The Evaluation and Treatment of Chronic Inflammatory Response Syndrome

A Summary of the Shoemaker Protocol and Directions for Future Research

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Chronic Inflammatory Response Syndrome (CIRS) describes a constellation of symptoms, associated laboratory findings and test results associated with biotoxin exposure in genetically susceptible individuals. First identified by Dr. Ritchie Shoemaker, a family physician with keen diagnostic skills and a scientific approach to individual patient care, there have been over 1700 scientific articles published on CIRS to date, many authored by him. Dr. Shoemaker’s clinical research has resulted in a step-wise approach to patient care that has been demonstrated to treat and prevent symptoms in susceptible individuals.

The diagnosis of CIRS relies on four major criteria:

1. Clinical picture consistent with biotoxin exposure:
   1. History of exposure to biotoxins
      1. Mold: exposure to toxin-producing molds and the interior environment of water-damaged buildings
      2. Lyme disease: tick bite, symptoms or signs consistent with Lyme disease (EM rash, flu-like illness following tick bite), testing consistent with history of Lyme disease
      3. Neurotoxin-producing algae or dinoflagellates: Cylindro or Microcystis, Pfiesteria or Ciguatera exposure
   2. Symptoms of biotoxin-related illness: Thorough evaluation of 36 symptoms associated with biotoxin-related illness (see symptom history below)
   3. Clinical signs of biotoxin-related illness (see physical exam below)
2. Genetic predisposition to biotoxin-related illness: inheritance of HLA DR/DQ genes that confer susceptibility to biotoxin illness as a result of impaired antigen presentation and thus decreased biotoxin removal from the body.
3. Abnormal Visual Contrast Sensitivity (VCS)
4. Abnormal laboratory results and clinical tests consistent with CIRS that may include the following:
   1. Biomarkers that are decreased in CIRS: MSH, VIP, VEGF, ADH (in relation to Osmolality); (ADH and VEGF can also be elevated)
   2. Biomarkers that are increased in CIRS: TGF-beta 1, C4a, C3a (in bacterial illness), MMP-9, Leptin, PAI-1, anti-gliadin Ab, Anti-cardiolipin Ab, von Willebrand panel; (Von Willebrand panel can be low or high)
   3. Positive culture for multiply antibiotic resistant coagulase-negative staph (MARCoNS) associated with low MSH
   4. Specific MRI NeuroQuant abnormalities
   5. Abnormal VO2 Max
   6. Abnormal pulmonary arterial pressure in response to exercise

In order to correctly diagnose CIRS, a thorough evaluation must be performed to identify the source of the biotoxin, the susceptibility of the individual, and the resulting biomarkers indicating that a chronic inflammatory response has indeed been initiated by the exposure. Once CIRS is suspected on clinical evaluation, laboratory testing is done to determine the degree of involvement. Depending on the level of suspicion, treatment can be initiated immediately, or following confirmation with laboratory tests. Follow up testing is done at the end of each step of treatment to evaluate response and the need for ongoing treatment.

**Exposure**

Sources of biotoxin exposure often come from the stew of mold, mold fragments and toxins, bacteria, and other microorganisms found in water-damaged buildings (WDB). The NIOSH estimates that up to 50% of all American buildings have water damage. Mold grows in damp environments but different mold species have different tolerance for relative humidity and the degree of saturation of building materials can predict the type of mold that might be growing. In general, a building with humidity under 60% in the summer and 45% in the winter is at a lower risk for mold growth, but any building that has suffered water damage is at risk. Sources of water damage can come from leaking pipes, poorly fitting drains, roof leaks, water intrusion into basements, and poorly ventilated crawl spaces. There was much controversy over whether a crawl space is best sealed or vented with negative pressure (air flow going from the crawl space to the outdoors), and solutions may vary by location, saturation of the crawl space dirt by ground water, and risk of flooding. When identifying potential sources of WDB biotoxins, consideration should also be given to the buildings in which one works or routinely spends time. Often individuals with CIRS will identify that they don’t feel well in a building and that they improve when they’re away, but they are not returned to the level of health experienced prior to the onset of CIRS.

Testing for biotoxin-producing mold may require a two-step evaluation: ERMI testing through Mycometrics and evaluation by a certified Indoor Air Quality (IAQ) specialist. The Environmental Relative Moldiness Test (ERMI) measures relative amounts of 26 mold species/clusters associated with WDB (Group 1) versus 10 species/clusters not associated with WDB (Group 2). Developed by EPA scientists, the index is the difference between the two groups and is reported as a number from -10 to 20. The higher the number, the greater the relative mold burden; an ERMI of 14 is in the top 25% of homes for relative moldiness, while a value of -6 is in the lowest 25% of homes. ERMI scores have consistently predicted the likelihood of relapse for patients who have successfully treated CIRS. The second step is an on-site evaluation by a certified IAQ specialist, who can determine sources of water damage and devise a plan for remediation.

In addition to WDB, biotoxins can come from other environmental sources as outlined above. The onset of illness in association with the consumption of seafood, swimming or drinking water known or suspected to harbor biotoxin-producing dinoflagellates or algae, or after a tick bite (and/or symptoms consistent with Lyme or associated co-infections), should be investigated.

