WHY CAN'T I GET BETTER?

SOLVING THE MYSTERY OF LYME AND CHRONIC DISEASE

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The Horowitz Lyme-MSIDS Questionnaire: An Essential Tool in Determining the Probability of Lyme Disease and MSIDS

My patients typically fill out the following symptom questionnaire while in the waiting room. I then use the document to go through the thirty-eight items in Section 1 in great detail and get expanded information on each of the symptoms to develop a comprehensive set of differential diagnoses. This essential questionnaire is based on one developed by Dr. Joseph Burrascano when he started treating Lyme disease patients. He found, and other physicians have verified, that there were a number of common patient symptoms, and these complaints make up the items of the questionnaire.

You can use the following questionnaire to determine the probability of a Lyme-MSIDS diagnosis for yourself. I also highly recommend that new and experienced physicians use this as a screening tool to determine if their patients might have Lyme disease. This process ensures that no symptoms are left out and gives the provider an initial opportunity to develop a broad range of differential diagnoses while reviewing the symptom list early on in the patient visit. It provides the health-care provider with clues that point to whether the patient has a high probability of having Lyme disease, a possible case of Lyme disease, or is unlikely to have Lyme disease. It also reassures the patient that the provider will pay close attention to all of their complaints.

All of the points on the list in Section 1 are symptoms that can be seen with Lyme disease. They are not specific to Lyme disease in and of themselves, and can be found in many other illnesses. However, the gestalt that can be perceived by looking at all of the symptoms simultaneously helps the clinician reach a probability as to whether the patient may suffer from Lyme disease and associated tick-borne disorders. At the same time this list can also be used to identify simultaneous overlapping disease states, so that the true source of the patient's suffering is discovered. These multifactorial causes of illness are often at the heart of most chronic disease states, and this led me to create the MSIDS model. It can be immensely helpful in ruling out other disease processes on the MSIDS map while looking for specific symptom complexes that are frequently seen in Lyme disease (such as symptoms coming and going with good and bad days, migratory joint and muscle pain, neuralgia that comes and goes and migrates, headaches, and sleep disorders, with associated cognitive deficits).

Sections 2 and 3 of the questionnaire represent those signs and symptom complexes most associated with Lyme and MSIDS, which I have compiled after examining hundreds of our patients' charts over the last decade. Section 4 is based on two of the four questions in the Healthy Days Core Module used by the CDC to track population trends nationally and identify health-care disparities, and it helps us identify the frequency of physical and mental health problems in the preceding month.

Talk to your doctor about the results of this questionnaire. Depending on your score, you may want to follow up with blood tests for Lyme disease IFA (immunofluorescent assay), ELISA (enzyme-linked immunosorbent assay, and a Western blot, through a reliable laboratory), with confirmatory evidence of other tick-borne diseases as well. Do not just rely on the CDC criteria of using an ELISA in a two-tiered testing protocol, as this is not sensitive enough to confirm the diagnosis. You can use this questionnaire as the starting point of the decision-making detective work that will lead you to the proper diagnosis. Remember, Lyme disease is a clinical diagnosis, and blood tests only help to confirm your clinical suspicion.

Answer the following questions as honestly as possible. Think about how you have been feeling over the previous month and how often you have been bothered by any of the following problems. Score the occurrence of each symptom on the following scale: none, mild, moderate, severe.

Section 1: Symptom Frequency Score

0 None 1 Mild 2 Moderate 3 Severe

1. Unexplained fevers, sweats, chills, or flushing
2. Unexplained weight change; loss or gain
3. Fatigue, tiredness
4. Unexplained hair loss
5. Swollen glands
6. Sore throat
7. Testicular or pelvic pain
8. Unexplained menstrual irregularity
9. Unexplained breast milk production; breast pain
10. Irritable bladder or bladder dysfunction
11. Sexual dysfunction or loss of libido
12. Upset stomach
13. Change in bowel function (constipation or diarrhea)
14. Chest pain or rib soreness
15. Shortness of breath or cough
16. Heart palpitations, pulse skips, heart block
17. History of a heart murmur or valve prolapse
18. Joint pain or swelling
19. Stiffness of the neck or back
20. Muscle pain or cramps
21. Twitching of the face or other muscles
22. Headaches
23. Neck cracks or neck stiffness
24. Tingling, numbness, burning, or stabbing sensations
25. Facial paralysis (Bell's palsy)
26. Eyes/vision: double, blurry
27. Ears/hearing: buzzing, ringing, ear pain
28. Increased motion sickness, vertigo
29. Light-headedness, poor balance, difficulty walking
30. Tremors
31. Confusion, difficulty thinking
32. Difficulty with concentration or reading
33. Forgetfulness, poor short-term memory
34. Disorientation: getting lost; going to wrong places

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

Add up your totals from each of the four columns. This is your first score.

Score: _____

Section 2: Most Common Lyme Symptoms Score

If you rated a 3 for each of the following in section 1, give yourself 5 additional points:

- Fatigue
- Forgetfulness, poor short-term memory
- Joint pain or swelling
- Tingling, numbness, burning, or stabbing sensations
- Disturbed sleep: too much, too little, early awakening

Score: _____

Section 3: Lyme Incidence Score

Now please circle the points for each of the following statements you can agree with:

1. You have had a tick bite with no rash or flulike symptoms. *3 points*
2. You have had a tick bite, an erythema migrans, or an undefined rash, followed by flulike symptoms. *5 points*
3. You live in what is considered a Lyme-endemic area. *2 points*
4. You have a family member who has been diagnosed with Lyme and/or other tick-borne infections. *1 point*
5. You experience migratory muscle pain. *4 points*
6. You experience migratory joint pain. *4 points*
7. You experience tingling/burning/numbness that migrates and/or comes and goes. *4 points*
8. You have received a prior diagnosis of chronic fatigue syndrome or fibromyalgia. *3 points*
9. You have received a prior diagnosis of a specific autoimmune disorder (lupus, MS, or rheumatoid arthritis), or of a nonspecific autoimmune disorder. *3 points*
10. You have had a positive Lyme test (IFA, ELISA, Western blot, PCR, and/or *borrelia* culture). *5 points*

Score: _____

Section 4: Overall Health Score

1. Thinking about your overall physical health, for how many of the past thirty days was your physical health not good? _____ days
Award yourself the following points based on the total number of days:

0–5 days = 1 point
6–12 days = 2 points
13–20 days = 3 points
21–30 days = 4 points

2. Thinking about your overall mental health, for how many days during the past thirty days was your mental health not good? _____ days
Award yourself the following points based on the total number of days:

0–5 days = 1 point
6–12 days = 2 points
13–20 days = 3 points
21–30 days = 4 points

Score: _____

Scoring:

Record your total scores for each section below and add them together to achieve your final score:

Section 1 total: _____
Section 2 total: _____
Section 3 total: _____
Section 4 total: _____

Final Score: _____

If you scored 46 or more, you have a high probability of a tick-borne disorder and should see a health-care provider for further evaluation.

If you scored between 21 and 45, you possibly have a tick-borne disorder and should see a health-care provider for further evaluation.

If you scored under 21, you are not likely to have a tick-borne disorder.

MSIDS: Overlapping Factors Contributing to Chronic Illness

1. Lyme disease and co-infections
2. Immune dysfunction
3. Inflammation
4. Environmental toxins
5. Functional medicine abnormalities with nutritional deficiencies
6. Mitochondrial dysfunction
7. Endocrine abnormalities
8. Neurodegenerative disorders
9. Neuropsychiatric disorders
10. Sleep disorders
11. Autonomic nervous system dysfunction and POTS
12. Allergies
13. Gastrointestinal disorders
14. Liver dysfunction
15. Pain disorders/addiction
16. Lack of exercise/deconditioning

Table 1: Symptoms and Associated Medical Conditions on the Sixteen-Point MSIDS Map

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Unexplained fevers, sweats, chills, or flushing	• Lyme disease (chronic and other bacterial, viral, parasitic, and fungal infections) • Babesiosis • Malaria • Brucellosis • Hyperthyroidism • Hormonal failure (early menopause) • Tuberculosis* • Non-Hodgkin's lymphoma* • Panic disorders • Autoimmune disorders • Inflammation	• CBC with a white cell count • CMP with liver functions • Giemsa stain and malarial smears • *Babesia* IFA • *Babesia* WA-1/*duncani* titers • *Babesia* FISH • *Babesia* PCR • Thyroid function tests (TFTs) • Sex hormone levels • Chest X-ray/PPD • Antinuclear antibody (ANA) • Rheumatoid factor (RF) • Erythrocyte sedimentation rate (ESR) • C-reactive protein (CRP) • Cytokine panel
Unexplained weight change, either loss or gain	• Lyme disease • Certain co-infections (brucellosis, among others) • Hormonal disorders (thyroid, adrenal, low sex hormones) • Metabolic syndrome with increased insulin secretion • Malignancy*	• Lyme ELISA • IgM/IgG Western blot • *Brucella* antibodies/agglutination test • TFTs • Sex hormones • DHEA/cortisol • HbA1c with insulin levels • Lipid profile • Appropriate cancer screening
Fatigue, tiredness	• Lyme disease and associated co-infections • Immune dysfunction • Inflammation • Environmental toxins and mold • Functional medicine abnormalities with nutritional deficiencies • Mitochondrial dysfunction • Endocrine abnormalities • Neurodegenerative disorders	• Lyme test, including IgM/IgG Western blots (IGeneX/specialty labs preferable; evaluate for Lyme specific bands, 23 [OspC], 31 [OspA], 34 [Osp B], 39, 83–93) • *Babesia microti* IFA • *Babesia duncani*/WA1 • *Babesia* FISH • *Babesia* PCR • *Borrelia hermsii*

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Fatigue, tiredness *(continued)*	• Neuropsychiatric disorders • Sleep disorders • Autonomic nervous system dysfunction and POTS • Allergies • Gastrointestinal disorders • Liver dysfunction • Pain disorders/addiction • Lack of exercise/deconditioning	• *Ehrlichia* and *Anaplasma* titers • *Bartonella* IFA, PCR +/– FISH • *Mycoplasma* (including *M. fermentans*) • Chlamydia pneumonia • RMSF, Q-fever, typhus • Tularemia • *Brucella* • Viruses (HHV6, EBV, CMV, West Nile) • CBC, CMP • ANA, RF • ESR, CRP • Ganglioside antibodies • Complement studies • CPK • HLA testing (DR2, DR4, B27) • GM1AB IgM/IgG, Mag IgM/IgG ABs, ASI GM AB IgM/IgG • Immunoglobulin levels (IgM, IgA, IgG) • Cytokine panels • Six-hour urine DMSA challenge for heavy metals • Mineral levels (serum magnesium, RBC mag++, iodine, zinc) • Parasite studies (stool CDSA, blood) • Food allergy panel (IgE and IgG) • Antigliadin AB/TTG • Hormonal studies (thyroid: T3, free T3, T4, reverse T3, TSH, DHEA/cortisol salivary testing, sex hormone levels: estradiol, progesterone, testosterone, both total and free, DHT, SHBG, pregnenolone, IgF1) • Five-hour glucose tolerance, with insulin levels • Tilt table with ANS evaluation • B_{12}, folate • MMA and HC levels

