitting B. burgdorferi.
3. Persons bitten by a tick capable of transmitting B. burgdorferi, where the tick is engorged, or the attachment duration of the tick is greater than four hours, and/or the tick was improperly removed. This means when the body of the tick is squeezed upon removal, irritated with toxic chemicals in an effort to get it to back out, or disrupted in such a way that its contents were allowed to contact the bite wound. Such practices increase the risk of disease transmission.
4. A patient, when bitten by a known tick, clearly requests oral prophylaxis and understands the risks. This is a case-by-case decision.

The physician cannot rely on a laboratory test or clinical finding at the time of the bite to definitely rule in or rule out Lyme Disease infection, so must use clinical judgment as to whether to use antibiotic prophylaxis. Testing the tick itself for the presence of the spirochete, even with PCR technology, is not reliable enough to guide your decision to treat, as false positives and false negatives occur.

An established infection by B. burgdorferi can have serious, long-standing or permanent, and painful medical consequences, and be expensive to treat. Since the likelihood of harm arising from prophylactically applied spirochetal antibiotics is low, and since treatment is inexpensive and painless, it follows that the risk benefit ratio favors tick bite prophylaxis.

Basic Information*

Updated 12/1/05

1. Lyme disease is **prevalent across the United States**. Ticks do not know geographic boundaries. A patient's county of residence does not accurately reflect their total Lyme disease risk, since people travel, pets travel, and ticks travel. This creates a dynamic situation with many opportunities for exposure for each individual.
2. Lyme disease is a **clinical diagnosis**. Spirochetal infection of multiple organ systems causes a wide range of symptoms. Familiarity with its varied presentations is key to recognizing disseminated Lyme disease. Case reports in the medical literature document its protean manifestations.
3. **Fewer than 50%** of patients with Lyme disease recall a **tick bite**. In some studies this number is as low as 15% in culture proven Lyme borrelial infection.
4. **Fewer than 50%** of patients with Lyme disease recall any rash. Although the bull's eye presentation is considered classic, it is not the most common dermatologic manifestation of early-localized Lyme infection. Atypical forms of this rash are seen far more commonly. It is important to know that the Erythema Migrans rash is pathognomonic of Lyme disease and requires no further verification prior to starting 6 weeks of antibiotic therapy. Shorter treatment courses have resulted in upwards of a 40% relapse rate, especially if treatment is delayed.
5. The CDC **surveillance** criteria were devised to track a narrow band of cases for epidemiologic change and were **never** set up to be used as diagnostic criteria nor were they meant to define the entire scope of Lyme disease. This is stated in the 3/25/91 NIH report.
6. The **ELISA** test is unreliable, and **misses 35%** of culture proven Lyme (only 65% sensitivity!) and is unacceptable as the first step of a two step screening protocol. (By definition a screening test should have 95% sensitivity.)
7. Of patients with acute culture proven Lyme disease, **20-30% remain seronegative** on serial **Western Blot** sampling. Antibody titers also appear to decline over time; thus, the IgG Western Blot is even less sensitive in detecting chronic Lyme infection yet the IgM Western Blot may work. For "epidemiological purposes" the CDC eliminated from the Western Blot analysis the reading of **bands 31 and 34**. These bands are so specific to *Borrelia burgdorferi* that they have been chosen for vaccine development. However, for patients not vaccinated for Lyme, a positive 31 or 34 band is highly indicative of *Borrelia burgdorferi* exposure.

Basic Information*

8. When used as a part of a diagnostic evaluation for Lyme disease, the Western Blot should be performed by a **laboratory that reads and reports on all 16 bands** as part of their routine comprehensive analysis. Laboratories (such as SmithKline) that use FDA approved kits (for instance, Mardex's Marblot) are restricted from reporting all of the bands, as they must abide by the rules of the manufacturer. These rules are set up in accordance with the CDCs surveillance criteria. and increase the risk of false negative results. These kits may be OK for surveillance purposes, but offer too scanty of an analysis to be useful in patient management.
9. A preponderance of evidence indicates that **active ongoing spirochetal infection** is the **cause of the persistent symptoms in chronic Lyme disease**.
10. **There has never in the history of this illness been one study that proves even in the simplest way that 30 days of antibiotic treatment cures chronic Lyme disease**. However there is a plethora of documentation in the US and European medical literature demonstrating histologically and in culture that short courses of antibiotic treatment fail to eradicate the Lyme spirochete.

11. An uncomplicated case of chronic Lyme disease requires an average of 6-12 months of high dose antibiotic therapy. The return of symptoms and evidence of the continued presence of *Borrelia burgdorferi* indicates the need for further treatment. The very **real consequences of untreated chronic persistent Lyme infection** far outweigh the potential consequences of long term antibiotic therapy.
12. Many patients with chronic Lyme disease require treatment for 1-4 years, or until the patient is symptom free. Relapses occur and maintenance antibiotics may be required. There are no tests available to assure us whether the organism is eradicated or the patient is cured.
13. There are 5 subspecies of *Borrelia burgdorferi*, **over 100 strains in the US**, and 300 strains worldwide. This diversity is thought to contribute to *Borrelia burgdorferi*'s antigenic variability and its various antibiotic resistances.
14. Antibody titers for Babesia, Anaplasma, Ehrlichia and Bartonella (other tick transmitted diseases) should be performed. The presence of **co-infection** points to probable Lyme infection, and when left untreated, **increases morbidity** and complicates successful treatment of Lyme disease.
15. Lyme disease is the **latest great imitator** and should be considered in the differential diagnosis of MS, ALS, and other neurologic conditions, as well as chronic fatigue syndrome, fibromyalgia, hypochondriasis, somatization disorder and patients with difficult-to-diagnose multi-system syndromes.

*** Note: The information presented here will be updated as research reveals new data.**

Controversies in Neuroborreliosis

Audrey Stein Goldings, M.D.

Updated October, 2002

III. THE ASSOCIATION BETWEEN MULTIPLE SCLEROSIS AND LYME DISEASE: THREE DIFFERENT SCENARIOS

1) LYME CAN LOOK LIKE MS BUT SYMPTOMS AND PATHOLOGY RESIDE OUTSIDE THE CENTRAL NERVOUS SYSTEM

Lyme may present as a MS-like illness, but on many occasions the pathology is not actually in the CNS. Since chronic Lyme symptoms often are predominantly shifting, vague, behavioral-psychological, psychiatric, and, as mentioned, neurological, they are likely to conjure up the diagnosis of MS in patients and physician alike. However, the existence of pathology outside the CNS should rule out the diagnosis of MS. Some of the vague symptoms that can be mistaken for MS include those that are better attributed to peripheral nervous system damage, as part of the mononeuritis multiplex that may occur. This might cause numbness, tingling, facial weakness, diplopia, etc. The diagnosis of MS cannot be made in the absence of CNS symptoms and signs. MRI and CSF findings would also help support the diagnosis of MS. In addition, a significant CSF pleocytosis may occur with Lyme disease, which should not be present with MS.