**Symptom Hisotry**

A thorough review of a patient’s history involves not only the symptoms commonly associated with CIRS, but also a review of the patient’s personal circumstances. Symptoms of CIRS can be grouped into eight categories; symptoms in at least four of these categories for more than 2 weeks is suggestive of CIRS:

1. General symptoms: Fatigue and weakness,
2. Muscles: aches, cramps (especially claw-like cramping of the hands and feet), unusual pain (ice pick, lightening bolt or electrical), joint pains, morning stiffness
3. Unique symptoms: Headache, frequent urination and increased thirst, night sweats, static electricity or shocks, appetite swings
4. Eye symptoms: light sensitivity, red eyes, blurred vision, tearing
5. Respiratory symptoms: sinus congestion, cough, shortness of breath
6. Gastrointestinal symptoms: abdominal pain, diarrhea
7. General neurological symptoms: numbness, tingling, metallic taste, vertigo, temperature regulation problems, dizziness, tics, atypical seizures, fine motor skill problems
8. Central nervous system symptoms: memory loss, concentration difficulty, confusion, learning difficulties, difficulty finding words, disorientation, mood swings, anxiety or panic

(2004 Neurotox and Teratol, Shoemaker)

When determining an individual’s risk for CIRS, the following information should also be considered:

1. Sleep history: are there problems initiating sleep? How often does the patient wake up? Can he/she resleep easily? Does he/she awaken feeling refreshed?
2. Bleeding tendencies: Does he/she tend to bleed easily? Any history of nose bleeds? Do women have heavy periods? Is there a history of blood clots? Pulmonary emboli?
3. Living conditions: Is there any visible mold in the home? Any history of water damage? Roof leaks? Do windows show condensation in the wintertime? Has there been a house fire? Do other family members complain of asthma, respiratory symptoms? If not in the current home, do any previous homes have these problems?
4. Work/school conditions: Is there any evidence of water damage in these buildings? Are coworkers, other students/teachers sick?
5. Work/school performance: Have evaluations/grades worsened? Are there developmental concerns? Are there problems multitasking?

When multiple symptoms are present in an individual with exposure to a source of biotoxins, further evaluation with lab testing should be initiated.

**Physical Examination and Clinical Evaluations**

Because many of the symptoms of CIRS are neurological, the physical examination for CIRS focuses predominantly on neurological signs:

1. resting tremor, (often subtle, can be Parkinsons-like)
2. cool and/or discolored hands and feet,
3. pallor,
4. unilateral weakness, especially in shoulder muscles (note: evaluating the ability to maintain the arms outstretched with downward pressure on the hands and then rechecking this will usually reveal weakness)

A complete examination is important to evaluate for other possible diagnoses, including thyroid dysfunction, other neurological disorders, intestinal, respiratory, and cardiac disease.

**HLA Testing**:

HLA refers to the Human Leukocyte Antigen genes on chromosome 6, which encode for proteins that present antigens (foreign proteins) to cells for removal from the body; they help our immune system distinguish between our own cells and foreign or abnormal cells and are important for healthy immune function. The HLA DR/DQ proteins on antigen presenting cells (macrophages, B cells, and dendritic cells), present proteins from outside the cell to T lymphocytes, which in the process of eliminating the antigen transfer to B lymphocytes the ability to identify the antigen as something that needs to be removed.

We inherit our HLA types from our parents. Just as we inherit one red blood cell type (A, B, or none (O)) from each of our parents, and become A, B, AB, or O, we also can inherit a susceptibility to chronic inflammatory response syndrome. The ABO red blood “types” refer to the presence or absence of two different proteins on red blood cell membranes. In the same way, we inherit our white blood cell types, but rather than 2 possible proteins, there are many different proteins that have significance for white blood cells. The combination of HLA protein into groups of two or three results in over 50 possible HLA types. Some of these HLA types are associated with susceptibility to different diseases and conditions such as biotoxin exposure.

Our immune system is comprised of the evolutionarily earlier *innate immune system* and the later *adaptive immune system* found only in vertebrates. The innate immune system is non-specific and acts as the first line of defense, by presenting antigens to activate the adaptive immune system, recruiting immune cells to the site of infection with cytokines, and activating the complement cascade to identify cells to be removed from the body. The adaptive immune system, or the acquired immune system, confers long-term immunity by creating immunological memory after an initial exposure to a specific pathogen. This is the mechanism by which vaccines work.

It is estimated that one in four Americans have HLA types that cause them to be susceptible to mold biotoxins. These HLA proteins are unable to recognize mold biotoxins as antigens and therefore they cannot present them to the T lymphocyte for removal. As a result, the adaptive immune system does not learn to recognize the biotoxin and the body remains “stuck” with a chronic innate immune response. In *Surviving Mold*, Dr. Shoemaker includes a critical guide for interpreting HLA test results (see Appendix 2: Rosetta Stone), including a list of susceptibility of different HLA DR types. The science of HLA typing is continually evolving and this interpretive guide may need updating in the future. The following is a list of correlation between HLA haplotypes and associated CIRS susceptibility:

1. Multiple susceptible: 4/3/53; 11/3/52B; 12/3/52B; 14/5/52B
2. Mold susceptible: 7/2/53; 7/3/53; 13/6/52A, B or C; 17/2/52A; 18/4/52A
3. Borrelia susceptible: 15/6/51; 16/5/51
4. Dinoflagellate susceptible: 4/7/53; 4/8/53
5. MARCoNS susceptible: 11/7/52B
6. Low risk for mold: 7/9/53; 12/7/52B; 9/9/53

**VCS:** With an index of suspicion, a series of tests should be considered, beginning with a test of visual contrast sensitivity (VCS). In the presence of neurotoxins, visual contrast sensitivity often decreases, while with adequate treatment an abnormal VCS will return to normal. In 1997, Shoemaker and Hudnell conducted a study of VCS which “showed a sharp and apparently persistent reduction in North Carolina watermen exposed to estuaries inhabited by TPC relative to unexposed offshore watermen.” Subsequent studies of patients with exposure to WDB revealed similar correctable VCS deficits. The VCS remains one of the essential evaluations of possible CIRS; only approximately 8% of patients with CIRS have normal VCS results.