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Fatigue, tiredness *(continued)*		• MTHFR (methylenetetra-hydrofolate reductase), genetic • Mold (*Stachybotrys* titers, mold plates) and ERMI (Environmental Relative Moldiness Index) testing • Organix test (Metametrix Labs) for EI • Lipid oxidation: thiobarbituric acid reactive substances assay (TBARS) and lipid peroxides • DNA oxidation (8-OhdG, autoanti-bodies to oxidized DNA, modified Comet assay) • Protein oxidation (protein carbonyls) • Sleep studies • Neuropsychiatric evaluation with SPECT scans • MRI brain scan
Unexplained hair loss	• Lyme disease and co-infections • Stress • Inflammation • Dermatological disorders* • Autoimmune disorders • Pregnancy* • Mineral deficiencies • Hormonal disorders	• Infections • Mineral levels • Iron deficiency • Thyroid deficiency • ANA • ESR, CRP • Cytokine panel • Dermatological evaluation
Swollen glands	• Lyme disease and co-infections, especially *Bartonella* and tularemia if lymph nodes are significantly enlarged • Viruses such as mononucleosis/ Epstein-Barr virus • Malignancy*	• Lyme and co-infections • Appropriate cancer screening
Sore throat	• Lyme disease (if symptom comes and goes in monthly cycles) • Strep* • Viral infections • Allergies	• Throat swab and/or culture for strep • Test for viruses • Lyme and co-infections • Allergy testing

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Testicular pain (men), pelvic pain (women)	• Lyme disease • Epididymitis with or without orchitis* • Testicular torsion* • Endometriosis/ovarian cysts* • Urinary tract infection (UTI)*	• Lyme • Physical examination with urethral swabs • Abdominal/pelvic ultrasounds • Urinalysis and culture
Unexplained menstrual irregularity	• Lyme disease • Hormonal dysregulation • Stress	• Female hormones and prolactin levels • Lyme
Unexplained milk production, breast pain	• Lyme disease • Hormonal dysregulation • Fibrocystic breast disease*	• Female hormones and prolactin levels • Serum iodine levels • Significant caffeine use? • Lyme testing
Irritable bladder or bladder dysfunction	• Interstitial cystitis, with or without Lyme disease and *Bartonella* • Dropped bladder* • BPH (benign prostatic hypertrophy with outlet obstruction)* • UTI (bacterial)* • Fungal infections • MS and diseases that affect nerve function	• Urinalysis (UA) • Culture and sensitivity (C+S) • Urological examination with scope and cystometric studies • Lyme and co-infection • Testing for MS (VEP, AEP, MRI, spinal tap checking for oligoclonal bands and MBP)
Sexual dysfunction or loss of libido	• Lyme with overlapping co-infections • Low sex hormones (testosterone, estrogen) • Psychological factors	• Lyme and co-infections • Hormone evaluations: testosterone, free T, DHT, DHEA-S, SHBG, estradiol, pregnenolone and progesterone (women) • Check thyroid and adrenal if sex hormones normal • Psychological evaluation
Upset stomach	• GERD with reflux* • *H. pylori** • Gallbladder dysfunction* • Food allergies	• GI testing: serum antibodies for *H. pylori* +/– breath test • Upper endoscopy • Food allergy testing

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Upset stomach *(continued)*	• Stress • Medications* • Lyme disease	• Evaluation of side effects of medications • Lyme
Change in bowel function (constipation or diarrhea)	• Irritable bowel syndrome (IBS) • Small intestinal bowel overgrowth (SIBO) • Inflammatory bowel disease (IBD) • Celiac disease • Food allergies and intolerances • Stress • Dehydration* • Infections (*E. coli* 0:157, *Salmonella, Shigella, Campylobacter, Yersinia, Clostridium difficile,* rotaviruses, parasites) • Magnesium deficiency • Lyme disease • *Candida*	• CBC • CMP with electrolytes, BUN/creatinine, liver functions (LFTs) • Mineral levels • Antigliadin and TTG levels • Food allergy panel • Breath test for small intestinal bowel overgrowth (SIBO) • Stool cultures: bacteria, parasites, *Candida* • Stool for *Clostridium difficile* toxin A and B • Stool CDSA (comprehensive digestive stool analysis) • GI evaluation with colonoscopy • Lyme
Chest pain or rib soreness	• Lyme disease • Costochondritis (inflammation in the ribs) • Coronary artery disease* • Fractures*	• Lyme • EKG and cardiac evaluation, if necessary • Physical examination (pushing on the ribs is usually painful with costochondritis) • X-ray if suspecting fractures (pain, rub on auscultation)
Shortness of breath, cough	• Over 90 percent of coughs are due to allergic rhinitis with a postnasal drip, with or without asthma with reactive airway disease, and GERD with reflux* • *Babesia* presents with an atypical cough and "air hunger" • COPD* • Interstitial lung disease • Malignancy in smokers* • Inflammation	• *Babesia microti* and *duncani* IFA, FISH, PCR, Giemsa stain • Allergy evaluation • Pulmonary function tests (PFTs) • Arterial Blood Gas (ABG)/oximetry • Diffusing capacity (Dlco) • Chest X-ray • Rapid CT scan chest • Ongoing cough should be evaluated by a pulmonologist, with bronchoscopy if a cough persists without an obvious etiology • Cytokine panel

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Heart palpitations, pulse skips, heart block	• Lyme disease, co-infections • Inflammation • Stress • Anxiety • Reactive hypoglycemia • POTS • Caffeine* • Medications* • Heart disease with arrhythmias*	• Lyme disease and co-infections • Cytokine panel • EKG • Holter monitor and stress testing in appropriate clinical settings • Five-hour GTT, with insulin levels • Tilt table with ANS evaluation • Evaluate side effects of medications
Any history of a heart murmur or valve prolapse	• Q-fever endocarditis • *Brucella* endocarditis • Bacterial endocarditis* • Mitral valve prolapse* • Heart valve abnormalities* • History of rheumatic fever* • PFO (patent foramen ovale)* • Lyme disease	• EKG • Echocardiogram +/– transesophageal echocardiogram (TEE) • Cardiac evaluation • Lyme disease and co-infections • Q-fever with phase I and phase II antibody titers • *Brucella* titers/agglutinating antibodies
Joint pain or swelling	• Lyme disease and co-infections • Autoimmune diseases • Inflammation • Osteoarthritis (OA)* • Gout* • Acute bacterial infections (joint sepsis)* • Acute trauma*	• Lyme disease and co-infections • ANA, RF • CCP • ESR, CRP • Autoimmune markers if appropriate (ss and ds-DNA, anti-RNP, etc.) • Cytokine panel • Uric acid levels • X-rays • MRI of the joint, if appropriate • Tap of joint to check for infection
Stiffness of the joints, neck, or back	• Lyme disease and co-infections • OA • Autoimmune diseases • Muscle strain* • Trauma*	• Lyme disease and co-infections • X-rays • Autoimmune markers

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Muscle pain or cramps	• Lyme disease and co-infections • Inflammation • Myositis • Trichinosis • Potassium and magnesium deficiencies • Dehydration*	• Lyme disease and co-infections • Cytokine panel • CPK • Aldolase and LDH levels • Eosinophil count with *Trichinella* ELISA • Serum and RBC magnesium levels • K+ level • BUN/creatinine on CMP
Twitching of the face or other muscles	• Lyme disease • *Bartonella* • Magnesium deficiency • Stress • Caffeine* • Sleep deprivation • Motor neuron diseases (ALS causes characteristic twitching in the extremities, tongue with loss of the muscles in the thenar eminence)	• Lyme disease and co-infections • *Bartonella*: IFA, PCR • RBC and serum magnesium levels • EMG to rule out ALS and motor neuron diseases
Headaches	• Lyme disease and co-infections • Food allergies • Reactive hypoglycemia • Migraines • Mineral deficiencies with environmental toxins • Mold • Tension headaches with stress • Inflammation • Caffeine withdrawal* • Medications* • Trauma* • CNS infections • Tumor*	• Food allergy • Five-hour glucose tolerance, with insulin levels • Serum and RBC mineral levels • Six-hour urine DMSA testing for heavy metals, and Organix, if environmental toxin exposure • *Stachybotrys*/mold toxins, ERMI • Lyme disease and co-infections • Cytokine panel • Psychological evaluation if history of trauma and PTSD • CT scan/MRI brain
Neck cracks, neck stiffness	• Lyme disease • OA*	• Lyme disease • X-rays or MRI, if severe

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Neck cracks, neck stiffness *(continued)*	• Muscle strain* • Bacterial and viral meningitis (stiff neck, often with associated light and sound sensitivity, headaches, occasional vomiting, if meningitis. Meningococcal and other bacterial meningitis are often clinically more severe than the presentation with acute neurological Lyme disease)*	• Neurological evaluation with spinal tap, if clinically appropriate
Tingling numbness, burning or stabbing sensations	• Lyme disease • *Bartonella* • Autoimmune disorders • Carpal and cubital tunnel or any nerve entrapment syndrome (thoracic outlet)* • Diabetes* • Hypothyroidism* • Pregnancy* • Heavy metal toxicity (Hg, Pb, As) or other environmental toxins (TCE) • Vitamin deficiencies • Immune deficiency • Mitochondrial dysfunction • MS • Strokes or TIAs* • Anxiety, with hyperventilation	• Lyme disease and co-infections • GM1 AB IgM/IgG, Mag IgM/IgG ABs, ASI GM AB IgM/IgG • EMG • Small fiber nerve biopsy +/– ANS evaluation • Hypothyroidism (T3, T4, free T3, TSH) • B-HCG • Blood sugar and HbA1c levels • B_{12} • Folate • MMA and HC levels • Immunoglobulin levels with subclasses • Six-hour urine DMSA challenge for heavy metal burdens • Accuchem laboratory evaluation for environmental toxin exposure, if appropriate (blood, fat biopsy) • Lipid peroxide levels and other markers of oxidative stress • MS (MRI, VEP, AEP, spinal tap for MBP, oligoclonal bands) • CT head or MRI, if suspecting acute stroke or TIA • Neuropsychiatric evaluation

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Facial paralysis (Bell's palsy)	• CNS Lyme disease • CNS viral infections (herpes viruses) • Stroke* • Sarcoidosis* • Trauma*	• Brain CT scan or MRI • Lyme disease with lumbar puncture (LPs can be negative in early and late Lyme) • Spinal tap, rule out lymphocytic meningitis • Viral titers • Kveim test with ACE level and chest X-ray, if ruling out sarcoid
Eyes/vision: double, blurry, floaters	• Lyme disease • Co-infections, especially *Bartonella* • Inflammation • Environmental toxins • Functional medicine abnormalities • Concussion* • Trauma* • Stroke* • Brain tumor compressing the optic nerve* • Accommodation problems with aging*	• Lyme disease and co-infections • Eye examination • Cytokine panel • Brain CT scan or MRI • Organix/ION, with functional medicine workup
Ears/hearing: buzzing, ringing, ear pain	• Lyme disease • Co-infections • Heavy metal burdens (Hg) • Medications*	• Lyme and co-infections • Six-hour urine DMSA challenge for heavy metals • Evaluate medication side effects (macrolides)
Increased motion sickness, vertigo	• Lyme disease and co-infections • Viral infections (acute labyrinthitis) • Environmental toxicity, including heavy metal burdens • Eighth nerve or cerebellar disorders	• Lyme disease and co-infections • Six-hour urine DMSA challenge for heavy metals • Organix/ION • Brain CT Scan or MRI • ENT evaluation with ENG
Light-headedness, wooziness, poor balance, difficulty walking	• Lyme disease and co-infections • Metabolic disorders • Environmental toxin exposure • Functional medicine abnormalities	• Lyme disease and co-infections • Blood alcohol and ammonia levels • Six-hour urine DMSA challenge • Organix/ION