2) OTHER LYME PATIENTS DO HAVE CNS LESIONS, BUT THESE ARE GENERALLY DISTINCTLY DIFFERENT, CLINICALLY, AND PATHOLOGICALLY FROM MS

Patients can have CNS lesions in the brain or spinal cord with Lyme disease. The European literature includes many more cases than the American for encephalomyelitis, strokes, etc. In

those cases where there is focal involvement of the brain or spinal cord, it may be more difficult to distinguish neuroborreliosis from MS. Again, a brisk CSF pleocytosis would help diagnose Lyme and the specific aforementioned test for CNS Lyme antibodies. Simultaneous appearance of peripheral nervous system abnormalities or arthritis should suggest the diagnosis of Lyme.

3) ANOTHER GROUP OF PATIENTS HAS MULTIPLE SCLEROSIS AND LYME

There are some patients who have a clear-cut preexisting history of MS before the onset of Lyme disease. The Lyme appears to accelerate their clinical course. For others, it appears to be the initiating infection that triggers the MS. These patients are most likely genetically predisposed to MS and the Lyme bacteria exerts its major effect by “turning on” immunologically directed CNS injury. It is not uncommon to get a history of the onset of an exacerbation of MS related to infections, so Lyme exacerbating MS would be expected. HLA Class II molecules determine the intensity of the immune response to pathogenic foreign or self-antigens. With MS, the HLA-DR4 DQw8 haplotype has been associated with chronic progressive MS and the HLA-DR2 DQw6 haplotype has been associated with susceptibility to both chronic progressive and relapsing or remitting MS. It is possible that in genetically predisposed patients of certain HLA types that infection by Lyme bacteria would cause a high production of cytokines that would mediate the demyelination and destruction of oligodendrocytes.

Most recently, researchers are studying positive outcomes when antibiotics that are most useful in treating Lyme disease are used to treat “MS.”

IV. WHAT'S WRONG WITH “CURRENT GUIDELINES FOR TREATMENT” OF NEUROBORRELIOSIS?
First, read the fine print.

It is interesting to note that recommendations for treatment in the medical literature may carry provisos in small print that can easily be overlooked but are instrumental to understanding how important individualization of therapy is at the current time. For instance, in the past and in small print Dr. Alan Steere has written, **“treatment failures have occurred in all these regimens, and retreatment may be necessary; the duration of therapy is based on clinical response, and the appropriate duration of therapy with late neurological abnormalities may be longer than two weeks.”** A more recent article written by Rahn and Malawista states “these guidelines are to be modified by new findings. It should always be applied with close attention to the clinical course of individual patients.” Dr. Katzel surveyed several Lyme Borreliosis conferences, including international ones. He finds a trend towards the use of antibiotics for longer periods than previously described and lack of standardization of care worldwide. 50% of physicians responding considered using antibiotics for time periods greater than one year in symptomatic seropositive patients, with almost as many extending therapy up to one and a half years when necessary.

THE CASE FOR PERSISTENT INFECTION

Studies have shown that Lyme bacteria can be an intracellular pathogen and may evade the normal host immune response. The causative spirochete, *B. burgdorferi*, for instance, may persist within fibroblasts and survive at least 14 days of exposure to ceftriaxone. In addition, *B. burgdorferi* has been cultured from CSF more than a half year after a standard regimen of IV antibiotics, according to Preac-Mursic. Logigian and Steere looked at patients with chronic neuroborreliosis, evaluating them six months after two weeks of IV ceftriaxone. Over one-half of the patients had already been treated with therapy that was thought appropriate for their stage of illness, yet the illness progressed. The majority of patients studied had subacute encephalopathy and polyneuropathy. Most had persistent fatigue, and almost one-half had headaches. One-third of these patients had to stop working or had to go part-time, underscoring the disability that may be seen with Lyme disease on an individual and societal level. After therapy, two-thirds of patients improved markedly, but seldom completely. Twenty-two percent improved but then relapsed, and fifteen percent had no change in their condition.

This study suggests that additional antibiotics greatly helped the majority with neuroborreliosis but they were insufficient to cause long lasting remission in those patients who subsequently relapsed. Persistent residual or irreversible disease may explain the fifteen percent who had no change in their condition.

For those clinicians who have had extensive experience with chronic neuroborreliosis, more recent recommendations suggesting that a regime of only 20 to 28 days or even 6 weeks of intravenous antibiotics is sufficient for cure proved contrary to clinical experience. That brief dosing does not appear to prevent relapse or improve long-term outcome dramatically in many cases. Perhaps, as recent information has instructed, that is because the immune system does not begin to repair itself until the beginning of the fourth month of antibiotic treatment. A trial of prolonged use of oral antibiotics seems more reasonable in many cases, given these circumstances.

Antibiotics used for chronic neuroborreliosis should be able to penetrate the blood-brain barrier, express activity against intracellular organisms, and assure good intraphagocytic penetration. It is anticipated that the microbe during late disease has achieved maximal adaptation to its host environment. Also, because of the long generation time of the organism, lengthier therapy is warranted.

V. WE DON'T HAVE ALL THE ANSWERS BUT HERE'S WHAT IS RECOMMENDED

If a patient has meningitis or appears acutely ill, particularly with possible arrhythmia, admit him or her to the hospital for intravenous antibiotics and observation. Generally, however, in patients with stable late disease, oral antibiotics can be tried first. The majority of patients will have some improvement or gradual resolution of encephalopathic symptoms with a better energy level. After a six-week trial of appropriate antibiotics, the patient is re-evaluated. If there is no Herxheimer response or some clinical improvement during this interval, it is worrisome, and the physician needs to be concerned about: 1) misdiagnosis, 2) noncompliance, and/or 3) permanent end organ damage. These possibilities should be addressed with the patient before proceeding with intravenous antibiotics since they may not be maximally beneficial either

Over the long haul, whether intravenous antibiotics are used for two weeks or longer, with chronic refractory disease, ultimately other methods are necessary. A lengthier use of oral antibiotics seems more logical than intravenous antibiotics for some patients. Unfortunately, there are no current tests that adequately measure disease activity with neuroborreliosis in all patients.

We are sorely in need of a test similar to the CSF VDRL for syphilis that would give us a measure of disease activity. Culture negativity or disappearance of a specific immune response in the serum or CSF has not been useful at this time to establish cure. CSF antibodies may persist for years after otherwise successful treatment. Particularly in the CNS, judging response of therapy is problematic because pathological changes may incompletely or, at least, very slowly reverse. Any clinical improvement would be expected to occur in a delayed fashion after therapy is given. Likewise, one would expect neuropathy related to axonal degeneration to remit slowly and/or incompletely. Formal neuropsychiatric testing is of value in documenting pathology and following the patient. It also helps delineate what the patient can and cannot do. It also can help to define the disease for the patient, family, insurer, and the employer. The patient needs to be told that his or her symptoms should remit slowly and incompletely, when on antibiotic treatment. This is particularly important when the symptoms have been chronic.

VI. IN SUMMARY

The premise of this approach to diagnosing and treating neuroborreliosis needs to be reinforced.