**Blood testing:**

CIRS is a multi-system immunologic illness that results in predictable and measureable inflammatory responses. These biomarkers present with a unique pattern of dysregulation, which follow a predictable timeline after exposure to WDB. These biomarkers include the following:

1. Melanocyte Stimulating Hormone (MSH; normal range 35-81 pg/ml): MSH is a critical hormone of the nervous system and has receptors in the hypothalamus. It helps the immune system’s surveillance of mucus membranes and likely plays an important role in protection from candida infections. It is decreased in over 95% of patients with CIRS. MSH is made under the influence of leptin in the pituitary gland, when pro-opiomelanocortin (POMC) is split into three parts: alpha-MSH, adrenocorticotrophin (ACTH) and beta-endorphin. MSH has many functions, including regulating neurohormones such as anti-diuretic hormone (ADH) and vasoactive intestinal peptide (VIP), reducing inflammation, and controlling peripheral cytokine release. The result is increased susceptibility to mold illness, including candida overgrowth, insomnia, chronic pain, leaky gut and malabsorption causing diarrhea, prolonged illness, fatigue, nasal colonization with MARCoNS (see below), inability to handle stress, reduced or imbalanced sexual hormones, and increased thirst and urination due to relative low ADH. Normal values for MSH are 35-81, not the values reported by Labcorp (0-40). Please see *Surviving Mold* for an excellent discussion of how corporate greed and insurance claim losses influenced this unjustified change in normal values.
2. Vasoactive Intestinal Peptide (VIP; normal range 23-63 pg/ml): VIP is another important neuroregulatory hormone with hypothalamic receptors. VIP regulates blood flow and distribution. VIP acts to regulate the release of secretory granules in a wide variety of neuronal and non-neuronal cells in the body. Like MSH, it regulates peripheral cytokine responses and inflammation throughout the body, but it also regulates pulmonary artery pressures, which can result in unusual shortness of breath, especially with exercise. VIP induces smooth muscle relaxation in the intestinal tract (especially the lower esophageal sphincter, stomach and gall bladder), stimulates water secretion into bile and pancreatic fluid, and can reduce stomach acid and absorption of nutrients from the intestinal tract. The end result is diarrhea. Patients with CIRS can have low VIP levels. Shoemaker has found that 100% of over 500 patients with multiple chemical sensitivity (MCS) have had low VIP levels. VIP replacment is the important last step of the Shoemaker protocol, and can restore energy in chronically fatigued patients. Patients must first be removed from mold (ERMI < 2), have normal VCS test, and have eradicated any existing MARCoNS. When used appropriately, VIP suppresses overly active inflammatory pathways and activates T regulatory cells.
3. Transforming Growth Factor Beta-1 (TGF Beta-1; normal range <2380 pg/ml): TGF Beta-1 is an important regulatory protein that has a dual function in the innate immune system. Elevated levels indicate an overactive immune system. TGF Beta-1 helps control the growth and differentiation of cells, cell motility, and cell death (apoptosis). TGF Beta-1 is important in utero, has a role in the formation of blood vessels, regulates muscle and body fat development, wound healing and has a critical role in immune system, especially with T regulatory cells). Its dual role in the immune system can result in impairment of T regulatory cell function and the activation of autoimmunity, or in reduction of autoimmunity. TGF Beta-1 is elevated in neurological, autoimmune, and other systemic, chronic illnesses. It has a role in increased rates of asthma, which Dr. Shoemaker theorizes may be due to exposure to WDB; wheezing after exposure to WDB may be the result of remodeling (endothelial to mescenchymal transformation, EMT), or increased airway reactivity. TGF Beta-1’s role in transforming cells can cause endothelial cells to become thick fibroblasts and result in an acquired pulmonary hypertension. Pulmonary function testing can look for signs of this restrictive (as opposed to obstructive) disease. Pulmonary stress testing to determine VO2 max and a stress echocardiogram to estimate pulmonary arterial pressure (measuring tricuspid jet and right atrial pressure) can further suggest pulmonary cell transformation. Normalizing TGF Beta-1 requires reducing exposure to toxic molds and other inflammatory triggers. Certain mold species, such as *Stachybotrys* found in WDB or *Fusarium* which can contaminate grains, produce toxins that can increase inflammatory responses to food-borne pathogens, resulting in chronic gut inflammation. Avoiding grains and amylose in the diet can be important for an individual with high TGF Beta-1 levels. TGF Beta-1 can convert CD4+CD25+ Treg cells into pathologic T cells through the amplification of the TH17 (autoimmune) system. Losartan can prevent TH17 conversion of T reg cells, and may correct TGF Beta-1 levels. A presentation at the XIth International Symposium on Transfer Factor on the role of Transfer Factor on MT4 cells reported that Transfer Factor inhibits TNF alpha and TGF Beta-1 gene expression and may play a role in the future treatment of elevated TGF Beta-1.
4. C4a (Normal range 0-2830 ng/ml) : C4a is a marker of activation of the complement cascade of the innate immune system and is an important tool for evaluating how reactive one has become to a moldy environment. C4a levels above 20,000 with low MSH levels mean that the individual cannot safely be in a building with an ERMI above -1. Because the complement system doesn’t change or adapt, it is part of the innate immune system. It helps antibodies and phagocytic cells remove infections and toxins from the body. Complement proteins circulate throughout the body as inactive precursors, but when split into active components they amplify the immune response of the membrane attack complex (MAC). The MAC disrupts the outer layer of cells causing their death. C4a is the split product of complement component 4 and is often seen in chronic exposure to bacteria and mold. C4a has anaphylatoxin activity, stimulating the degranulation of mast cells and triggering an immune response. When mast cells degranulate near the skin, dermatographia can be seen. The resulting increased vascular permeability and smooth muscle contraction contribute to the symptoms seen in CIRS, such as cognitive deficits, respiratory problems, and fatigue. High C4a levels are also seen in Lyme disease and lupus. C3a, a split product of the anaphylotoxin C3, becomes elevated in response to MASP2 activation on bacterial membranes and can be seen in Borreliosis.