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Light-headedness, wooziness, poor balance, difficulty walking *(continued)*	• Reactive hypoglycemia • POTS • Inflammation • Neurological diseases (MS, ALS) • Strokes*	• Five-hour GTT with insulin levels • Tilt table, with ANS evaluation • Cytokine panel • Brain CT Scan or MRI • Neurological evaluation
Tremor	• Lyme disease and co-infections • Mercury toxicity • Environmental toxins (pesticides) • Functional medicine abnormalities • Hyperthyroidism • Hypoglycemia • Anxiety • Caffeine* • Medication*	• Lyme disease and co-infections • Six-hour urine DMSA challenge • Organix/ION • Blood sugar (5-hour GTT) • Thyroid functions (T3, free T3, T4, TSH) • Evaluate medication side effects
Confusion, difficulty thinking	• Lyme disease and co-infections • Viral encephalitis • Metabolic abnormalities • Inflammation • Reactive hypoglycemia • POTS • Strokes and neurological injury* • Hypothyroidism • Heavy metal burdens and other environmental toxins • Mold • Functional medicine abnormalities • Alzheimer's disease • Jacob-Creutzfeldt (prion disease)* • Vitamin deficiencies	• Lyme disease and co-infections • Blood alcohol and ammonia levels • Cytokine panel • Five-hour GTT, with insulin levels • Tilt table • Thyroid (T3, free T3, T4, TSH) • Six-hour urine DMSA challenge for heavy metals • Mold (*Stachybotrys* titers, mold plates, ERMI) • Organix/ION testing, (Metametrix/Accuchem) • Lumbar puncture with CT or MRI, with neurological consultation if appropriate for severe cases • Apo E positive • B_{12}/folic acid
Difficulty with concentration or reading	• Lyme disease and co-infections • Inflammation • ADD/ADHD* • Reactive hypoglycemia • POTS • Food allergies and intolerances • Heavy metals or environmental toxins (TCE, mold)	• Lyme disease and co-infections • Cytokine panel • Five-hour GTT, with insulin levels • Tilt table, with ANS evaluation • Food allergies • Six-hour urine DMSA challenge • Organix/ION testing

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Difficulty with concentration or reading *(continued)*	• Functional medicine abnormalities • Sleep deprivation • Hypothyroidism • Metabolic abnormalities • Depression/anxiety • Vitamin deficiencies	• Testing for environmental toxin exposure • Mold (*Stachybotrys* titers, mold plates, ERMI) • Sleep studies • Thyroid function (T3, free T3, T4, TSH) • Blood alcohol and ammonia levels • Neuropsychiatric evaluation • B_{12}/folic acid
Forgetfulness, poor short-term memory	• Lyme disease and co-infections • Inflammation • Viral encephalitis • Metabolic abnormalities • Reactive hypoglycemia • POTS • Strokes and neurological injury* • Hypothyroidism • Heavy metal burdens and other environmental toxins • Mold • Functional medicine abnormalities • Alzheimer's disease • Jacob-Creutzfeldt (prion disease)* • Vitamin deficiencies	• Lyme disease and co-infections • Cytokine panel • Blood alcohol and ammonia levels • Five-hour GTT, with insulin levels • Tilt table, with ANS evaluation • Thyroid (T3, free T3, T4, TSH) • Six-hour urine DMSA challenge • Organix/ION • Testing for environmental toxin exposure (Metametrix/Accuchem) • Mold (*Stachybotrys* titers, mold plates, ERMI) • Lumbar puncture with CT or MRI, with neurological consultation if appropriate for severe cases • Apo E positive • B_{12}/folic acid
Disorientation: getting lost, going to wrong places	• Lyme disease and co-infections • Inflammation • Viral encephalitis • Metabolic abnormalities • Strokes and neurological injury* • Hypothyroidism • Heavy metals; environmental toxins • Mold exposure • Functional medicine abnormalities • Alzheimer's disease • Jacob-Creutzfeldt (prion disease)*	• Lyme disease and co-infections • Cytokine panel • Blood alcohol and ammonia levels • Thyroid (T3, free T3, T4, TSH) • Six-hour urine DMSA challenge for heavy metals • Organix/ION • Environmental toxin exposure • Mold (*Stachybotrys* titers, mold plates, ERMI) • Lumbar puncture with CT or MRI, with neurological consultation, if appropriate for severe cases • Apo E positive

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Difficulty with speech or writing	• Lyme disease and co-infections • Inflammation • Viral encephalitis • Metabolic abnormalities • Reactive hypoglycemia • Strokes and neurological injury* • Parkinson's disease • Hypothyroidism • Heavy metals and other environmental toxins • Mold exposure • Functional medicine abnormalities • Alzheimer's disease • Jacob-Creutzfeldt (prion disease)*	• Lyme disease and co-infections • Cytokine panel • Blood alcohol and ammonia levels • Five-hour GTT with insulin levels • Thyroid (T3, free T3, T4, TSH) • Six-hour urine DMSA challenge for heavy metals • Organix/ION • Environmental toxin exposure • Mold (*Stachybotrys* titers, mold plates, ERMI) • Lumbar puncture with CT or MRI, with neurological consultation if appropriate, for severe cases • Apo E positive
Mood swings, irritability, depression	• Lyme disease and co-infections • Inflammation • Heavy metal burdens • Environmental toxins • Mineral deficiencies • Functional medicine abnormalities • Mold • Sleep deprivation • Trauma* • PTSD • Depression • Medication* • Food allergies and intolerances • Reactive hypoglycemia	• Lyme disease and co-infections • Cytokine panel • Neurotransmitter levels • Six-hour urine DMSA challenge for heavy metals • Serum mineral levels • Organix • Environmental toxins • Mold (*Stachybotrys* titers and mold plates, ERMI) • Sleep evaluation • Food allergy profile • Five-hour GTT, with insulin levels • Evaluate medication side effects
Disturbed sleep: too much or too little or early awakening	• Lyme disease and co-infections • Inflammation with pain • Nocturia (urination several times per night secondary to bladder problems, BPH)* • Depression or anxiety • Medication* • Caffeine use late in the day*	• Sleep study • Lyme disease and co-infections, • Cytokine panel • Neurotransmitter levels • Urological evaluation, with urinalysis/culture and sensitivity • Medication evaluation

Table 1 (*continued*)

Symptoms	Possible Related Medical Conditions	Laboratory Testing to Consider
Disturbed sleep: too much or too little or early awakening *(continued)*	• Reactive hypoglycemia • Obstructive sleep apnea (OSA)* • Restless leg syndrome (RLS)*	• Five-hour GTT with insulin levels • Neuropsychiatric evaluation
Exaggerated symptoms or worse hangover from alcohol	• Lyme disease and co-infections • Nutritional deficiencies • Functional medicine abnormalities	• Lyme disease and co-infection • Serum and RBC mineral levels • Organix/ION
*These medical conditions are not generally part of the MSIDS map but are part of a differential diagnostic list that should be considered in a patient with those symptoms.		

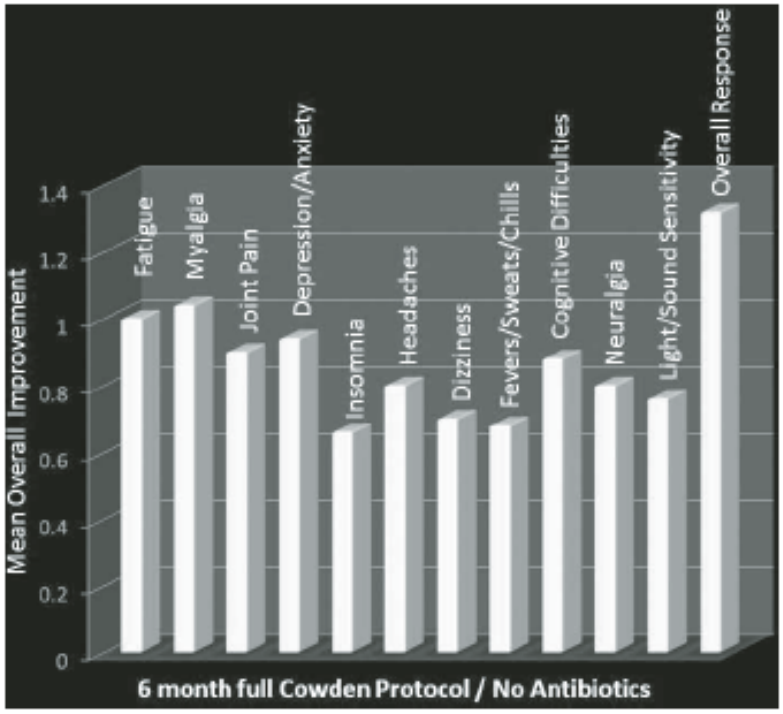
Table 2: Designing Combination Treatment Therapies

Cell Wall Form	Cystic Forms	Intracellular Location
Penicillins: • Amoxicillin • Augmentin • Bicillin (intramuscular)	Plaquenil	Macrolides: • Zithromax • Biaxin
Cephalosporins: • Ceftin • Omnicef • Cedax • Suprax	GSE	Quinolones: • Cipro • Levaquin • Avelox • Factive
IV Cephalosporins: • IV Rocephin • IV Claforan	Flagyl Tindamax	Rifampin tetracyclines: • Doxycycline • Minocycline • Tetracycline HCL
Other IV Medication: • IV vancomycin • IV Primaxin		Other IV medication: • IV doxycycline • IV Zithromax • IV Levaquin/Avelox • IV rifampin

Table 3: GI Dysfunction and Other Medical Conditions

Inflammatory Bowel Disease	• Glutamine is a primary fuel for the formation of healthy intestinal cells. • Fiber/probiotics promote the formation of short-chain fatty acids (SCFA). • Essential oils promote healthy GI function.
Chronic Fatigue Syndrome	• Bowel permeability results in systemic translocation of toxins, which may uncouple adenosine triphosphate (ATP), causing fatigue.
Fibromyalgia	• O_2 deprivation (Krebs cycle) results in cell death and tissue damage, leading to tender muscles.
Chronic Inflammation (Arthritis)	• Bowel permeability results in the uptake of antigenic protein, which may be deposited in joints.
Food Allergies	• The translocation of antigenic proteins results in allergic reactions or sensitivities with subsequent inflammation.
Hormone Imbalance (PMS, Menopause)	• Enterolactone (good estrogen) is formed in the bowel by the bacterial fermentation of fiber (i.e., flaxseed, lignans). • Impaired liver function (phases I and II) results in excessive circulating estrogens.
Cognitive/Neurological Dysfunction	• Impaired liver function facilitates free radicals attacking the CNS (myelin sheath). • Heavy metal deposits in neurons result in neurological disorders (e.g., aluminum and Alzheimer's).