1. There is no current laboratory test that makes or breaks the diagnosis of neuroborreliosis. It is a clinical diagnosis substantiated by laboratory data when possible. Fortunately, the majority of cases are fairly uniform in their lack of uniformity, and other diagnoses are easily ruled out. In situations where the physician simply cannot achieve diagnostic certainty, he or she should notify the patient that the diagnosis is "possible" or "probable" neuroborreliosis. This has been done previously with MS (i.e., possible, probable, and definite MS), another disease where laboratory testing does not make the diagnosis in and of itself.
2. There is no perfect current laboratory test to monitor success of therapy, and this is critically needed. Until better testing is available, assessing progress, or lack thereof, will largely be determined with clinical acumen.
3. The infection is difficult to eradicate and may require long-term treatment. The spirochete, particularly in later stages, becomes well adapted to survival within its host environment. There are some patients that we may not be able to cure, but will be able to palliate with currently available antibiotics.
4. Although immunopathogenic factors may play a crucial role in disease presentation, the presence of chronic infection appears necessary to perpetuate the process and play a causative role in persistence of immunologically triggered symptoms.
5. There is no Diagnostic and Statistic Psychiatry Manual (DSM IV) category for "antibiotic seeking behavior." It is common for physicians who are unable to explain patients' symptoms or effect their cure to ascribe a psychiatric cause to their malady. This is easily done with Lyme since objective findings may be subtle or non-existent. Because neuropsychiatric symptoms may pre-dominate, it is easy in some patients to attribute their symptoms to depression or secondary gain. These patients do not in any other way seek other medication that would be associated with habituation or addiction (i.e., pain medicine).

Many patients suffer unfairly at the hands of physicians who refuse to make the diagnosis because blood tests are either contradictory or negative. "Lyme bashing," for instance, referring to Lyme disease as "yuppie flu," is demeaning. The "just say no" attitude of certain physicians towards Lyme patients who request retreatment with antibiotics should not be condoned in the face of continuing experience with this potentially chronically disabling infectious disease.

Audrey Stein Goldings, MD is a private practice neurologist in Dallas. She is member of ILADS and a founding member of the Board of Directors.

Controversies in Neuroborreliosis

Audrey Stein Goldings, M.D.

Updated October, 2002

The objectives of this article are to cover issues related to Lyme disease that are not even-handedly addressed in the current literature. It will:

1. Present a practical approach for making the diagnosis of neuroborreliosis,
2. Explore the other side of the post-Lyme syndrome (i.e. the likelihood of chronic ongoing infection),
3. Discuss the relationship between MS and Lyme,
4. Critique the current regimens published for treating neuroborreliosis, and
5. Present my own approach which may differ from some leading authorities.

"Anyone who, in discussion, relies upon authority uses not his understanding but rather his memory."

—**Leonardo da Vinci**, Notebooks (c. 1500)

It is hoped this data will provide the reader with a broader understanding of neuroborreliosis so that he or she may better use current and evolving knowledge for clinical decision making.

I. NEUROBORRELIOSIS: MAKING THE DIAGNOSIS

Because of difficulties in making the diagnosis of neuroborreliosis, the physician will need a familiarity with the most common forms of presentations, which will be emphasized. The following points will help evaluate the patient for neuroborreliosis:

1. For most patients, systemic features of disease coexist with, or predate, neurologic manifestations.
2. Both central nervous and peripheral nervous system involvement is frequent with Lyme disease and typically occur together.
3. Laboratory data may or may not confirm the diagnosis, and other disease in the differential diagnosis must be evaluated thoroughly in cases where diagnostic ncertainty exists.
4. Although history of exposure to B. burgdorferi should be sought, for various reasons, patients may not remember a history of a tick bite, or the pathognomonic rash particularly if the disease is presenting years after the exposure.
5. Early on, personality changes, psychiatric symptoms, or cognitive manifestations may be the first, and occasionally the only, symptoms that the patient or family is aware of.

CLINICAL DESCRIPTIONS OF NEUROBORRELIOSIS

CENTRAL NERVOUS SYSTEM INVOLVEMENT

- Meningismus with normal CSF
- Lymphocytic Meningitis
- Meningoencephalomyelitis
- Subacute Encephalopathy (SAE)

PERIPHERAL NERVOUS SYSTEM INVOLVEMENT

- Cranial Neuropathy
- Painful Radiculitis
- Distal Neuropathy
- Plexopathy
- Myositis
- Polymyalgia Rheumatica

CENTRAL NERVOUS SYSTEM

MENINGISMUS

Patients may present with headache and stiff neck without evidence of CSF inflammation. Since early CNS seeding has been described, as well as culture positivity during latent disease without concurrent CNS inflammatory changes, these symptoms probably indicate active infection. Stiff neck might alternatively be due to axonal degenerative changes of the cervical paraspinal

musculature, but there should be other evidence of a more widespread neuropathy when this is the case.

LYMPHOCYTIC MENINGITIS

Lymphocytic Meningitis may appear to be indistinguishable from aseptic meningitis during early-disseminated disease (weeks to months after inoculation with *B. burgdorferi*). Most patients will have headaches that will fluctuate in intensity. Associated features may include a cranial neuropathy in about one-third. Low-grade encephalopathy is present in up to one-half, with mild memory concentration deficits, mood changes, and sleep disturbance.

MENINGOENCEPHALOMYELITIS

Rarely, focal parenchymal CNS lesions occur. The MRI may show punctate white matter lesions best seen on T2-weighted images; larger lesions occur infrequently. One brain biopsy showed increased numbers of microglia cells, rare spirochetes, and minimal inflammation. Transverse myelitis, movement disorders (extrapyramidal cerebellar, chorea and myoclonus), and hemiparesis can occur.

PSYCHIATRIC DISORDERS

Psychosis, mood swings (mild or bipolar), profound personality changes, depression, anorexia nervosa, obsessive-compulsive disorder, and panic attacks may occur. CSF may be normal.

SUBACUTE ENCEPHALOPATHY (SAE)

The most common chronic CNS manifestation is a SAE, characterized by memory problems and depression. Many patients (or their families) will complain of their excessive daytime sleepiness and extreme irritability. These patients generally come to the office disorganized (despite a supreme effort to be organized), unable to give a coherent history. They will bring copious notes, which are invariably in the wrong order. Most patients will complain of fatigue, and about one-half have headaches. Coincident polyneuropathy is very common with spinal or radicular pain, or distal paresthesias. Quantifiable deficits in memory, learning and retrieval, attention and concentration, perceptual-motor skills, and problem solving are common. MMPI testing generally shows a stable psychological pattern without significant psychopathology, similar to other medically ill patients.

ADDITIONAL CNS TESTING:
NEGATIVE TEST RESULTS DO NOT RULE OUT THE DIAGNOSIS OF NEUROBORRELIOSIS

Confirmation by CSF CULTURE is seldom practical because the organism is very fastidious, present in small numbers, takes a long time to grow out, and may undergo changes to forms which cannot be cultured easily.

CSF ANTIBODY TITERS may be present but are inconsistent and therefore their absence does not rule out CNS infection. The MRI is seldom abnormal and the findings, when present, are not specific for Lyme.

CSF PCR (test for spirochetal DNA) is a useful tool, but at present, because the capture of DNA is inconsistent, a few questions still need to be addressed.

OLIGLOCLONAL BANDS AND IGG INDEX — Looking for evidence of an intrathecal immune response may be helpful, but it is not specific. As a rule, oligoclonal bands and an elevated IgG index are not present in North American Lyme disease and their presence should suggest other diseases.