5. Vascular Endothelial Growth Factor (VEGF, normal range 31-86 pg/ml): VEGF is s growth factor that stimulates the growth of new blood vessels in response to hypoxia inducible factor (HIF) and increases the blood flow in capillary beds. Low VEGF levels, seen in CIRS as a result of high cytokine levels, causes poor capillary perfusion, which contributes to muscle aches and the sense that tissues are not getting enough oxygen or nutrients. The lack of blood flow contributes to muscle cramping and post-exertional fatigue. Because cancer cells often highjack blood vessels and induce new growth to feed their increased nutrient demand, it is not surprising that low VEGF levels can protect against cancer. Unfortunately, the tissue starvation that results is not an acceptable trade-off for this protection. It has been reported that Bartonellosis can cause high VEGF levels.
6. Anti-diuretic hormone/Osmolality (ADH, normal rage 1.0-13.3 pg/ml; Osm, normal range 280-300 mosmol): ADH (also known as vasopressin or AVP), is a pituitary hormone, made in the hypothalamus, that controls the free water available to the body. Osmolality measures the concentration of electrolytes and other chemicals in the serum. A high Osm suggests that the blood is concentrated, a low Osm suggests that there is more water in the blood. When we drink water, our kidneys work to remove the water; ADH helps us retain it. ADH levels are reduced in CIRS (relative to the Osm level) and cause increased thirst, frequent urination, and increased static electricity or shocks due to increased salt on the skin. Relative dehydration can cause migraine headaches. Initial correction of ADH can lead to edema and rapid weight gain due to fluid retention.
7. Adrenocorticotropic Hormone/Cortisol (ACTH, normal range: 8-37 pg/ml; Cortisol normal ranges: a.m. 4.3-22.4 and p.m. 3.1-16.7 ncg/dl): ACTH is released in the pituitary gland with the breakdown of POMC (see MSH above). Its job is to stimulate the adrenal gland to produce cortisol. Cortisol, a steroid hormone made in the cortex of the adrenal glands, is our stress hormone. Its job is to maintain higher blood sugar levels, store ensure good blood flow to the brain, heart, and muscles in times of stress. Cortisol levels are normally highest in the morning upon awakening (a phenomenon known as the cortisol awakening response), and this give us the “I’m awake” feeling. Over the course of the day, levels decline and we get tired. While we sleep, the adrenal glands rest and recover in order to produce high cortisol levels the next morning, which wakes us up. When the adrenals are chronically overstimulated, adrenal reserves decline and the production of cortisol becomes more erratic and the normal diurnal pattern can shift to a pattern of low cortisol in the morning and high cortisol in the middle of the night. This causes daytime fatigue, nighttime insomnia and awakening with problems resleeping. When ACTH levels fall in CIRS, adrenal regulation becomes even more difficult. Evaluation of ACTH levels must be made in relationship to cortisol levels. Lower than expected cortisol should produce a higher level of ACTH production. In CIRS ACTH levels are low in relationship to the cortisol. Treatment of CIRS can correct this dysregulation, but in some cases, addressing adrenal reserves is necessary.
8. Matrix metallopeptidase 9 (MMP-9, normal range 85-332 ng/ml): MMP-9 is an enzyme that breaks down the basement membrane portion of endothelial cells which provides a barrier between blood contents and tissues. With the basement membrane dysfunctional, inflammatory compounds from the blood enter tissues and cause inflammation, pain, and damage to solid organs such as muscles, joints, the brain, the lungs, and the peripheral nervous system, including the autonomic nervous system. Normally used to breakdown extracellular matrix in utero, reproduction, and tissue remodeling, when it is not under adequate control, MMP-9 may contribute to the destruction of lung elastin seen in COPD, connective tissue seen in arthritis, cardiomyopathy, aortic aneurysms, and in atherosclerosis.
9. Leptin (normal ranges: men 0.5-13.8 ng/ml; women 1.1-27.5 ng/ml): Leptin is a hormone that controls how tightly fat cells store fatty acids. High levels are a sign of disrupted leptin receptors in the hypothalamus. As discussed above under MSH, leptin helps to regulate the POMC pathway. Low hypothalamic leptin levels contribute to low MSH, ADH, VIP, and ACTH. Outside of the brain, leptin binds to immune cells and increases inflammatory cytokines. When levels are high, fatty acids are stored in fat tissue, causing weight gain. While leptin levels can improve with CIRS protocol treatment, it is a relatively weak marker compared to the above.
10. Anti-gliadin Antibodies (AGA; normal range: 0-19): AGA are antibodies that target gliadin, a protein found in wheat, barley, and rye. When a patient has elevated AGA levels, exposure to gliadin in these foods causes an inflammatory response, which may resemble the symptoms of attention deficit disorder. Per Shoemaker, over 58% of children with biotoxin-associated illness have AGA above normal limits. Although AGA is not specific for Celiac disease, the presence of elevated AGA suggests that consumption of these foods should be avoided in patients with CIRS.
11. Dysfunctional bleeding biomarkers:
    1. Plasminogen activator inhibitor-1 (PAI-1; normal range 5-40 mg/l): PAI-1 is an inhibitor of tissue plasminogen activotr (tPA) and urokinase (uPA), which activate fibrinolysis, the breakdown of blood clots. In inflammatory conditions such as CIRS, elevated PAI-1 is associated with increased blood clotting as well as fibrosis (abnormal formation of connective tissue which can result in skin nodules).
    2. Von Willebrand panel: Von Willebrand syndrome (VWS) is a disorder of decreased coagulation that can be either inherited or acquired (AVWS). In CIRS, acquired VWS causes increased bleeding and can be seen as nosebleeds, heavy periods, and increased bleeding from wounds or surgery. VWS can result in decreased levels of von Willebrand Factor (VWF) as well as changes in other biomarkers. Although the mechanism by which biotoxin-associated illness causes AVWS is not known, it may be due to autoantibodies, which may interfere with plateletor collagen binding, or may increase VWF clearance from the plasma.
12. Myelin basic protein antibodies (MBP Ab): Myelin basic protein is a protein thought to be involved in the myelination of nerves but MBP associated proteins are also present in the bone marrow and the immune system. Myelin is the insulating sheath found on axons and dendrites, which connect nerve cells with one another and form the synapse of neuronal communication. MBP abnormalities have a role in demyelinating diseases such as multiple sclerosis (Berger) and researchers have found that antibodies to MBP increase the permeability of the blood-brain barrier (Lotosh). Automimicry, in which T lymphocytes confuse Human Herpesvirus-6 (HHV-6) with MBP, is thought to be one possible cause of MS (Tejada-Simon). In some patients adequately treated for biotoxin-associated illness, this marker normalizes along with MRI scans.
13. Anti-cardiolipin antibodies (ACLA; normal ranges: IgA 0-12; IgM 0-9; IgG 0-10): ACLA are antibodies that target our own tissues. ACLA interfere with phospholipid proteins in cell membranes. These auto-antibodies are elevated in connective tissue diseases such as scleroderma and lupus, and are associated with first trimester miscarriages. Per Shoemaker, over 1/3 of children with biotoxin-associated illness have elevated ACLA levels.