Graph 1



This is a graph showing the mean overall improvement in symptoms after six months of being on the full Cowden protocol, without antibiotics. Improvements were seen with fatigue, muscle and joint pains, neurological symptoms (light sensitivity, dizziness, headaches, and cognitive problems), as well as with sleep and moods.

Table 4: Effective Herbal Protocols Used at Hudson Valley Healing Arts Center

Name	Regimen	Reasons
Zhang protocol (TCM)	Combination therapies including Allicin, HH, R-5081, Circulation P, *Cordyceps*, Puerarin, *Artemesia*, AI#3, Herbsom	Lyme disease and co-infections (*Babesia*, *Bartonella*), inflammation, sleep disorders

Table 4 (*continued*)

Name	Regimen	Reasons
Cowden protocol	Samento, Banderol, Cumunda, *Quina*, Houttuynia, Parsley, Burbur, Serrapeptase, Amantilla, *Chlorella*, zeolite	Lyme disease, certain co-infections, biofilms, detoxification, sleep disorders, anxiety
Buhner protocol	Samento, *Andrographis polygonum* (Japanese knotweed), *Stephania* root, *Smilax*	Lyme disease, co-infections, inflammation, Jarisch-Herxheimer reactions
Byron White	Combination therapies, including A-L, A-BAB, A-BART, A-BIO, A-Myco, A-P, A-V, A-EB/H6, A-FNG, Detox 1 and 2, NT-Detox, A–INFLAMM, among others	Lyme disease and co-infections (including parasites, viruses, and fungus), detoxification, inflammation

Appendix A: Treatment Protocols for Lyme Disease-MSIDS for Health-Care Providers

Treatment of Lyme disease

Treatment of Lyme disease can be divided into two major categories: acute Lyme disease and persistent Lyme disease. In both cases, the most important thing to keep in mind is that *Borrelia burgdorferi* has several forms: the cell wall form, cystic forms, and organisms in the intracellular compartment and biofilms. We also must take into account aspects of the biology of the organism, such as its long replication time, and that certain antibiotics that are bactericidal, such as penicillins and cephalosporins, will only work when the organism is actively dividing and reproducing. This implies that several rounds of antibiotics may be necessary to cover the cycles of the organism. Other antibiotics, such as the tetracyclines, are bacteriostatic, so we must have a healthy immune system to fight the infection. Unfortunately, *Borrelia* and multiple co-infections can suppress the immune system, so we must take this into account when simultaneous infections need to be cleared.

ACUTE LYME DISEASE

In the case of an uncomplicated EM rash with no systemic symptoms

According to the scientific literature, approximately 75 percent of patients are cured with a three-week course of doxycycline (100 mg PO BID) or cefuroxime axetil (500 mg PO BID). However, if patients have multiple EM rashes, or a stiff neck, headache (central nervous system symptoms), or tingling/numbness in the extremities (peripheral nervous system symptoms), then the organism has disseminated, and one month of antibiotics is insufficient, since such patients often go on to develop persistent symptoms. Another explanation as to why a three-week course of doxycycline alone may be inadequate is that doxycycline does not address cystic forms and allows spirochetes to survive.

Although three weeks of doxycycline 100 mg PO BID, or Ceftin 500 mg PO BID, cures a significant percentage of all uncomplicated EM rashes, the biology of *Borrelia burgdorferi* suggests that it may be worthwhile to offer patients the following regimen with their consent for an uncomplicated EM rash:

Month one: Plaquenil 200 mg, one PO BID, doxycycline 100 mg, two PO BID, nystatin tablets 500,000 units, two PO BID, with pulse Flagyl or Tindamax three days a week, based on body weight (body weight less than 120 pounds: 750 mg per day; between 121 and 150 pounds: 1,000 mg per day; greater than 150 pounds: 1,500 mg per day). The addition of the Flagyl or Tindamax eradicates some of the cystic forms that may arise during initial treatment. Serrapeptase, one PO BID (or similar enzymes that affect biofilms) may be used concurrently.

Month two: Plaquenil 200 mg PO BID, Omnicef 300 mg PO BID, Zithromax 250 mg PO BID (pulsed four days in a row per week), with Flagyl or Tindamax three days a week (the days off the Zithromax), with Serrapeptase one PO BID, and nystatin tablets, 500,000 units one PO BID. In the second month, we have now added a cell wall drug (Omnicef, or a different cephalosporin, such as Suprax, Cedax, or Ceftin; or a penicillin, such as amoxicillin), since cell wall forms may have persisted during the initial month of treatment with a tetracycline. Rotating the regimens in this fashion attempts to address all of the different forms of *Borrelia*, and prevent the establishment of a persistent infection.

Once the patient becomes asymptomatic for two months on treatment, stop the antibiotics and consider moving them over to an herbal protocol, as described in Chapter 9. They should remain on that for several months to ensure that there are no new symptoms.

Each situation is unique, and general guidelines may not be applicable to a specific patient. For example, a patient presenting with early neuropathy, or with a history of severe *Candida*, may not be an ideal candidate for Flagyl or Tindamax, as these drugs have the potential to increase those symptoms. However, these medications play an important role in clearing complicated infections and may help prevent patients from going on to the chronic form of Lyme disease, with the inherent suffering and disability that often ensues. Choosing a treatment regimen for a specific patient requires an open and informed dialogue. The discussion should cover the potential side effects and likely benefits of the different treatment options, as well as the patient's goals and preferences.

For an EM rash with systemic symptoms, or multiple EM rashes

Complicated EM rashes (multiple EM rashes, with or without peripheral and/or nervous system involvement) imply dissemination of the organism, and since a single tick bite may transmit multiple co-infections, it is inherent upon the practitioner to choose drugs with good CNS penetration (e.g., doxycycline, minocycline, high-dose amoxicillin, IV Rocephin), to treat all forms of *Borrelia burgdorferi*, and to expand the regimen so as to simultaneously treat associated co-infections.

If the patient presents with an EM rash and has associated day sweats, night sweats, chills, an unexplained cough, and air hunger, these symptoms are suggestive of babesiosis, and adjuvant treatment with Mepron or Malarone may be indicated early on in the treatment course. Babesiosis can go on to develop into a chronic carrier state, like Lyme disease, and keep the MSIDS patient chronically ill, so early and aggressive treatment is indicated. Testing for *Babesia* often requires a panel approach to pick up the organism (Giemsa stain, IFA for *Babesia microti* and *duncani*, *Babesia* FISH test, and/or PCR), so one negative test does not rule out the disease. An inadequate response to a Lyme regimen, and a positive clinical response to antimalarial therapy, most likely indicates the presence of the organism.

When a patient presents with unusual stretch marks, new severe neurological symptoms (neuropathy, severe encephalopathy, and a new onset of a seizure disorder), or new ophthalmological symptoms, with or without enlarged lymph nodes, consider a diagnosis of *Bartonella*. In that case the patient may require rotations of double intracellular drug combinations such as doxycycline and rifampin, doxycycline and a macrolide, or doxycycline and a quinolone drug.

Lyme Disease: Diagnosis and Treatment Regimens

SYMPTOMS	TESTING	TREATMENT
• EM rash • Flulike symptoms • Migratory joint & muscle pain • Fatigue • HA • Paresthesias c&g • Cognitive difficulties • Psych abnormalities • Sleep disorders • Neck stiffness • Photophobia & photophobia • Sx generally c&g	• ELISA/C6 peptide • Western blot IgM, IgG (combining multiple strains yields better results. Look for *Borrelia* specific bands, i.e., 23, 31, 34, 39, 83–93 kDa) • PCR urine and blood • Lyme dot blot/RWB • Lyme serum antigen • Lymphocyte transformation test • Test for co-infections • Rarely, biopsy & culture • Silver staining	• Cell wall: penicillins, cephalosporins, carbapenems, vancomycin • Cystic: Plaquenil, GSE Flagyl, Tindamax • Intracellular: macrolides, tetracyclines, quinolones, rifampin

LYME DISEASE AND ASSOCIATED INFECTIONS

Bacterial Infections

Lyme disease (*Borrelia burgdorferi*)**:** Combine antibiotics to address all bacterial forms of *Borrelia* so as to overcome its ability to shift between different forms or go dormant and evade immune surveillance. Use natural enzymes to address biofilms, and continue treatment until the patient is symptom-free for two months.

Cell wall forms: Use cell wall agents (primarily penicillins and cephalosporins). Oral options include amoxicillin, Augmentin, Ceftin, Cedax, Omnicef, or Suprax, and intramuscular (IM) Bicillin is an extremely effective choice in persistent Lyme disease/MSIDS. IV medications such as Rocephin and Claforan are especially useful in patients with significant CNS disease, or who have failed oral and IM regimens. Although Rocephin has been better studied, Claforan can be used in patients with gallstones, where IV Rocephin is relatively contraindicated. Other useful cell wall agents include IV vancomycin. IV vancomycin can be a particularly effective choice in the patient whose other drug regimens have failed. The initial dosage is based on the patient's body weight and may be adjusted subsequently based on trough levels. Most patients have required dosages in the range of 1,000 to 1,250 mg Q twelve hours to get a trough level in the proper range (check with your laboratory for trough ranges).

The following are examples of dosages of oral cell wall medications in adults: amoxicillin 500 mg, and 875 mg capsules or tablets are frequently used in several different combinations. Typical dosages of antibiotic regimens described in the medical literature to treat Lyme disease have often been found to be ineffective in clinical practice. Higher dosages may be necessary, and in my clinical experience, I have found them to be safe and well tolerated. Examples: amoxicillin 875 mg, two to three PO BID with probenecid 500 mg, one PO BID with meals.

Beginning dosages will depend on the patient's body weight. Check an amoxicillin peak and a trough level and adjust the dose. The peak should be between 12 and 15. If the peak is suboptimal, or the patient has an inadequate response, increase the dose. Effective dosages are typically 875 mg, three PO BID or 500 mg, six PO BID in adults. Some physicians increase dosages to 7,000 mg to 8,000 mg/per day if CNS disease is present or the response to treatment is inadequate. Probenecid is used to increase the levels of the cell wall drugs in the blood, but probenecid should be avoided if there is a sulfa sensitivity, and used with caution if there is a history of kidney stones.

Other cell wall drugs/penicillins include: Augmentin, 875 mg to 1,000 mg, one to two PO BID or Q 12. This may be used alone or added to amoxicillin if the patient has done well with longer-acting drugs in the past (such as Bicillin) but has clinical breakthroughs due to inadequate trough levels when solely on amoxicillin. For severely ill patients, and patients who cannot easily tolerate oral medications (GI intolerance, *Candida*), IM Bicillin 1.2 million units IM, two to four times per week versus 2.4 million units two times per week should be considered. This is one of the most effective treatment regimens we have found to treat Lyme disease, especially in patients who have failed with other oral medications. The higher the dose of Bicillin, often the better the clinical efficacy. Use Emla or lidocaine cream one hour prior to the injection and warm the Bicillin to body temperature just prior to use to decrease pain over the injection site. An ice pack may also be applied one or two minutes before the injection to minimize discomfort. Massage the area well right after the injection for two to three minutes, and repeat several times per day, to both prevent localized inflammation, and ensure deep tissue penetration of the drug.