THE PERIPHERAL NERVOUS SYSTEM

Cranial neuropathy, painful radiculitis, distal neuropathy, and plexopathy are seen and generally reflect different clinical presentations of mononeuritis multiplex (polyneuropathy). Bell's Palsy occurs in almost 11% of all Lyme patients and is bilateral in up to 1/3. Therefore, a bilateral Bell's Palsy is very suspicious for Lyme in an endemic area. Painful radiculitis or cranial neuropathy can be seen with meningitis but also with normal CSF due to axonal neuropathy. Myositis may occur with Lyme as well as polymyalgia rheumatica. Symptoms of chronic involvement of the peripheral nervous system in a series of patients with chronic neurologic manifestations of Lyme disease developed a median of 16 months after the onset of infection, while CNS involvement began a median of 26 months after the onset of disease.

PERIPHERAL NERVOUS SYSTEM TESTING

Electrophysiological testing may show evidence of a mild peripheral neuropathy. Axonal degeneration and perivascular inflammatory infiltrates are noted on pathological specimens.

CHRONIC NEUROBORRELIOSIS

THE MOST COMMON PRESENTATION IS SAE, POLYNEUROPATHY, AND ARTHRITIS

Most typically, patients present with SAE, most often combined with polyneuropathy. Brief episodes of arthritis, primarily involving the knees, generally predate the symptoms and may persist after onset of neurological abnormalities. The TRIAD OF SAE, POLYNEUROPATHY, AND ARTHRITIS IS HIGHLY SUSPICIOUS FOR NEUROBORRELIOSIS.

Since serologies may be contradictory or negative, the physician will have to settle for treating if clinical suspicion is strong enough and assess whether the patient has "possible" or "probable" neuroborreliosis. Vigilant attempts to rule out other disorders should be undertaken. Screening should be done for collagen vascular disease, other infections, cancer, metabolic or endocrinological disturbances, etc. when a definite diagnosis cannot be made.

II. CURRENT MEDICAL MYTHOLOGY

"YOU HAVE FIBROMYALGIA. YOU MIGHT HAVE HAD LYME DISEASE IN THE FIRST PLACE, AND EVEN IF YOU DID, YOU WERE GIVEN ENOUGH ANTIBIOTICS. RETREATMENT WILL NOT HELP."

PERSISTENT INFECTION VERSUS POST-LYME SYNDROME

Many patients are sent home with antidepressants, muscle relaxers, but no antibiotics from doctors' offices because they have symptoms of fibromyalgia. Pictures similar, or identical, to fibromyalgia may be part of the constellation of symptoms of Lyme; it may occur more rarely as an isolated symptom, or surface after what would otherwise be considered successful treatment.

Symptoms of fibromyalgia due to Lyme disease have not been cured with short-term oral or intravenous antibiotics, so some argue fibromyalgia is not due to active infection. I would question whether those particular antibiotic regimens were adequate to eliminate the infection, rather than assume the patient has developed "Post-Lyme Syndrome" (some yet to be defined immunologically triggered disorder).

THE SCOPE OF THE PROBLEM

Bujak et al. evaluated patients a mean of almost five years after treatment. 15% of these patients had symptoms of fatigue and arthralgia. Almost one-half met criteria for fibromyalgia or chronic fatigue syndrome. Fibromyalgia is thought to be a variant of the chronic fatigue syndrome. Of note, nearly all patients continued to complain of memory loss or concentration difficulties. One quarter had objective evidence of cognitive impairment, and 15% manifested depression.

SYMPTOMS OF FIBROMYALGIA AND CHRONIC FATIGUE SYNDROME IN LYME DISEASE MAY BE ATTENUATED FORMS OR CHRONIC MANIFESTATIONS OF THE FLU-LIKE SYMPTOMS ASSOCIATED WITH EARLY DISSEMINATION

All physicians experienced with treating Lyme disease have had patients who present with a recurrence of flu-like symptoms, months to years after they have completed the usual antibiotic course of therapy, oral or intravenous, and re-exposure had not occurred. These patients describe their flu-like symptoms as identical to their early-disseminated stage of Lyme disease. The flu-like symptoms may reoccur following what appears to be a trivial stressor, such as an uncomplicated viral URI. Patients may be able to “contain” their symptoms without specific antimicrobial therapy, but many will have to resume antibiotics. These patients complain of having to go to bed due to excessive fatigue or hypersomnolence. They cannot think straight, their muscles and joints ache, and they may have a low-grade fever. Do these symptoms sound like a “fibromyalgia-like syndrome” or “acute fatigue syndrome?” Prior medical experience suggests reactivation of infection. Despite what may appear to have been a previous “cure,” relapse of symptoms in this context would appear to be due to failure to eradicate the infection and with reactivation after a period of dormancy. Reoccurrence of symptoms due to immunologically triggered disease, INDEPENDENT of persistent infection seems unlikely. In reality, DISTINCTIONS BETWEEN FLU-LIKE SYNDROME, FIBROMYALGIA, AND CHRONIC FATIGUE BLUR. It seems more logical to postulate that fibromyalgia and chronic fatigue syndrome, when seen with Lyme disease, may be attenuated forms of chronic manifestations of earlier flu-like symptoms associated with early dissemination.

The Question:=How does one distinguish between Multiple Sclerosis and neurologic Lyme Disease?

The Answer:=Multiple Sclerosis and Lyme Disease may have similar clinical and neuroimaging manifestations. Further, MS patients can get superimposed Lyme Disease - a concomitant infection which might make the MS worse by triggering an exacerbation. Similar to MS, infection with the agent of Lyme Disease can cause a progressive encephalomyelitis characterized by para- or tetraspastic pareses with gait difficulties, ataxia, bladder dysfunction, visual disorders, impaired hearing. Other manifestations of encephalomyelitis might include lateral nystagmus, intention tremors, dysarthric speech, seizures, facial palsies, retrobulbar neuritis, mild cognitive disorders (though rare dementia-like manifestations may occur). MS and Lyme Disease may cause brain and spinal MRI hyperintense lesions. Lyme Disease however more often causes a CSF pleocytosis and elevated protein. In Lyme Disease, evoked potential studies are generally but not always normal. MS patients do not have extra-neural features, as one may often find in patients with neurologic Lyme Disease (arthralgias, arthritis, myalgias, erythema migrans, carditis). Generally with MS, the laboratory studies reveal "abnormal evoked potentials (50%), CSF oligoclonal bands (90-95%), intrathecal IgG production (70-90%), and CSF myelin basic protein." (Coyle, 1992, Seminars in Neurology). If one finds intrathecal production of antibodies against Borrelia burgdorferi in the CSF, then the diagnosis of Lyme encephalomyelitis is confirmed. If one finds elevated myelin basic protein and oligoclonal bands and no signs of intrathecal Lyme antibody production, then the diagnosis of MS is much more likey. A case of a man with an

MS-like illness that ultimately proved to be Lyme Disease responsive to antibiotics is described in the following citation: Psychiatric Clinics of North America, v21: 693-703, 1998)

Sensory Evoked Potential Testing. Evoked potentials (visual, brainstem auditory, and somatosensory) may be useful in demonstrating the presence of subclinical lesions in sensory pathways or in providing objective evidence of lesions suspected on the basis of subjective complaints. (3) Of the sensory evoked potential tests, the visual evoked potential is the most useful because it can provide objective evidence of an optic nerve lesion that may not be evident on an MRI scan. Cerebrospinal Fluid (CSF) Analysis. In approximately 90 percent of patients with definite MS, the CSF IgG concentration is increased relative to other CSF proteins (e.g., albumin), and CSF gel electrophoresis reveals oligoclonal bands that are not present in a matched serum sample. (4) However, an increased CSF IgG index and the presence of oligoclonal bands are not specific for MS and therefore are not diagnostic of the disease. CSF analysis probably is most useful for ruling out infectious or neoplastic conditions that mimic MS.