**Additional Tests:**

1. Multiply Antibiotic Resistant Coagulase Negative Staph epidermis (MARCoNS): These bacteria have been found to colonize the deep nasal cavity of 80% of individuals with low MSH levels and approximately 60% of these are also resistant to methicillin (MRCoNS). While most people harbor coagulase negative staph epidermis species, the presence of resistance to multiple antibiotics has a significant effect. MARCoNS produce biofilm, a protective environment in which bacteria produce an extracellular polymeric substance (EPS) that helps them adhere to a surface and allows them to avoid detection and destruction by immune cells. Within a biofilm, bacteria function like a multicellular organism through quorum sensing. Connected via pilli (hollow tubules through which individual bacteria can transfer DNA material from one to another), bacteria in a biofilm can rapidly confer antibiotic resistance. In the nasal cavity MARCoNS biofilm provides an environment for colonization of other bacteria and can result in chronic sinusitis. But the most significant aspect of MARCoNS biofilm is the ability of the bacteria to produce an endotoxin which breaks down MSH, therefore any patient with a low MSH level should be tested. Testing for MARCoNS is done via a simple nasal swab, which is sent out to Diagnostic Laboratory Medicine for culture by an API-staph technique that identifies the resistance to antibiotics. Relatively easy to eradicate, patients may become recolonized if they are in close contact with dogs that also harbor MARCoNS. Avoidance of close contact (licking) and/or treating the dog can help prevent this recolonization.
2. Pulmonary function testing (PFTs): In patients with unusual shortness of breath, PFTs can help to determine the type of respiratory difficulty. In patients with CIRS, PFTs may reveal a restrictive (rather than an obstructive) pattern. A pulmonary stress test may reveal an abnormally low VO2.
3. Stress echocardiogram: Useful in the evaluation of patients with poor exercise tolerance, a stress echo can estimate if there is abnormal pulmonary artery (PA) pressure response to exercise. Normally the PA pressure drops with exercise, allowing increased oxygenation, but in CIRS the PA pressure may increase, reducing the amount of oxygen absorbed into the blood during exercise.
4. MRI NeuroQuant: NeuroQuant (NQ) is a computer program applied to MRI studies of the brain that quantifies volume of 15 different brain regions. NQ of patients with CIRS has revealed specific patterns of atrophy.
   1. Patients with CIRS due to WDB, demonstrate a unique and replicable pattern of atrophy not found in other illnesses:
      1. Forebrain parenchyma increased
      2. Cortical gray increased
      3. Hippocampus increased
      4. **Caudate decreased**: reversible through the appropriate use of VIP
      5. **Pallidum increased**
      6. No other posterior gray matter is altered
   2. Patients with CIRS due to Borreliosis demonstrate a different pattern on NQ testing:
      1. Small forebrain parenchyma
      2. Small putamen
      3. **Large thalamus** (isolated post gray matter change)
      4. Large cerebellum