Other cell wall drugs: Oral and IV cephalosporins. These are also particularly effective in the patient with Lyme-MSIDS.

Simply because a patient has not responded to one cell wall drug (penicillin or cephalosporin) does not mean that they won't have a positive clinical response to different drugs in the same class. Frequently used medications and dosages that have been found to be effective include:

> Oral cephalosporins: Ceftin, 500 mg, one to two PO BID; Omnicef, 300 mg one to two PO BID; Cedax, 400 mg one QD to BID; Suprax, 400 mg one QD to BID. Second- and third-generation cephalosporins are preferable to first-generation drugs (Keflex is ineffective and should not be used).
>
> IV cephalosporins: IV Rocephin or similar agents should be considered for patients with resistant neurological syndromes or manifestations of Lyme disease that could lead to significant disability (optic neuritis, Bell's palsy, severe meningitis/encephalitis) and in those who did not respond to oral or intramuscular therapies. Informed consent as to the potential side effects of the drugs and IV lines must be discussed with patients, including allergic reactions, line infections, phlebitis, and gallbladder complications.
>
> Rocephin: 2 g IV QD, five to seven days per week, up to 2 g IV Q 12 pulsed four to five days per week. Use Actigall, 300 mg one PO BID, to help prevent sludge and gallstones. The utility of Actigall has not been demonstrated in a published clinical trial, but we have found it to be effective in our clinical practice in helping to prevent gallbladder complications. A gallbladder ultrasound prior to the start of treatment may be appropriate in patients with risk factors for cholecystitis. We also regularly use a baby aspirin and

fish oils to try and prevent the occurrence of phlebitis. While on Rocephin, check a CBC and CMP with liver functions every two weeks, and use liver support (e.g., NAC, alpha-lipoic acid, Hepa #2, milk thistle) as necessary if there is any evidence of a transaminitis (elevated liver functions). Liver functions often return to normal quickly after the drug is stopped.

Other common IV medications: Claforan, 2 g IV Q8–12. May be used as a substitute for Rocephin if there are gallbladder problems. Precautions: agranulocytosis (leukopenia/ neutropenia, thrombocytopenia, with or without anemia). Check a CBC and CMP every two weeks, or more frequently if any significant hematological abnormalities appear.

IV vancomycin: 1 to 1.25 gms/Q 12 hours is the typical dose for most patients (check peak and trough levels—acceptable trough levels vary by laboratory, but the usual range should be between 10 and 15). "Red man syndrome," which is not a true allergic reaction but a common side effect of the drug, can often be prevented or minimized by administering Benadryl 25 mg to 50 mg PO or IV before each dose. Using a nonsedating antihistamine (Zyrtec, Allegra, Claritin) to block H1 histamine receptors with Zantac or Pepcid to block H2 histamine receptors can be helpful if there are breakthrough symptoms. IV vancomycin can be useful in patients if other IV regimens have failed, and with those patients who are allergic to penicillins and cephalosporins.

IV Primaxin: 500 mg IV Q6. It is a less commonly used drug regimen, due to the inconvenience of the frequent dosing regimen.

IV Cleocin: This is the last of the common IV regimens to consider. It may be useful for Lyme patients with overlapping babesiosis for whom other oral *Babesia* regimens have failed and with patients who are intolerant of other medications. The dosage is typically 600 mg IV Q8, or 900 mg IV Q12.

Cystic forms (L-forms, S-forms, spheroplasts, cell wall deficient forms): Use Plaquenil, +/– grapefruit seed extract (GSE), Flagyl, or Tindamax. GSE can be used when there is a contraindication to using Plaquenil (such as in the case of psoriasis) and also when Flagyl and Tindamax need to be avoided because of a history of associated *Candida* or a significant neuropathy (although they also can decrease neuropathy in certain Lyme patients). Flagyl and Tindamax can also cause an Antabuse-type effect (alcohol should be avoided while using them) and have the potential to cause severe Jarisch-Herxheimer reactions. Therefore, they may need to be pulsed (i.e., several days in a row per week, or two weeks on, two weeks off), and we routinely use high doses of B vitamins (B_6, B_{12}) and nystatin to decrease potential side effects. If any new neuropathic symptoms appear, or older neuropathic symptoms increase in severity and/or duration (i.e., increased tingling, numbness and/or burning), the drug should be stopped, and the patient reevaluated.

Intracellular location: Use tetracyclines (doxycycline, minocycline, tetracycline), macrolides (Zithromax, Biaxin), quinolones (Cipro, Levaquin, Avelox, Factive), and rifampin. Since many intracellular co-infections can persist in the Lyme-MSIDS patient with single-drug therapy, combination regimens are often more successful.

Macrolides: Zithromax: 250 mg one PO BID with meals versus 500 mg to 600 mg QD or, rarely, 2 g one to two times per week. Biaxin or Biaxin XL: 250 mg one PO BID, children; 500 mg one PO BID, adults. Biaxin XL is generally tolerated better and may be more effective with its longer half-life. Biaxin has more potential interactions with other medications than Zithromax, and both must be used carefully in patients, especially if they are on other drugs that can affect QT intervals on the electrocardiogram.

Other options: roxithromycin (Europe), ketolides such as Ketek. I have used roxithromycin effectively in treating European patients. Ketek is no longer commonly used due to black box warnings in the United States (increased LFTs).

Tetracyclines: doxycycline 100 mg, 2 PO BID with meals. Use 100 mg one PO BID/TID with meals if smaller body weight or GI intolerance. Higher doses are usually used to help get better CNS penetration. Tetracyclines should not be used while pregnant, or with children under eight years old, to avoid staining the teeth. A short course will occasionally be used by some pediatricians (ten days or less) in children under eight years old if the benefit outweighs the risk, but it is prudent to avoid the use of tetracyclines until most of the adult teeth have developed (usually by eleven to twelve years old). Don't mix with dairy, antacids, or vitamins with minerals. Avoid direct sun; wear a 45 SPF or higher sunblock. Do not lie down within one hour of ingestion to avoid reflux esophagitis. Consider Doryx if there is severe gastrointestinal intolerance to tetracyclines, or Monodox, as these may be better tolerated forms of doxycycline.

Minocycline: 50 to 100 mg PO BID. Watch for staining of skin and autoimmune reactions. Higher doses may cause dizziness.

Tetracycline: 250 mg or 500 mg capsules: one to two g per day total, BID–QID. GI intolerance may be higher with this form of a tetracycline, which is taken on an empty stomach, and therefore other forms of tetracyclines may be preferable.

Quinolones: (PO/IV). Cipro 500 mg one PO BID, Levaquin 500 mg one PO QD, Avelox 400 mg QD, Factive 320 mg one PO QD. Cautions with quinolones: prolonged QT intervals on the electrocardiogram with the potential for arrhythmias. Check with a PDR drug checker, and do not mix with certain drugs, such as macrolides, Diflucan, Sporanox, Lariam, Coartem, certain SSRIs such as Celexa, PPIs, such as Prilosec, and any other drugs affecting QT intervals. Advise patients of possible tendonitis/tendon rupture and that they should be avoiding strenuous exercise to prevent overuse of tendons during the use of a quinolone drug. Discontinue immediately if any pain is felt over the sites of tendons in the body. Antioxidants, such as alpha-lipoic acid and curcurmin, as well as magnesium, which relaxes smooth muscle and skeletal muscle, should be considered to decrease potential side effects. The higher the generation the quinolone, often the more effective the drug. Pulsing quinolones such as Factive, which is the highest generation quinolone (fourth generation) in five-day cycles may also be effective and reduces the risk of tendon damage. When patients follow these instructions, we have found the use of quinolones to be safe and effective, especially in patients co-infected with *Bartonella*. The same precautions for quinolones apply as with the tetracyclines: Do not use in

pregnancy; do not mix with antacids, or vitamins with minerals; and there may be some sun sensitivity, although usually less than is seen with tetracyclines.

Rifampin: 150 mg (if smaller body weight/children) to 300 mg PO BID with meals. Do not use when pregnant. Watch for drug interactions, as rifampin often may lower or raise levels of other medications being administered. Rifampin should be used in combination with other intracellular antibiotics to avoid resistance, and it is particularly useful in the Lyme-MSIDS patient who is suffering with multiple intracellular co-infections, such as *Bartonella*, or *Brucella*.

Designing Combination Treatment Therapies

LYME DISEASE	*BARTONELLA*	*BABESIA*
*Amoxicillin+Probenecid + Macrolide + Plaquenil *Bicillin+Macrolide+Plaquenil *Cephalosporin (oral or IV) +Macrolide+Plaquenil	+ Septra	+Mepron/Artemesia +Malarone/Artemesia +Lariam/Artemesia +Cryptolepis/or Neem
*Doxy + Plaquenil	+ Quinolone + Rifampin	+Lariam/Artemesia +Malarone/Cryptolepis
*Macrolide + Plaquenil	+ Septra + Quinolone	+Mepron+/–herbal tx +Malarone+/–herbal tx +Lariam+/–herbal tx +Artemesia or Neem +Cryptolepis

*+/–Flagyl or Tinidazole (? pulsed), +/– GSE, + Serrapeptase (or other biofilm protocol if no contraindication, i.e., bleeding tendency). Do not mix macrolides, quinolones, and/or Lariam together.
*When multiple intracellular infections are present (*Mycoplasma, Chlamydia, Brucella,* etc.), consider two intracellular antibiotics simultaneously (i.e., Plaquenil-Doxy-Quinolones). Cleocin + macrolides can also be a first-line therapy for babesiosis Cleocin + Quinine is infrequently used due to side effects.

Examples of combining cell wall/cystic/and intracellular antibiotics to treat Lyme

- Amoxicillin/probenecid/Plaquenil/Zithromax
- Ceftin or Omnicef/probenecid/Plaquenil/Biaxin
- IM Bicillin/Plaquenil/Zithromax
- IV Rocephin/Plaquenil/Zithromax

The above medications should be used with Mepron or Malarone if the patient also has babesiosis or another piroplasm. Nystatin 500,000 units 2 PO BID/TID should be used routinely to decrease yeast with a sugar-free/yeast-free diet with high-dose acidophilus/probiotics. Do not mix macrolides and quinolones and/or Lariam or other drugs that may affect the QT interval on the electrocardiogram. Consider checking an EKG in appropriate clinical circumstances. Flagyl or Tinidazole and/or GSE can be added to extend coverage for cystic forms, as well as simultaneously using a biofilm protocol (i.e., Serrapeptase).

BIOFILM FORMS

Lyme disease spirochetes have also been found to survive in biofilm forms. There are several mechanisms to prevent the formation of *Borrelia* biofilm, including using natural enzymes such as nattokinase (for maximum effect), and the destruction of *Borrelia* biofilms can be accomplished with the enzyme lumbrokinase (for maximum effect). The antibiotic doxycycline in high concentrations also has an effect on the destruction of biofilms, but there is no synergistic effect when enzymes and doxycycline are used together.