CSF glucose level normally approximates 60% of the peripheral blood glucose level at the time of the tap. A simultaneous measurement of blood glucose (especially if the CSF glucose level is likely to be low) is recommended. Low CSF glucose level usually is associated with bacterial infection (probably due to enzymatic inhibition rather that actual bacterial consumption of the glucose). It also is seen in tumor infiltration, and may be one of the hallmarks of meningeal carcinomatosis, even with negative cytologic findings. High CSF glucose level has no specific diagnostic significance and is most often spillover from elevated blood glucose level.

Introduction

A series of 3 talks on the second day of the 13th Lyme Disease Conference examined the latest findings in the diagnosis and treatment of neurologic Lyme disease.

Brain Imaging in Lyme Disease

Structural and functional brain imaging can be useful to the clinician in the evaluation of patients with neurologic Lyme disease. Dr. Brian A. Fallon, Director of the Lyme Disease Research Program at the NYS Psychiatric Institute and Associate Professor of Clinical Psychiatry at Columbia University, New York City, presented a review of these brain imaging procedures in Lyme disease. This presentation reviewed published research and presented possibilities of how brain imaging can be used to answer important pathophysiologic and treatment questions about Lyme disease.

Structural brain imaging. MRI scans among patients with neurologic Lyme disease may demonstrate punctate white matter lesions on T_2-weighted images, similar to those seen in demyelinating or inflammatory disorders such as multiple sclerosis, systemic lupus erythematosus, or cerebrovascular disease. In Lyme disease, this is most often the case among patients with evidence of meningitis or encephalitis. In a report of patients with CSF-confirmed European Lyme disease with CNS symptoms, 50% of 14 patients had abnormal CT findings, most commonly hypodense areas corresponding with ischemic lesions caused by putative vasculitis. In each of the 3 studied cases, MRI revealed smaller, multiple sclerosis-like lesions and larger lesions also suspected to indicate vascular involvement. The authors concluded that, comparable to meningovascular and cerebrovascular syphilis, CNS micro- and macrovasculitis may cause both clinical symptoms and MRI changes in patients with CNS borreliosis.

The usefulness of MRI scans in American chronic Lyme encephalopathy is less clear. The general impression is that in chronic neurologic Lyme disease, brain MRI scans may be abnormal less often. In a report of a series of 24 patients with chronic neurologic abnormalities of at least 3 months' duration after Lyme disease, 4 (16.6%) had MRI abnormalities characterized as small round periventricular white matter lesions and 3 of these 4 patients had abnormal CSF studies. Among patients with Lyme encephalopathy in particular, the rate of MRI scans with white matter hyperintensities varied from 15% of 13 patients to 41% of 17 patients. In the latter study, when scans were repeated after treatment, half of the patients showed resolution of the signal hyperintensity. Among 8 children with neurologic Lyme disease, 25% had MRI abnormalities consisting of multiple focal areas of increased signal intensity in the white matter on long TR (both proton-density and T2-weighted) images.

In late-stage encephalomyelitis, MRI scanning often demonstrates focal areas of inflammation, most commonly in the white matter. In a series of 34 patients with acute or indolent encephalomyelitis, 26 (76.5%) had small multifocal hyperintense T2 signals, most commonly in the white matter and occasionally in the cortical and subcortical gray matter of the brain. Because encephalomyelitis clinically may result in prominent pyramidal, sensory, or cerebellar syndromes and because the MRI lesions resemble

demyelination, patients with Lyme disease may be mistakenly diagnosed as having multiple sclerosis.

Despite the preponderance of evidence indicating a substantial rate of MRI hyperintensities in some patients with CNS Lyme disease, as of yet there have been no studies to examine the pathophysiology of these hyperintense areas (perfusion, reactivity to hypercapnia, metabolism) and whether they have prognostic significance. Do these hyperintensities represent demyelination or perivascular inflammation? Is the disease process underlying the hyperintensities primarily neuronal metabolic or vascular? These questions can be examined by a study that couples structural imaging with functional imaging, comparing cerebral blood flow and cerebral metabolic rate deficits. The more sensitive FLAIR sequence and magnetization transfer techniques can be used to maximize the yield on identifying white matter hyperintensities.

In other disease states, such hyperintensities have usually been attributed to ischemic cerebrovascular disease secondary to increased water content in perivascular space, axon and myelin loss, astrocyte proliferation (gliosis), and/or frank infarction. If the hyperintensities occur primarily in the arteriole-supplied watershed areas, then the most likely cause is vascular insufficiency, as these areas receive limited collateral supply. Risk factors that increase the likelihood of having hyperintensities include older age, hypertension, diabetes, coronary heart disease, and other vascular risk factors. The presence of hyperintensities has been shown to predict subsequent stroke, new-onset dementia, myocardial infarction, and vascular death.

Histopathologic studies of hyperintensities in neurologic and normal samples commonly show arteriolar hyalinization, ectasia, enlarged perivascular space, gliosis, spongiosis, and/or lacunar infarcts. Van Swieten found that white matter hyperintensities in the elderly were invariably accompanied by demyelination and gliosis, and less consistently with increased perivascular space. The demyelination was strongly associated with increased wall thickness of small arterioles. They concluded that arteriosclerosis in small arterioles (<150 microns) is the primary cause, leading to demyelination, and then cell loss with progression.

The hypothesis that MRI hyperintensities in Lyme encephalopathy are attributable to impaired blood flow (vascular insufficiency) in subcortical areas can be tested with in vivo perfusion imaging. In stroke samples, PET and SPECT studies consistently have shown correspondence between the identified areas of hypoperfusion and the structural abnormalities identified by CT, MRI, or pathology. The spatial extent of the perfusion deficit is typically larger than the areas of tissue necrosis defined by pathology or structural imaging, and remote functional changes may be observed (diaschisis).

Functional brain imaging. Single photon emission computerized tomography (SPECT) and positron emission tomography (PET) provide a dynamic picture of the brain's functioning: metabolism, blood flow, and chemistry. In comparison to SPECT scans, PET scanning is able to provide better spatial resolution images (4-6 mm vs 6-9 mm) and can be used to provide an absolute quantitative assessment of regional perfusion or

metabolic abnormalities. SPECT has recently been reported to be a useful tool in the evaluation of patients with Lyme disease, showing multifocal areas of decreased perfusion in both the cortex and the subcortical white matter.