**TREATMENT**

Treatment for CIRS begins with the understanding that the syndrome is an immunologic disorder due to uncontrolled inflammatory responses of the innate immune system; it is found in genetically susceptible individuals. CIRS-WDB results in abnormal levels of MSH, VIP, inflammatory cytokines, C4a, VEGF, TGF Beta-1, and may include other signs of autoimmunity. Dysregulation of neuroendocrine hormones and coagulation factors can also be seen. Therefore, treatment of CIRS cannot merely involve removal of toxins as it is not the direct toxigenic effect but the innate immune response to these toxins that produces symptoms.

**Step 1: Removal from exposure**

The first and most important step in treating CIRS is to halt any ongoing exposure to the suspected source of biotoxins. For individuals exposed to water damaged buildings (WDB), this means removal from the building, proper remediation and cleaning or removal of contents (including furniture, clothing, and personal effects). Remediation of the home can be the most overwhelming and challenging aspect of treatment. Proper evaluation of water damage and remediation can be costly, time-consuming, and may require the use of professionals; ensuring that they are ethical, honest, and well trained is vital. For an individual who is suffering from CIRS this process may seem like an impossible challenge. Making a step-by-step plan, getting prompt treatment (which can improve brain function), and finding a good support network can help. If there is no one who can help support the patient, finding someone to oversee the remediation project, preferably through referrals from physicians or other CIRS patients in the area, can be a tremendous help.

The use of HEPA vacuums and air filters (such as the IQAir which removes particles down to 0.003 size) or purifiers (such as the AirFree purifier which incinerates spores, toxins, and fragments circulating in the air) can help clean the air in rooms that do not require remediation. Remediation continues until ERMI levels are at a safe level for the patient (ERMI less than or equal to 2 in patients with C4a <20,000 and MSH <35; ERMI <0 for C4a >20,000 and MSH <35)

For individuals with biotoxin exposure from infections such as Lyme disease, co-infections (such as Bartonella or Babesia), periodontal disease, food and water related toxins such as Ciguatera and Mycosistis, eradicating the underlying infection is an important part of the treatment.

**Step 2: Adsorption of biotoxins**

Biotoxins are released into the bile by the liver but in CIRS patients these biotoxins are re-absorbed in the intestinal tract. Orally administered cholestyramine (CSM)or Welchol adsorb biotoxins, preventing their reabsorption into the body, effectively removing the source of inflammatory response. CSM has two binding affinities; it can bind positively charged chemical toxins and negatively charged ionophore toxins. Because it can also adsorb minerals and nutrients from food and supplements, it must be taken away from meals and supplements. Amylose from the diet can also occupy binding sites on CSM, reducing its efficacy, therefore a no-amylose diet is important when using CSM therapeutically. Welchol, only approximately 20-25% as effective an adsorbent can be taken with food and may be combined with CSM in individuals who cannot manage the four-times-a-day schedule of CSM.

In order to reduce the likelihood of an intensification reaction to CSM, high dose fish oil (which helps to repair damage due to elevated MMP-9) is begun 3-7 days before initiating therapy. In patients with Lyme disease, CSM-induced biotoxin mobilization can produce a significant inflammatory response and pre-treatment along with strict adherence to a no-amylose diet can provide substantial relief.

Cholestyramine can be purchased at most pharmacies, as Questran (with sucrose) or Questran Light (with aspartame, which should be avoided due to its potential liver toxicity). It can also be prescribed as a pure form with or without stevia and microcellulose from Hopkinton Drug. Although the compounded form may be more expensive for most patients, in the critically sensitive patient, the pure form of CSM is preferable. Dosing is 4 grams four times daily for adults or three times a day for patients between 60 and 120 pounds (60 mg/kg/dose three times daily for patients under 60 pounds). Mixing well with water or juice and following administration with an additional 6-12 oz of water reduces constipation.

CSM and to a lesser degree, Welchol, can produce constipation, bloating, reflux, and heartburn. Treating these symptoms with magnesium supplementation (taurate, glycinate, or citrate), 70% sorbitol (Miralax), or the German product Iberogast (which acts as a promotilic agent) may help tolerance of the treatment. Finally, since these medications rely on hepatic detoxification pathways, supplementing with liver supportive herbals such as milk thistle might improve toxin clearance and further decrease symptoms of intensification. Treatment is continued for a minimum of one month and until VCS scores are normalized.

**Step 3: Eradication of MARCoNS**

If MARCoNS are present on API-Staph culture, treatment using BEG spray (Bactroban, EDTA, and Gentamicin nasal spray compounded through Hopkinton Drug) should be initiated at two sprays three times a day in adults, one spray twice a day (alternating nares) in children. Treatment continues for 30 days and then the patient is retested to see if the culture has become negative. If it is still positive, BEG spray can be continued with the addition of Rifampin 600 mg daily for 30 days in adults (or 10-20 mg/kg/day in children). Evaluation and treatment of any family dogs (or improved hygiene after being licked) is also important to prevent re-colonization after adequate treatment as dogs can harbor MARCoNS in their nasal cavities.