Serrapeptase, which is another proteolytic enzyme, has the added advantage of both preventing the formation of biofilms and destroying them. It is also capable of digesting blood clots (some researchers believe that *Borrelia* can persist in fibrin clots in the body), cysts, and reducing inflammation. We therefore will use enzymes like Serrapeptase, one to two capsules two times per day (NutraMedix) in select patients during and after antibiotic therapy for Lyme disease. There have been no controlled clinical trials to date on the effectiveness of using biofilm protocols in Lyme disease.

General recommendations regarding diet and the need for probiotics (acidophilus) with the use of antibiotics

It is necessary to follow a sugar-free diet, and occasionally a stricter yeast-free diet, depending on the number of antibiotics prescribed. That is because antibiotics can cause an overgrowth of yeast and deplete beneficial bacteria in the GI tract, which can lead to diarrhea. To avoid the possibility of the overgrowth of yeast and *Clostridium*, it is necessary to try and avoid all simple sugars (candies, cakes, pies, honey, molasses, white bread, white pasta, white rice, sweet fruits, such as, for example, bananas, raisins, grapes, dates, melons, mangoes) and to take an adequate amount of beneficial probiotics. Examples of commercial probiotics include Ultra Flora, *Saccharomyces boulardii*, Probiomax, and Theralac, one dose, two times per day, away from the antibiotics (one hour before or several hours later); this will generally prevent the occurrence of yeast or diarrhea. Occasionally patients will break through with loose stools and/or yeast and require the addition of another probiotic, such as VSL3, which can be ordered online. A prescription for VSL3 DS (double strength) may be provided by a health-care practitioner, if the patient's insurance covers it.

If a patient happens to develop diarrhea or yeast despite following these guidelines, they should stop taking the antibiotics until the diarrhea resolves, and call their health-care provider for further instructions. Any diarrhea that persists for more than one or two days should be evaluated with a stool specimen to check for the presence of *Clostridium difficile*. Other natural supplements, such as oregano oil (Oregacyn or OregaRESP), garlic (allicin), and GSE may also be used concomitantly two times a day to help control yeast. These can be taken at the same time as antibiotics. A prescription for Diflucan may be necessary if yeast continues to be an issue, but we usually find that it is the failure to follow a strict sugar-free diet that is often the cause of

recurrent yeast. If it is necessary to take Diflucan, it should not be taken at the same time as other drugs that can affect QT intervals, so occasionally we may prescribe it only on the weekends, away from those drugs with potential interactions, if it is absolutely necessary (excluding Lariam, which has a long half-life). Other dietary restrictions, in addition to avoiding sugar and yeast, may also be necessary if the patient has tested positive for celiac disease and food allergies/sensitivities. These dietary modifications should be integrated into the treatment plan to ensure optimal health, and to minimize any side effects of the medications.

Treatment of Bacterial Co-infections

Ehrlichiosis/anaplasmosis:

Doxycycline 100 mg, one to two BID for seven to ten days is usually adequate to treat *Ehrlichia* and *Anaplasma*. If there is an allergy, intolerance, or contraindication to using tetracyclines, then rifampin can be used instead (150 mg PO BID to 300 mg PO BID), depending on body weight. Precautions described above should be followed with the use of these medications. *Ehrlichia* can be life-threatening in the very young and elderly, so prompt therapy is essential when there is a high clinical suspicion.

Bartonella: B. henselae (cat scratch disease, ticks); B. Quintana (trench fever, lice); B. bacilliformis (Carrion's disease, sand flies):

Treatment regimens generally include rotations of intracellular antibiotics, using dosages previously described for the treatment of Lyme disease.

Combination Antibiotic Regimens for *Bartonella* and Other Intracellular Organisms

- Plaquenil/doxycycline/rifampin/nystatin
- Plaquenil/doxycycline/Zithromax/nystatin
- Plaquenil/doxycycline/Levaquin/nystatin
- Plaquenil/Zithromax/Septra
- Plaquenil/Zithromax/rifampin
- Plaquenil/rifampin/Factive
- Plaquenil/rifampin/Factive/tetracyclines (doxycycline, minocycline)

Malarone (and Mepron) may be added to the above regimens if there is associated babesiosis, but its use in regimens with rifampin may lead to lower drug levels (the same is true for tetracyclines, but may still be efficacious if dosed at higher levels).

Several patients in our practice have remained PCR positive for *Bartonella* months after treatment with single-drug therapy, so combination therapy with at least two intracellular antibiotics for several months is preferable in the treatment-resistant patient.

***Mycoplasma spp.*:**

We have had patients test positive for Mycoplasma infections such as *M. fermentans* with single-drug therapy after almost one year of continuous treatment. Therefore, combination

therapy with at least two intracellular antibiotics is preferable when there is proof of active *Mycoplasma* infection.

***Chlamydia spp.*:**

Chlamydia is an intracellular bacteria, so the same treatment regimens apply as with *Bartonella* and *Mycoplasma*.

***Rickettsial spp.*:**

Rocky Mountain spotted fever (*Rickettsia rickettsii*), typhus, Q fever (*Coxiella burnetii*): These are all gram-negative intracellular bacteria and are treated effectively in the acute stages with tetracyclines such as doxycycline 100 mg PO BID. As with ehrlichiosis, RMSF can be life-threatening in immunocompromised individuals, so prompt therapy is essential if there is a high clinical suspicion. Neither tetracyclines nor chloramphenicol (second-line therapy) are rickettsicidal, so an adequate immune system is required to use them effectively. Any high clinical suspicion (tick bite, exposure in a highly tick-endemic area) and laboratory testing showing an abnormal WBC count, thrombocytopenia, and/or elevated liver functions (similar to abnormal laboratory testing seen with *Ehrlichia/Anaplasma*) should prompt immediate treatment. Q fever titers are not specific, and false positives can be seen with other rickettsial infections and viruses. Chronic Q fever endocarditis requires long-term treatment with antibiotics. Several regimens that have been published in the medical literature include the use of doxycycline and Plaquenil for up to three years and doxycycline and quinolones (or rifampin) for several years. Use the same dosages previously described for Lyme disease and associated co-infections. These cases are best managed in conjunction with a cardiologist and infectious disease specialist.

Tularemia

Treatment regimens for Lyme patients with MSIDS infected with tularemia include IV/PO doxycycline (200 mg to 400 mg per day), quinolones, such as IV/PO Cipro (dosage based on body weight), IM/IV streptomycin (1 gram Q 12 x ten days in adults, lower dosing in children, i.e., 20 to 40 mg/kg day in divided doses), IV gentamycin (5 mg/kg per day in three divided doses), and rarely, chloramphenicol in treatment-resistant cases (50 mg/kg per day, up to 100 mg/kg per day in four divided doses). There have been treatment failures reported with beta lactam antibiotics and with intracellular antibiotics, including ciprofloxacin, tetracyclines, and macrolide antibiotics used alone. These resistant patients often required combination therapy such as doxycycline or chloramphenicol plus streptomycin or gentamycin treatment, or they responded to IV gentamycin alone for seven to ten days.

Brucellosis

Treatment for *Brucella* needs to be for a minimum of six weeks, and relapses are common if it is not caught early. Tetracyclines (500 mg PO QID) or doxycycline (100 mg to 200 mg PO BID) plus streptomycin 1 g IM QD-BID helps to decrease relapse rates. IV gentamycin (5 mg/kg per day in three divided doses) has also been effective in decreasing relapses, as has been the addition of Septa DS, one tab TID-QID, or rifampin 300 mg PO BID to a tetracycline regimen, especially in patients with CNS involvement (meningoencephalitis). In the case of *Brucella endocarditis*, triple antibiotic regimens (doxy, rifampicin, and streptomycin; or doxy, rifampicin,

and cotrimoxazole) are recommended for at least six months, until titers decrease to a minimum of 1:160.

Treatment of Parasitic Infections

Babesiosis:

First-line treatment protocols include Mepron 750 mg one to two tsp PO BID, with a high-fat meal, and Zithromax 500 mg per day (or Biaxin 500 mg PO BID), Plaquenil 200 mg PO BID, and nystatin tablets 500,000 U PO BID. Septra DS one PO BID may be added to that regimen if there are resistant or severe symptoms, and if the patient does not have a sulfa allergy. If there is an overlapping *Bartonella* infection, adding Septra DS may also be useful. Antimalarial herbs, such as artemesinin, cryptolepis, or neem may also be layered onto this regimen if the patient's malarial-type symptoms persist. Dosing varies by body weight, but average doses of artemesia are one three times per day (liposonal artemesia is one twice a day), cryptolepis one teaspoon TID (start ½ teaspoon or less, if sensitive, TID), and neem dosing may vary between thirty drops, three to four times per day. Antimalarial herbs are generally used one at a time and may be rotated, depending on the patient's clinical response. Layering up *Babesia* medications and herbs in this manner can be very helpful in treating resistant malaria-type symptoms.

Malarone is also a good choice for patients with babesiosis as there is now Mepron resistance in the United States. Malarone is usually dosed at four tablets a day for three days as a loading dose, followed by one tablet two times per day. Some MSIDS patients with severe malarial symptoms require two tablets PO BID to control their symptoms. We have seen clinical and laboratory evidence of persistent and relapsing babesiosis at lower doses and have not seen adverse effects in patients using this regimen. Patients should avoid taking CoQ10 as a vitamin supplement while on Malarone or Mepron, as it can interfere with its clinical efficacy. Malarone can be used alone as a single agent, but Mepron should always be used with a macrolide to prevent drug resistance.

Patients who previously failed regimens of Mepron or Malarone, or have intolerances to the drugs, should be rotated to clindamycin. Cleocin 300 mg, 2 PO BID-TID with Plaquenil 200 mg, 1 PO BID, Zithromax 250 mg PO BID, and nystatin 500,000 U PO BID +/– Septra DS 1 PO BID is one commonly used effective combination. Mepron, Malarone, and/or antimalarial herbs can be layered onto this treatment regimen if the patient has severe or resistant symptoms. We use IV Cleocin, 600 mg to 900 mg BID in patients with severe GI intolerance to oral clindamycin (dosing depends on body weight), or in those with severe malarial symptoms who have failed oral regimens. We do not often use the classic *Babesia* therapy of Cleocin 600 mg PO TID and quinine 325 mg two PO TID as a first-line therapy (although it may be helpful) because of the severe side effects of quinine, which include nausea, vomiting, tinnitus, and rashes in up to 50 percent of the patients. Cleocin and quinine may be reserved for babesiosis in late-stage pregnancy, as it is one of the few regimens that have been proven safe for the fetus.

Many patients who were not treated early relapse once treatment is stopped. Many of these patients still have positive PCRs (DNA probes) and positive FISH testing (RNA probes), despite months of antibabesial therapy. In those patients we often have to rotate to other antimalarial regimens, such as Coartem, four tablets PO BID for three days (day one, 7:00 A.M. and 3:00 P.M., days two and three, 7:00 A.M. and 7:00 P.M.), or Lariam 250 mg, 1 PO HS every five to seven days. Coartem is an antimalarial combination of lumafantine and artemether, and has some clinical efficacy in babesiosis. It can be used alone or with Daraprim 25 mg, 2 PO QD for three days in severely ill patients, and/or in combination with doxycycline.