Logigian contrasted the brain perfusion patterns of 13 patients with definite Lyme encephalopathy (defined by objective memory deficits on cognitive testing and/or CSF with intrathecal Ab production or positive PCR), 9 patients with possible Lyme encephalopathy (no objective deficits), and 26 normal controls. Patients with definite Lyme encephalopathy had significantly more perfusion deficits than patients with possible Lyme encephalopathy, who in turn had significantly more deficits than normal controls. After the patients with definite Lyme encephalopathy were given 4 weeks of IV ceftriaxone, a partial reversal in brain perfusion deficits was observed. These results suggest that perfusion deficits are greater with more severe disease and that perfusion deficits may be seen in the absence of objective neuropsychological deficits.

Notably, although the treated patients did show improved perfusion, significant perfusion deficits remained. Several limitations of this study should be noted. First, because this study did not have age- and sex-matched controls, the results that suggested regions of deficit specific to Lyme encephalopathy (subcortical frontotemporal white matter and basal ganglia, frontal cortex, cingulate gyrus) need to be confirmed in a better-controlled investigation. Second, the relatively older control group did not have neuropsychological testing at baseline, thereby risking the inclusion of cognitively impaired individuals. This may explain why 4 of the 26 "normal" controls had perfusion deficits in the range of those seen in the Lyme encephalopathy patients. Third, because in this study 11 of the 13 treated patients with Lyme encephelopathy had never previously received a course of IV ceftriaxone of at least 3 weeks, the results of this study cannot be generalized to the larger group of patients with Lyme encephalopathy who have already received this standard course of treatment. The authors' impression that "patients with Lyme encephalopathy who have already been treated with oneor at most two 1-month courses of IV ceftriaxone rarely improve after further courses of ceftriaxone" needs to be tested in a carefully designed way. Fourth, patients did not undergo follow-up cognitive testing, thereby precluding objective investigation of the clinical significance of the improvement in perfusion.

Hypoperfusion defects visualized on SPECT scans may result from any process that alters the radiotracer distribution, including vascular delivery to neurons, transport of the tracer into the cells, and retention of the radioactive tracer in the cells. Problems may arise secondary to direct infection of neurons, from cellular dysfunction due to the indirect effects of neurotoxic immunomodulators such as cytokines, or from decreased perfusion through arterioles secondary to vasculitis. In other words, areas of hypoperfusion may result from a cellular-metabolic and/or a vascular problem. Although SPECT reports suggest that the use of imaging pre-and post-acetazolamide may be helpful in the indirect determination of a vascular from a metabolically induced area of hypoperfusion, only PET technology using glucose and oxygen studies is capable of addressing this question directly in a fully quantitative fashion.

In what ways, then, are functional imaging scans helpful in the diagnostic assessment? First, a scan with diffuse abnormalities may confirm that an objective abnormality is present in a patient considered to have a factitious disorder. Second, a normal scan in a patient with prominent neuropsychiatric symptoms may suggest that a psychiatric disorder is the primary cause of a patient's cognitive or emotional distress, and therefore may lead the clinician to recommend a re-evaluation of the patient's psychiatric treatment. Third, an improvement in a scan after treatment provides objective evidence of physiologic change.

It should be noted that one cannot conclude from a PET or a SPECT scan that a patient has Lyme disease, as similar patterns of abnormality may be seen with other diseases as well. A diffusely abnormal scan should alert the clinician to search for the presence of an organic etiology other than that which causes primary psychiatric disorders. Other disease processes that demonstrate a heterogeneous tracer uptake include vascular dementia, chronic fatigue syndrome, CNS lupus, HIV encephalopathy, and chronic or acute stimulant abuse.

There have been no metabolic imaging studies in Lyme disease; the limited data pertain to cerebral blood flow only. It remains to be determined how quickly the hypothesized perfusion and metabolic deficits improve and whether improvement in functional imaging is correlated with neuropsychological change. For example, it is known that metabolic or flow defects may persist after a stroke or trauma despite the presence of a normal neurologic exam. The Columbia Presbyterian Medical Center's clinical experience with Lyme disease patients indicates that improvement in SPECT abnormalities may occur rapidly or lag behind clinical improvement by many months.

Questions Raised by the Structural and Functional Imaging Data Studies of Chronic Lyme Encephalopathy. Several critical public health questions are raised. First, do patients with previously treated encephalopathy show an improvement in brain imaging (both functional and structural) and cognition after repeated courses of antibiotic treatment? Second, are there patient variables that predict who is more likely to respond? Third, are there neuroimaging pretreatment variables that are associated with treatment response? Fourth, can structural or functional neuroimaging be used as an objective tool to monitor response to treatment? And finally, is there a subgroup of patients with possible Lyme encephalopathy who no longer respond to treatment because of cerebrovascular disease?

These questions will be addressed by a newly funded study of persistent Lyme encephalopathy being conducted at the Columbia Presbyterian Medical Center in New York City. Under the direction of Dr. Brian Fallon, this 4-year study will enroll 60 patients with cognitive deficits secondary to Lyme disease and 20 healthy controls. The 60 patients must have well-documented Lyme disease and must have received a total of at least 8 weeks of IV antibiotic therapy previously. Patients and controls will get baseline serologic, CSF, and imaging tests at baseline. The imaging tests include MRI and PET. The PET imaging includes a test of neuronal metabolism (FDG), a test of vascular flow (O15-water), and a test of vascular flow after a hypercapnic challenge. The

hypercapnic challenge involves breathing in a small amount of CO_2-enhanced air which, in a person with normal blood vessels, would result in a broad increase in perfusion. In a patient with vasculitis with ischemia at which the vasculature may already be maximally dilated, however, the O15 PET scan after the hypercapnic challenge would reveal a relative deficiency of increased perfusion in the affected areas - thus providing a relative simple way of determining whether a patient's disease process involves vascular disease.

The treatment component of this new study (conducted at the patient's home) involves a placebo-controlled treatment with 10 weeks of IV ceftriaxone in which 40 patients get randomized to IV antibiotics and 20 patients get randomized to IV placebo. Patients will then be followed off antibiotics for 14 weeks, monitored both by cognitive tests and brain imaging 2 weeks after the end of treatment and 14 weeks after end of treatment. The aim is to determine whether patients who have persistent cognitive deficits despite considerable past IV antibiotic therapy benefit from a repeated course of intensive antibiotic therapy. This study should address questions regarding the time course of improvement cognitively and via imaging as well as whether the improvement between these 2 assessment modalities are closely correlated. Collaborators at other institutions will attempt to culture Borrelia organisms from the spinal fluid and examine the spinal fluid for markers of infection, such as matrix metalloproteinase, PCR, and *B burgdorferi*-specific immune complex. In addition, the investigation of multiple variables at baseline (serum, CSF, imaging, clinical) may help to identify markers that would predict who responds to treatment and who does not. Dr. Fallon concluded his talk by providing the phone number for physicians interested in referring patients to the study (212-543-5367).

Neurologic Manifestations of Lyme Disease in the Pediatric Population

In the second talk, Dorothy Pietrucha, MD, FAAP, of the Jersey Shore Medical Center, Neptune, New Jersey, discussed diagnostic and treatment issues in pediatric neurologic Lyme disease.