**Step 4: Correction of antigliadin antibody positivity**

Removal of gluten from the diet reduces the risk of gastrointestinal sources of inflammation. Patients who do not test positive for Celiac disease (negative TTG-IgA), but who demonstrate elevated AGA antibodies should remain off gluten for at least three months. Since the no-amylose diet prescribed during CSM administration is already gluten-free, this dietary restriction continues for approximately 2 months longer, assuming that the VCS has corrected in the first month of treatment. Longer avoidance may be necessary to eliminate AGA positivity, and may have further health benefits beyond the scope of CIRS treatment.

**Step 5: Normalization of MMP-9**

High dose fish oil and no amylose diet will address high MMP-9 levels, which produce intensification symptoms. Levels should be less than 322. If symptoms of intensification persist despite the use of fish oil and dietary restrictions, a slower adsorption protocol should be initiated. Starting with a low dose of Welchol instead of CSM, and slowly titrating up to the full dose (two 625 mg tablets three times a day), the protocol can progress with the addition of one to two doses CSM in place of one of the Welchol doses, and if tolerated, a return to the CSM dosage four times a day. Finally, if intensification persists, tick-borne illnesses such as Borreliosis should be considered.

The drug Actos can upregulate PPAR-gamma and reduce MMP-9 expression. Unfortunately, Actos has a black box warning for bladder cancer and must be used only in cases that do not respond to other treatments. Dosage is 45 mg/day for 30 days (only for adutls) along with a no-amylose diet. If leptin levels are under 7, Actos cannot be given.

**Step 6: Correction of ADH/Osm dysregulation**

Treatment of dysregulated water metabolism can be addressed through the use of DDAVP (vasopressin nasal spray), using 1 spray nightly for 5 nights/week and checking serum sodium, ADH, and Osmolality in one week. Dosage can be increased to one spray twice a day for 5 days if needed. This step may also help reduce MMP-9 levels and acquired von Willebrand syndrome.

**Step 7: Correct androgen deficiency/aromatase upregulation**

Aromatase is an enzyme that metabolizes androgens and when upregulated, can result in low testosterone levels. Treatment can be with DHEA (25 mg three times a day), HCG (human chorionic gonadotropin) injections or sublingual drops (125 mg/week) for five weeks, or if the use of VIP nasal spray four times a day for a month (only if the previous steps of the protocol have been successful; see step 11 below).

**Step 8: Correction of C3a**

High C3a can be eradicated with the use of high dose statins, such as Zocor 80 mg daily. Since statins affect HMG-CoA reductase function, causing a reduction in Coenzyme Q10 production, treating with good quality, high-dose Coenzyme Q10 (ubiquinol at 150 mg daily) beginning two weeks prior to administration of statins is an essential part of this step.

**Step 9: Correction of C4a**

C4a is a split product of the mannose binding lectin pathway of the complement system and predicts the severity of CIRS. Treatment with erythropoietin (Procrit) can rapidly reduce C4a. Since Procrit has a black box warning, careful use with informed consent is required. Pretreatment testing prior to each dose and after completion of the course includes evaluation of CBC, iron studies, C4a, TGF Beta-1, d-dimer, and Treg assays to keep the risk of thrombus formation low. Procrit is given as 8000 U IM twice a week over a 15 day period (5 doses). If the patient improves (respiratory symptoms, mental clarity improves, and C4a drops) then a second trial is initiated. Procrit should be considered in patients who feel better at high altitudes. If Procrit cannot be used, VIP spray four times a day should be considered.

**Step 10: Correction of elevated TGF Beta-1**

TGF Beta-1 can be reduced with the blood pressure drug losartan (Cozaar). Losartan is given at a starting dose of 25 mg twice a day (0.6-0.7 mg/kg/day in two divided doses in children) and titrated up in divided doses for six months. Careful monitoring of blood pressure and watching for signs of orthostasis (low blood pressure upon standing or sitting up as evidenced by dizziness, lightheadedness, or passing out) is essential.

**Step 11: Replacement of VIP**

For individuals deficient in VIP, this final step of the protocol can provide significant relief of CIRS symptoms, but only if all the prior steps have been successfully taken. Prior to initiating VIP treatment the following conditions must be met:

1. MARCoNS (if present) must be eradicated and repeat testing documented;
2. VCS must be normalized; and
3. Home and workplace must be cleared of WDB inflammagens and mold; ERMI must be less than or equal to 2 or HERTSMI-2 must be less than or equal to 10

Until these criteria are met, VIP treatment cannot begin.

Once the decision to use VIP is made, pre-treatment vital signs and laboratory studies are done to include:

1. TGF Beta-1 (by Cambridge Medical)
2. C4a by Quest (sent to National Jewish Hospital in Denver)
3. VEGF, MMP-9, 25 OH-Vitamin D, estradiol, total testosterone, and lipase

After the blood is drawn, a test dose of one spray is given in one nostril and the patient is observed for any symptom improvement and vital signs are followed every 5 minutes x 3. The initial improvement may include reduced shortness of breath, reduced joint pain, and improved cognition. After 15 minutes, a second set of TGF Beta-1 and C4a levels are drawn. If there is a twofold increase or more, hidden mold exposure may be present. After 30 minutes, if the patient tolerates this first dose, she/he may leave the office and a prescription is sent to Hopkinton Drug. Initial dosing is one spray four times a day for 30 days. After a month the dosage is adjusted (some people will need to increase to 8 sprays/day or more, others will reduce to fewer than four doses per day).