Lariam is an older drug used for malarial prophylaxis but which also has clinical efficacy against babesiosis. Both Coartem and Lariam can affect the QT interval on the electrocardiogram, so they should not be used with each other, or in combination with other drugs affecting QT intervals (macrolides, quinolones, fluconazole, itriconazole, certain SSRIs, and PPIs). Lariam has possible neuropsychiatric side effects, such as seizures, hallucinations, psychosis, increased depression and paranoia, as well as frequently causing vivid dreams with occasional nausea and dizziness (usually at higher doses, not clinically significant for most patients at a half tablet every three days, or one tablet every five to seven days). Its use must therefore be limited to patients who are neuropsychologically stable and who have failed other *Babesia* regimens. It may be combined with doxycycline, Plaquenil, and artemesinin for increased clinical efficacy. Lariam has an extremely long half-life (three weeks), so it is necessary to avoid medications with effects on QT intervals for up to fifteen weeks post-Lariam in select patients.

We have found all of these combinations to be helpful and generally well tolerated, but none are 100 percent effective. Clinically lowering down the parasitic load by rotating the drug regimens is useful, as it helps many patients with resistant Lyme-MSIDS symptoms. A recent 2013 FDA warning for Lariam noted possible persistent neurological and psychiatric effects, so the drug should only be used in treating resistant babesiosis with an informed consent. In patients with life-threatening babesiosis, who are immunocompromised and have failed all other regimens, exchange transfusion is a last resort to decrease the parasitic load. Other parasitic infections are also occasionally found in the MSIDS patient, especially intestinal parasites, such as giardia, amoeba, pinworm, and hookworm, with patients occasionally testing positive for parasites such as schistosomiasis, and strongyloides. These infections are found on both serum antibody testing and stool cultures (Metametrix GI Effects, stool CDSA). Regimens including biltricide, ivermectin, pyrantel pamoate (PinX), and Alinia have been effective in certain patients with not only persistent GI symptoms, but also fatigue, headaches, and myalgias resistant to classical tick-borne therapy. Dosing for these regimens is based on the patient's body weight.

LYME AND PREGNANCY

Borrelia burgdorferi may be transmitted transplacentally to the fetus, as may associated co-infections. *Borrelia burgdorferi* has also been isolated from breast milk in a study published in 1995 by Schmidt et al. Although the incidence of transmission through breast-feeding has been debated in the scientific literature, there is nevertheless a potential risk. An open and informed dialogue with expectant mothers regarding the risks and benefits of antibiotics during pregnancy and breast-feeding should routinely take place.

Antibiotics such as penicillins, cephalosporins, and macrolides are all category B, and proven to be safe in pregnancy. Flagyl is FDA category B, but trimester and population-specific risks exist, and it should not be routinely used unless clinically indicated. Dosages, side effects, and contraindications are the same as previously discussed. Examples of antibiotic regimens used in pregnancy include oral cell wall antibiotics such as Amoxicillin 500 mg two to three PO TID to QID, or 875 mg, two to three PO BID (based on body weight and/or peak serum levels), Omnicef 300 mg one PO BID, or other oral cephalosporins such as Suprax 400 mg, one PO BID. Intramuscular injections of Bicillin LA, 1.2 million units two to three times per week are also very effective, and are useful in women with severe symptoms unresponsive to oral medication, and/or significant nausea. The long-acting effect of Bicillin may also potentially decrease the risk of maternal-fetal transmission, as regular injections avoid some of the variations seen in peak

and trough levels with oral medications. We have seen positive PCRs for *Borrelia burgdorferi* on specimens of the placenta and/or cord blood post-partum, despite women remaining on PO antibiotics, although the babies were healthy at birth. Macrolides such as Zithromax and Biaxin do not penetrate well into the placenta, but may be useful for controlling symptoms in the mother. Rarely IV medication like Rocephin is needed for maternal neurologic and/or cardiac involvement, or will be considered in the first trimester when the fetal organs are forming, especially if a woman has a history of frequent miscarriages associated with Lyme disease.

Pregnant women with active tick-borne infections should be managed in conjunction with a high-risk OB-GYN, and all medication and nutritional regimens should be coordinated with the patient's gynecologist.

VIRAL INFECTIONS

There is no specific treatment for tick-borne viral encephalopathies like Powassan encephalitis, except supportive treatment. HIV medications are being studied as a possible option for these patients. Fortunately, most infections do not result in disease, as the fatality rate can be between 10 percent and 30 percent in certain studies.

Any patient who does not adequately respond to appropriate antibiotic protocols while addressing the 16 point differential on the MSIDS map, and who has high viral titers and/or a positive PCR, may suffer from chronic viral infections (which may have been present and/or reactivated), and a trial of antiviral medication is warranted. This could include a trial of Valtrex, Famvir, acyclovir, or Valcyte in severe cases. In our experience, classical antiviral drugs such as Valtrex and Famvir do not have a significant clinical effect in the majority of MSIDS patients. Valtrex was used successfully in clinical trials at Stanford University for patients with elevated titers of HHV-6 whose chronic fatigue started shortly after a viral illness. Valcyte has significant hematological side effects and should be used with caution.

Neutraceuticals such as transfer factors, and mushroom derivatives that increase NK and T cells (which are antiviral) such as 3–6 beta-glucan, are safer alternatives with scientific studies showing efficacy. Oleuropein, the active compound in olive leaf extract, has also scientifically been shown to be virucidal against many viruses.

FUNGAL INFECTIONS/*CANDIDA*

Protecting against yeast/*Candida* is extremely important while patients are on antibiotics. Oral nystatin (and occasionally Diflucan, in severe cases), neutraceuticals such as oregano oil, garlic, berberine, and grapefruit seed extract, and low-carbohydrate diets combined with high doses of probiotics can be beneficial. Nystatin is usually dosed at two 500,000 U tablets PO BID in our patients, taken at the same time as antibiotics, with probiotics including *Saccharomyces boulardi* taken in-between doses of nystatin. In resistant cases, Diflucan or other antifungal drugs may be added QD or pulsed one to two days a week (away from medications which affect the QT interval). Nystatin in powder, liquid, or capsules is also an option for patients with more severe clinical manifestations. A trial off antibiotics and treating for systemic yeast is occasionally warranted for patients whose antibiotics are failing and who present with symptoms consistent with a *Candida* syndrome.

Immune Dysfunction

We regularly use drugs like Plaquenil (hydroxychloroquine) 200 mg PO BID to modulate an overstimulated immune system, except in patients with psoriasis, when the drug is contraindicated. Regular eye exams once a year are advised, but we have never seen a Plaquenil-induced retinopathy.

Inflammation

Classical therapies include immune modulators (Plaquenil, DMARDs), drugs with anti-inflammatory effects (macrolides, tetracyclines), NSAIDS and COX-2 inhibitors, and 2 to 4 gms IVIG for decreased immunoglobulin levels or severe neuropathy, as in small-fiber neuropathy and CIDP (chronic inflammatory demylinating polyneuropathy). Properly treating Lyme disease and associated co-infections and lowering down the total load of organisms in the body is essential in order to significantly decrease inflammation and control symptom flares. This can be accomplished with the antibiotics and classical therapies discussed above, as well as integrative therapies that focus on the down-regulation of the nitric oxide pathway to help decrease inflammatory cytokines, prostaglandins, and leukotrienes. This would include the use of LDN combined with various antioxidants (especially curcurmin, up to 2 to 4 gms per day, resveratrol, green tea extract, 200 mg per day), CoQ10 (100 mg to 200 mg per day, starting dose), B vitamins (especially B_1, B_2, B_6, methyl B_{12}), α-lipoic acid (300 mg to 600 mg two times per day), minerals such as Mag++ (average dose: 500 mg per day) and Zn++ (average dose: 15 to 30 mg per day), omega-3 FAs (minimum 2 gm per day), glutathione precursors, such as NAC (600 mg two times per day), glycine, and oral liposomal glutathione (Wellness Pharmacy) 500 mg per day.

An alkaline Mediterranean-style anti-inflammatory diet (low levels of meat, eggs, dairy, sugar, and high in healthy fruits and vegetables, with olive oil) combined with the above medications and neutraceuticals can be of significant benefit in controlling inflammation. LDN is obtained through specialty pharmacies and is dosed at 2 mg PO HS for one month, 3 mg PO HS the next month, and 4 to 4.5 mg PO HS as a final dose. Side effects include insomnia, so dosing may need to go at a slower pace for certain patients, or taken on an empty stomach upon awakening if the drug interferes with sleep. LDN should not be used in patients with frequently dosed or long-acting narcotics since it interferes with their effects and may induce narcotic withdrawal. Using two Alka-Seltzer Gold tablets (or equivalent sodium bicarbonate) to alkalize the body, combined with 1,500 mg to 2,000 mg of oral liposomal glutathione, has been effective with or without LDN in decreasing inflammation and Jarish-Herxheimer flares in up to 70 percent of patients.

Chemical Sensitivity, Environmental Illness, Heavy Metals, Mold, and Neurotoxins (external and internal biotoxins)

Many patients test positive for heavy metals. Chelation can be performed by using an oral chelation regimen (DMSA, DMPS, D-penicillamine), transdermal chelation (for children), IV chelation (DMPS, EDTA), and rectal suppositories (Detoxamine, EDTA). We generally use low-dose oral DMSA at bedtime every several days (100 mg to 200 mg) or pulsed DMSA two days in a row on the weekends (5 mg/kg to 10 mg/kg PO BID, one hour before meals), as some Lyme disease patients do not tolerate standard dosages of oral chelating agents due to Jarish-Herxheimer flares. IV chelation therapy with Disodium EDTA has also been used to treat atherosclerosis and was recently found to modestly reduce the risk of adverse cardiovascular outcomes (*JAMA*, 2013).

Nutritional supplements used Q3rd night with DMSA include *Chlorella* (split cell, seven tablets) with 600 mg NAC, alpha-lipoic acid (600 mg), and occasionally Med Caps DPO (Xymogen) if phase I and phase II liver detoxification pathways are not functioning efficiently. EDTA suppositories (750 mg) can also be added, if the patient has very high levels of lead. It is essential to use a good multimineral supplement on days the patient is not chelating (with a minimum of 800 mg to 1,000 mg calcium per day, 400 mg to 600 mg magnesium per day, zinc 30 mg per day, with trace minerals), since the chelation process removes essential minerals. Blood levels of trace minerals should therefore be checked intermittently during or after chelation (such as serum Mag++, RBC Mag++, zinc, copper, iodine, selenium, etc.) or if the patient complains of muscle cramps. These mineral supplements should be taken at least several hours away from the antibiotics to avoid interfering with absorption. Higher dose DMSA 5 to 10 mg/kg TID, one hour before meals, three days on, eleven days off (standard chelation protocols) can be used in patients with very high levels of heavy metals, usually once they are off antibiotics. The above protocols have been proven to be safe and effective for our patients.