Involvement of CNS. According to Dr. Pietrucha, children with neurologic Lyme disease may present acutely with headache, blurry vision, double vision, confusion, irritability, fever, and/or stiff neck. Chronically, they may be encephalopathic and have lingering headache, personality change, and depression. Patients who present acutely may have an aseptic meningitis with pleocytosis and elevated protein in the spinal fluid. Occasionally, there may be lesions on the MRI, and about 20% of patients may have abnormal EEGs.

Increased intracranial pressure with an opening pressure above 200 mm/H_2O is seen much more often in children with Lyme disease than in adults. This is sometimes referred to as "pseudotumor cerebri," although it is not a classic pseudotumor picture as the children do not necessarily have to be overweight or have a problem with their menstrual cycle. The CSF pleocytosis usually improves. Frequently, it may improve even without treatment, but certainly, if the patient is treated with antibiotics, this will clear. The increased intracranial pressure responses to medications such as *Diamox* and seizures should be treated with anticonvulsant medications. The lesions on the MRI may remain or may disappear with time.

The most common lingering problem that patients have as a result of involvement of the CNS in Lyme is encephalopathy, which the children call "brain fog." These children complain of persistent headache and fatigue. There may be personality change, irritability, and frequently depression.

The impact academically is most significant. These children have fall-off in academic performance, difficulty learning new material, problems with short-term memory, problems with word finding, and a number of them have lost reading skills. Frequently, these children may present with a picture of ADD or may have an underlying ADD or ADHD that is made worse by the Lyme. Incidentally, Dr. Pietrucha noted that children with Tourette's may also have a worsening of their tics when they have been ill with Lyme disease symptoms. A case report published in *Lancet* indicated that a child with Tourette's who was found to have concurrent CNS Lyme disease experienced a remission of the Tourette's after the Lyme disease was treated.

This Lyme encephalopathy merits special attentions because it has a significant impact educationally and also economically. These children may require at-home tutoring, necessitating a parent to stay home from work to be with the child. When they return to school, many frequently need a shortened schoolday and continued home instruction. Many have to be classified as "other health impaired" and receive ongoing services, such as Resource Room. A number of these children need to be placed on medication for their short attention spans and distractibility, as any other ADD patient would require. Frequently, the depression has to be treated, both with medications and counseling.

In addition to the impact on these children educationally, there is a social burden because they cannot participate in extracurricular activities and they lose contact with peers.

Peripheral nervous system. Patients may present with a sudden onset of weakness. It may be facial weakness, weakness of an extremity, or an ascending weakness or paralysis. There may be pain, a burning sensation in the extremities, numbness, tingling, and myalgia.

Children do not have involvement of the peripheral nervous system as frequently as they have involvement of the CNS. The most common peripheral nervous manifestation in children is Bell's palsy, with a sudden onset of facial palsy. Rarely, there has been involvement of an isolated extremity or even an isolated nerve involvement, such as the peroneal nerve. Patients have presented with a picture very typical of Guillain Barré (GB), and many children do complain of a burning sensation, numbness, and tingling -- although this is a mild sensory neuropathy. There have been cases of children presenting with muscle pain, weakness, and elevated CPK.

In addition to treating their Lyme disease with appropriate antibiotic therapy, these patients may require physical therapy, anti-inflammatory medication, and analgesia. Patients presenting with a picture that is typical of GB should be treated like a GB patient, keeping in mind that if the underlying cause is Lyme disease, then that too must be treated. Overall, the prognosis for children to show a complete recovery from

involvement of the peripheral nervous system in Lyme disease is very good, probably better than in the adult population. Bilateral Bell's palsy has certainly been seen in Lyme disease in children. The incidence of bilateral Bell's palsy in Lyme is greater than the incidence of bilateral Bell's palsy from other causes.

Conclusion. Dr. Pietrucha's talk was based on years of clinical experience treating hundreds of children with mild-severe neurologic Lyme disease. In the question-and-answer session, she described one child with refractory generalized seizures not responsive to anticonvulsants who was also experiencing joint pain. This child tested positive for Lyme disease and responded with a remission of the seizures. The treatment course was prolonged and led to an overall dramatic improvement in clinical symptoms. Dr. Pietrucha also noted that complex partial seizures have been described in the medical literature among children with chronic Lyme disease.

Psychological Evaluation of Pediatric, Neurologic Lyme Disease

Background. Children with Lyme disease may experience cognitive difficulties that interfere with school performance. Studies have demonstrated deficits in the areas of attention, memory, language and reasoning in adult subjects.[1-4] Other studies have explored the nature and extent of cognitive or academic dysfunction in children with Lyme disease,[5-8] though little attention has been directed toward the development of educational programs to deal with the issue. Marian Rissenberg, PhD, of Columbia Presbyterian College of Physicans & Surgeons, New York, presented a talk on the neuropsychological evaluation of children with Lyme disease. Dana Leonardi, MA, has been an integral part of this research.

Methods. In this pilot study, Dr. Rissenberg evaluated 8 children aged 7 to 13 years (mean, 9.1) with physical, cognitive, and emotional symptoms related to Lyme disease who had neuropsychological evaluation, including academic testing early and again later in the course of their antibiotic treatment. Physical symptoms reported at the initial evaluation (E_1) included fatigue, joint pain headaches and irritability. Also reported were difficulties with schoolwork, concentration, and memory; sleep disturbance; sensory sensitivity; mood swings; impulsivity; depressed mood; anxiety; motor tics; word retrieval difficulty; balance problems; and temper outbursts.

Results. Dr. Rissenberg's results indicated that at the time of E_1, even after completing from 1 to 5 months of high-dose antibiotic treatment, children had significant cognitive deficits. As a group, the subjects had a significant discrepancy between Verbal and Performance IQ, and a significantly deficient Performance IQ. There was a significant degree of inter-subtest variability on the WISC-III, with scores ranging from the 20^{th} to 93^{rd} percentile. Scores were lowest on tests sensitive to speed of processing, visual scanning, sequencing, and causal reasoning. Deficits were noted on 2 attention tasks, one sensitive to visual scanning and sustained attention and the other to auditory tracking. While there were no statistically significant memory deficits evident at E_1, the data suggest that delayed recall of both verbal and visual material is deficient. On tests of language function, performance was deficient on a task requiring production of sentences containing a given word. On academic measures, half the S's were behind grade expectation in 2 measures of reading comprehension, as well as spelling. Most S's were

above grade expectation in Basic Reading, Mathematics Reasoning and Numerical Operations. Reading skills were more advanced than math skills.

At E_2, following 10 to 32 months (mean, 17) of additional antibiotic therapy, all subjects reported significant improvement of physical and emotional symptoms, with only 1 having continued headaches and another having sleep disturbance. Five experienced improvement in cognitive and academic difficulties, though 4 continued to have some cognitive complaints and 5 continued to have some emotional issues. Two continued to have both cognitive and emotional symptoms, and 1 had both physical and emotional symptoms.