Those individuals with chemical sensitivity/EI, and/or high levels of internal biotoxins (such as quinolinic acid) or mold neurotoxins (testing can be done through Real Time Labs) may require other detoxification protocols. This may include the use of infrared saunas, the use of binding formulas (bentonite clay, charcoal, zeolite), high-dose oral liposomal glutathione (GSH), IV GSH, increased nutritional supplementation to support detoxification (Mag++, NAC, GLY, α-lipoic acid, DIM, sulforaphane glucosinalate, methylation cofactors, and/or a phosphatidylcholine (PC) exchange) in conjunction with a diet high in protein and cruciferous vegetables. Other patients may require a modified Shoemaker protocol (cholestyramine, Welchol) as tolerated for mold toxins, apart from eliminating the sources of toxicity.

Allergies: Foods, Drugs, Environmental

Many Lyme disease patients have overlapping food allergies and sensitivities, usually secondary to an associated problem with *Candida* and a leaky gut. Classical treatment includes avoidance of allergens, rotation diets, and occasional immunizations against offending allergens. Integrative treatment includes treating an underlying *Candida* syndrome or leaky gut with dysbiosis if present, and using enzyme therapy if the patient is deficient. Some patients have reported benefits from using techniques such as Nambudripad's Allergy Elimination Techniques (NAET) to clear resistant food allergies, but we have not had enough experience with the technique to validate its effectiveness in our patient population.

NUTRITIONAL AND ENZYME DEFICIENCIES

Treatment: Replace vitamins, minerals, amino acids (AA), essential fatty acids (EFA), and enzymes (plant or pancreatic with amylase, lipase, proteases) as per test results.

MITOCHONDRIAL DYSFUNCTION

Treatment: NT factors (glycosylated phospholipids, such as those from Researched Nutritionals) three tablets two times per day, for two months, followed by three per day. Also use CoQ10, 200 mg to 400 mg per day (if not on Mepron or Malarone), and acetyl L-carnitine (1,000 mg PO BID). Other options include NADH (5 mg per day) and D-ribose, 5 gm scoops, two to three times per day for several months if there is an inadequate response. Avoid D-ribose for prolonged periods of time, due to possible effects of increasing glycosylation in patients with blood sugar problems.

NEUROPSYCHOLOGICAL DISORDERS

Health-care providers should ask about the patient's previous psychiatric history, and refer for counseling or psychiatric help, including cognitive processing therapy, *Journey* work (Brandon Bays), EMDR, or EFT (emotional freedom technique). Medications include SSRIs such as Zoloft 100 mg to 200 mg per day, buproprion (Wellbutrin XR 150 mg PO BID, Remeron 15 mg HS, and anxiolytics such as Xanax, Klonopin, and Ativan). Stress-reduction techniques include yoga, meditation, Tai Chi. Individualized herbal treatments include St. John's Wort, 5-HTP, SAM-e valerian root, kava kava, and L-theanine (typically dosed 100 to 200 mg per day).

Endocrine Abnormalities

The hypothalamic-pituitary axis may be affected in Lyme disease-MSIDS. Check FSH, LH, GH, and IgF1, antithyroid antibodies, TSH, T3 and T4, FT3/4, DHEA/cortisol, sex hormones, and occasionally leptin, MSH, ADH, and VIP levels. Use replacement dosages of hormones and correct underlying abnormalities to return levels to normal ranges.

Sleep disorders

Treatment: Activating agents in the A.M. (Provigil 100 mg to 200 mg, Nuvigil 150 mg PO QD) and/or sleep-promoting agents in the P.M., especially those that encourage deep, slow wave sleep (Lyrica 50 mg to 150 mg HS, Trazadone 50 mg to 150 mg HS, Gabitril 4 mg to 12 mg HS, Seroquel 25 mg HS, Xyrem 3 grams to 4.5 grams (6 ml to 9 ml), taken twice per night, four hours apart). Ambien and Lunesta may also be used with the above medications if necessary. Refer to the PDR for possible side effects and interactions.

Other options include balancing neurotransmitter levels (i.e., low serotonin) with 5-HTP 100 mg HS, and also using GABA for sleep. SeriPhos (phosphaditylserine) may be helpful if there are elevated levels of cortisol HS. We have also found valerian root (1,000 mg to 1,500 mg HS), L-theanine (100 mg HS), and melatonin (1 to 6 mg HS) to be effective, and they can all be mixed with classical sleep medications to increase efficacy.

Autonomic Nervous System (ANS) Dysfunction/POTS

Treatment: Salt (minimum 3 gm to 4 gm per day), increase fluids (3 liters +), consider Florinef (0.1 mg to 0.2 mg per day), Midodrine (starting dose 2.5 PO TID, maximum 5 mg to 10 mg PO TID), Cortef (5 mg PO QD starting dose, but dosing depends on level of symptoms and adrenal insufficiency), and/or B blockers (Toprol XL). Occasionally Catapres (oral 0.1 mg PO BID starting dose, or Catapres TTS patches), and SSRIs such as Zoloft are needed for an inadequate response.

Elevated LFTs

Treatment: Treat symptomatically once underlying etiologies have been ruled out and addressed. Herbal therapies can include milk thistle (silymarin) PO BID, Hepa #2 (Zhang, TCM) two capsules PO BID, NAC 600 mg PO BID, alpha-lipoic acid 600 mg PO BID.

Pain

High-dose narcotics should be avoided if possible (or used in limited quantity unless absolutely necessary, i.e., the patient has failed other therapeutic trials for pain), due to tolerance/addiction and possible effects on sleep and hormones. Low-dose Ultram may be a useful alternative in combination with other nonnarcotic drug regimens to control pain if

necessary. Narcotics also interfere with the use of LDN, which is a very useful medication in controlling inflammation and pain in the Lyme-MSIDS patient. Treating the underlying cause of the pain using the MSIDS map often helps to decrease levels of narcotics.

Appendix B: Glossary of Pharmaceutical Names

Brand Name	Generic Name
Actigall	ursodiol
Adderall (XR)	dextroamphetamine/amphetamine
Aldactone	spironolactone
Aleve	naproxen sodium
Allegra	fexofenadine
Allegra-D	fexofendadine/pseudoephedrine
Altace	ramipril
Ambien	zolpidem
Amoxicillin	amoxicillin (generics are generally used).
Anafranil	clomipramine
Arava	leflunomide
Arimidex	anastrazole
Ativan	lorazepam
Augmentin	amoxicillin/clavulanate
Avelox	moxifloxacin
Avonex	interferon beta 1 α
Baraclude	entecavir
Benadryl	diphenhydramine
Benicar	olmesartan
Betaseron	interferon beta 1b
Biaxin	clarithromycin
Bicillin	penicillin G benzathine
Biest	estradiol/estriol (compounded)
BuSpar	buspirone
Catapres	clonidine
Cedax	ceftibuten
Ceftin	cefuroxime axetil
Celebrex	celecoxib
Celexa	citalopram
Chemet	DMSA
Cimzia	certolizumab pegol
Cipro	ciprofloxacin
Claforan	cefotaxime
Claritin	loratadine
Claritin-D 24 Hr.	loratadine/pseudoephedrine
Cleocin	clindamycin
Climara	estradiol transdermal
Clomid	clomiphene
Coartem	artemether/lumefantrine
Copaxone	glatiramer

Brand Name	Generic Name
Cortef	hydrocortisone
Coumadin	warfarin
Cuprimine	penicillamine
Cymbalta	duloxetine HCl
Cytomel	liothyronine
Cytovene	ganciclovir
Daraprim	pyrimethamine
DDAVP Nasal	desmopressin nasal
Decadron	dexamethasone
Depakote	divalproex sodium
Deplin	methyltetrahydrofolate
Detrol LA	tolterodine
Diamox	acetazolamide
Dificid	fidaxomicin
Diflucan	fluconazole
Dilaudid	hydromorphone
DMSA	dimercaptosuccinic acid
Dynabac	dirithromycin
EDTA	ethylenediaminetetraacetic acid
Elavil	amitriptyline
Enbrel	etanercept
Epivir	lamivudine
Factive	gemifloxacin
Famvir	famciclovir
Fioricet	butalbital/acetaminophen/caffeine
Flagyl	metronidazole
Flexeril	cyclobenzaprine
Florinef	fludrocortisone
Fosamax	alendronate
Gabitril	tiagabine
Glucophage	metformin
Hepsera	adefovir
Humira	adalimumab
Imitrex	sumatriptan
Imuran	azathioprine
Incivek	telaprevir
Klonopin	clonazepam
Lanoxin	digoxin
Lariam	mefloquine
Lasix	furosemide
LDN	low-dose naltrexone
Levaquin	levofloxacin

Brand Name	Generic Name
Lexapro	escitalopram
Lunesta	eszopiclone
Lyrica	pregabalin
Malarone	atovaquone/proguanil
Medrol	methylprednisolone
Mepron	atovaquone
Mestinon	pyridostigmine
Mevacor	lovastatin
Minocin	minocycline
Mobic	meloxicam
Motrin	ibuprofen
MS Contin	morphine sulfate
Naprosyn	naproxen
Neurontin	gabapentin
Nuvigil	armodafinil
Oleptro	trazodone
Omnicef	cefdinir
Pamelor	nortriptyline
Parlodel	bromocryptine
Paxil	paroxetine
Percocet	oxycodone/acetaminophen
Phenobarbital (only generic)	phenobarbital
Plaquenil	hydroxychloroquine
PredForte (eye drops)	prednisolone acetate ophthalmic
Prilosec	omeprazole
Primaxin	imipenem/cilastatin
ProAmatine	midodrine
Procrit	epoetin alpha
Provigil	modafinil
Prozac	fluoxetine
Qualaquin	quinine sulfate
Questran	cholestyramine
Rebif	interferon beta 1 α
Reglan	metoclopramide
Remeron	mirtazipine
Restoril	temazepam
Rheumatrex	Methotrexate
Ribasphere	ribavirin
Rifampin	rifampin
Rilutek	riluzole
Risperdal	risperidone
Ritalin	Methylphenidate

Brand Name	Generic Name
Rocephin	ceftriaxone
Septra DS	trimethoprim/sulfamethoxazole
Seroquel	quetiapine
Solu-Medrol	methylprednisolone sodium succinate
Sonata	zaleplon
Sporanox	itraconazole
Strattera	atomoxetine
Sudafed	pseudoephedrine
Sumycin	tetracycline
Suprax	cefixime
Synthroid	levothyroxine
Tegretol	carbamazepine
Tenormin	atenolol
Tindamax	tinidazole
Topamax	topiramate
Toprol XL	metoprolol succinate
Tylenol	acetaminophen
Tyzeka	telbivudine
Ultram	tramadol
Valcyte	valganciclovir
Valium	diazepam
Valtrex	valacyclovir
Vancocin	vancomycin
Viread	tenofovir disoproxil
Victrelis	boceprevir
Vivelle-Dot	estradiol transdermal
Voltaren	diclofenac sodium
Vyvanse	lisdexamfetamine dimesylate
WelChol	colesevelam
Wellbutrin	bupropion HCl
Xanax	alprazolam
Xifaxan	rifaximin
Xyrem	sodium oxybate
Zanaflex	tizanidine
Zantac	ranitidine
Zipsor	diclofenac sodium
Zithromax	azithromycin
Zocor	simvastatin
Zofran	ondansetron
Zoloft	sertraline
Zovirax	acyclovir
Zyrtec	cetirizine
Zyrtec-D	certirizine/pseudoephedrine