Results from repeat administration of the WISC-III at E_2 revealed significant improvement in Verbal and Performance IQ, with less of a spread between the two. Full Scale IQ and the Perceptual Organization Index also showed significant improvement. Marked improvement in performance was shown on those subtests that were deficient at E_1, specifically Picture Arrangement, Comprehension, Object Assembly, and Coding, as well as Arithmetic. This strongly supports the notion that these deficits were secondary to Lyme disease and that their improvement is attributable to antibiotic treatment. Visual scanning and sustained attention improved, while auditory tracking showed less improvement. Performance on sentence production improved. Significant improvement was noted on the Verbal Immediate Memory Index and the General Memory Index of the CMS. Short-term memory impairment is no longer apparent. Gains were made in academic achievement in all areas, with the exception of Numerical Operations (paper and pencil calculations). However, even with 6 S's dropping an average of 1 year and 3 months, only 2 fell below their expected GE. Gains were demonstrated on 3 separate measures of reading comprehension and on reading speed and accuracy. Scores on tests of mathematical calculations and fund of general and word knowledge declined. This is interpreted as reflecting a decreased rate of learning and a widening of the gap between children with Lyme disease and their healthy peers over the course of the study.

Implications. Dr. Rissenberg noted that the results provide preliminary support for broadening the CDC diagnostic criteria, extending antibiotic treatment in children, and conducting careful neuropsychological evaluation and educational monitoring. Development of educational programs for the identification, accommodation, and remediation of Lyme disease-related academic difficulties is critical as the numbers of children with the disease increases. Lyme disease-related cognitive deficits represent acquired, as opposed to developmental, learning disabilities and attentional disorders. Educational services and modifications should include, when necessary, reduction of homework, extended time for tests, provision of classroom notes and course outlines, instruction in organizational, time management, and study skills strategies, availability of abridged or tape-recorded books, shortened schoolday, and home instruction. Support may be necessary even after treatment for Lyme disease has been completed. Education of teachers and other school personnel regarding the educational impact of Lyme disease, as well as resources for parents, must be available. Dr. Rissenberg noted that further study is needed, using larger groups and more stringent controls, of the cognitive and

academic functioning, physical and psychiatric symptomatology, and treatment response in children with Lyme disease.

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Multiple sclerosis and Lyme borreliosis.

Schmutzhard E.

Department of Neurology, University Hospital, Innsbruck, Austria.
erich.schmutzhard@uibk.ac.at

In a deductive approach the two disease entities of multiple sclerosis and chronic progressive neuroborreliosis are discussed. Various clinical features, seroepidemiology, neuroimaging, CSF findings, CSF serology, specific proteins within the CSF and antibodies against neuronal structures as well as the most recent findings of different dendritic cells within the CSF are discussed as a means of differentiating these two disease entities.

4. Clinical Picture of Lyme Borreliosis

The natural course of untreated* B. burgdorferi *infections varies considerably. In principle, each of the clinical manifestations specified in the following can occur either alone or in various combinations [7, 37, 38, 51, 53]. In the majority of cases the infection is self-limiting. However, even after antibiotic treatment, B. burgdorferi may persist in the tissue [39]. Persistence of the pathogen may be associated with clinical symptoms, yet has been observed in clinically asymptomatic persons as well.

Lyme borreliosis is a multisystem disease, manifesting primarily, and usually commencing, as a local skin infection (erythema migrans). Within days to weeks dissemination of the spirochetes into other organs, most frequently into the central nervous system, into the joints or the heart, may occur (cf. **Table 3**, **Table 10a, b and c**).

The clinical picture is divided into early and late manifestations (stages I and II as well as stage III, resp.). **Erythema migrans** is the most frequently occurring early manifestation and cardinal symptom of Lyme borreliosis. Days to weeks after the tick bite a macular or papular skin lesion develops, which in the course of further development usually takes the form of an annular erythema, fading in the centre and migrating at the edge. Its extension, colour intensity and duration may vary considerably. In addition, general symptoms such as fever, myalgia, headache and, rarely, meningism may occur. Hematogenic dissemination may cause multiple erythemata. These are less often observed in Europe, more frequently in America. The borrelial lymphocytoma is a special type of skin lesion (reddish to livid tumour in typical locations such as earlobe, mamilla or scrotum).

Neuroborreliosis is the most frequent manifestation of stage II, particularly in its appearance as lymphocytic meningoradiculitis, which usually reveals typical clinical symptoms. Cardinal symptoms are the radicular pain syndrome - characterised by excruciating, burning pains exacerbating mainly during the night - and/or cranial nerve palsy. Pareses of the extremities and the trunk are less frequent. Meningitis or even facial palsy as sole manifestation without any meningitic symptoms is more frequently found in children than in adults. Typical CSF findings characterised by lymphocytic pleocytosis (with cell counts ranging between 30/3 and 3000/3 cells/µl) and elevated CSF protein concentration are diagnostically indicative. Further clinical manifestations of stage II are Lyme carditis, which clinically presents as dysrhythmia, mainly in the form of atrioventricular blocks of different degrees, as well as various forms of ophthalmoborreliosis.

Lyme arthritis and acrodermatitis chronica atrophicans (ACA) are the most common manifestations of stage III. Lyme arthritis can take a monoarticular or oligoarticular, intermittent or, less frequently, a chronic course. Here, acute disease manifestations and asymptomatic intervals may alternate. Spontaneous remissions are frequent, transitions into the chronic stage rather seldom. Before establishing the diagnosis of Lyme arthritis, an extensive rheumatologic differential diagnosis is required. After a long incubation period (months to years), patients with ACA develop an

initially infiltrative stage, followed by the alterations characteristic of the atrophic stage: creased skin, the thinness of which is reminiscent of cigarette paper, with livid discolorations and plastic protrusion of vessels. It is notable that ACA is almost exclusively observed in Europe.

Chronic neuroborreliosis is a very rare manifestation of the third stage. Parapareses and tetrapareses are its most common symptoms. Examination of the CSF reveals a marked elevation of protein concentration with a low to moderate increase of CSF cells. The detection of intrathecally produced specific antibodies is currently regarded as the best marker for borrelial etiology and is also the most relevant criterion allowing differentiation from multiple sclerosis.

The early manifestations of Lyme borreliosis, such as EM and acute neuroborreliosis, are observed most frequently between spring-summer and autumn, correlating with tick activity. Late manifestations of Lyme borreliosis do not show any typical seasonal prevalence pattern.

Table 3. Specimen types used for the diagnosis of Lyme disease

	Specimen types for	
Clinical manifestation	**Direct pathogen detection**	**Antibody detection**
Stage I (early / localised) *(days through weeks after tick bite)* Erythema migrans	 Skin biopsy specimen	 Serum
Stage II (early / disseminated) *(weeks through months after tick bite)* Multiple erythemata Borrelial lymphocytoma Lyme carditis Neuroborreliosis Ophthalmoborreliosis	 Skin biopsy specimen Skin biopsy specimen Endomyocardial biopsy specimen CSF	 Serum Serum Serum Paired serum/CSF Serum
Stage III (late / persistent) *(Months through years after tick bite)* Arthritis Acrodermatitis chronica atrophicans Chronic neuroborreliosis	 Synovial fluid Synovial biopsy specimen Skin biopsy specimen CSF	 Serum Serum Paired serum/CSF