VIP may cause pancreatitis and increase lipase levels. For this reason, lipse levels should be monitored monthly. If any abdominal pain occurs, a lipase level must be checked. VIP administration must be stopped if lipase levels are found to be elevated. If lipase levels remain normal, then VIP treatment can resume. If evaluation of an elevated lipase reveals abnormal gall bladder function with “sludge”, then a cholecystectomy (removal of the gallbladder) may be indicated.

**AREAS FOR FUTURE RESEARCH**

Dr. Shoemaker’s 11-step protocol for treating CIRS has given thousands of patients their lives back. It is a well-researched, well-documented, evidence based approach to evaluate and treat chronic inflammatory response syndromes resulting from biotoxin exposure. The science behind his protocol raises further questions that hopefully will be addressed in future research.

**Transfer Factor:**

Patients with CIRS have dysfunction of Treg cells, which are converted into pathogenic T lymphocytes. B cells are the cells of the TH2 immunity: they fight infections outside cells and produce antibodies. T cells are the cells of the TH1 immunity: they fight infections within the cell and produce transfer factors. Under normal conditions, TH1 and TH2 balance each other through the modulating influence of cytokines, but under the influence of stress (through elevated or decreased cortisol levels), mercury toxicity, Borreliosis and likely other organisms, the balance shifts to TH2 dominance. This results in increased allergies with decreased ability to fight infections.

In 1949, Dr. Sherwood Lawrence, studying patients with tuberculosis, described a substance from lymphocyte cytoplasm that could transfer immunity to TB from a adequately treated patient to a volunteer. He called this substance Transfer Factor. By the 1990s, research (mostly in the veterinary community in the US and in human medicine in Europe) had determined that transfer factors are the product of T lymphocytes and are made in a fashion similar to B cells’ antibodies, in response to a specific illness. Transfer Factors were evaluated for their use in cancer, infections, and other conditions of immune dysregulation. By the late 1990s, transfer factor was available to purchase commercially as a non-specific, or multimmune, product.

Transfer factor is a well-tolerated, naturally occurring low molecular weight protein that can be absorbed orally. Sourced from bovine colostrum and egg, these products have very low allergenic potential and are available as a pure form, and two varieties with additional immunomodulating herbals, with or without mushroom extracts. Studies of transfer factor reveal increase in natural killer cell function, reflective of improved TH1 immunity. My experience has been that transfer factors appear to improve Treg function more than shift TH2:TH1 balance back towards TH1, which is pro-inflammatory. After 6 to 9 months of low dose transfer factor, patients with food sensitivities report significant improvement in these sensitivities and I have used the supplement to successfully treat individuals with idiopathic chronic urticaria.

I propose that a non-specific transfer factor product (such as Transfer Factor Multimmune from Researched Nutritionals) be studied to determine if it can help regulate the immune system in cases of CIRS.

**GcMAF:**

GcMAF is a protein that turns on the macrophages of the immune system, helping to eradicate infections, abnormal cells, and cellular debris. Under the influence of specific enzymes including sialidase, Vitamin D binding protein (DBP) can be converted into a Gc protein that activates macrophages. DBP is a protein with a trisaccharide structure, which can be selectively cleaved to contain only a single sugar moiety. The new structure, labeled Gc-Macrophage Activating Factor (GcMAF), combines with two vitamin D molecules and attaches to the vitamin D receptor, activating macrophages.

In the presence of nagalase, an enzyme produced by cancer cells and certain infections such as influenza, the entire trisaccharide moiety is cleaved, leaving behind an ineffectual sugar-free protein, which cannot activate the macrophages. As an adaptive mechanism to bypass the immune system, nagalase can have significantly untoward effects on the immune system. In the presence of elevated nagalase levels, treatment with GcMAF can assist with the initiation of macrophage activation; the resulting increased numbers of activated macrophages attack the source of the nagalase (tumor cells or infective organism) which over time reduces to normal levels and restores the immune system.

In a study of the mechanism of action in human neuronal cells and rat models of persistent pain with implications for chronic fatigue syndrome, Smith, et al found that, “GcMAF at pM concentration increased neuronal cell viability and metabolism through increased mitochondrial enzyme activity.” As discussed above, Brewer, et al, reported that 93% of patients with chronic fatigue syndrome exhibited urinary mycotoxins, which were undetected in normal controls. The correlation between CIRS symptoms and CFS, as well as the presence of mycotoxins in patients with CFS suggest that the immune modulating protein GcMAF should be considered as a possible treatment modality for severe CIRS patients. Testing CIRS patients for nagalase levels would be the first step in determining if GcMAF treatment should be considered as an adjunct in the treatment of CIRS.

**Phosphorylated Fatty Acids:**

Research on phosphorylated fatty acids suggests that in patients with moderate to severe CFS exhibit 40% improvement in energy following 8-12 weeks of replacement therapy. It has been demonstrated that one of the mechanisms of CIRS is the role of MMP-9 in destroying basement membranes and cellular membranes. Since cellular and mitochondrial membranes are made up of phosphorylated fatty acids, their use in patients with CIRS might prove promising.

**MARCoNS testing and treatment in family pets:**

As seen above, MARCoNS can be harbored in the noses of dogs and can be a source of recolonization in patients with persistent MARCoNS despite adequate treatment. Most patients with dogs refuse to remove them from their homes. While some patients have used BEG spray on their pets, it has not been determined if the MARCoNS biofilm in dogs is predominantly in their nasal cavities, or other respiratory or oral structures. Furthermore, treatment with BEG spray may not be the optimal treatment choice for animals. A study of concomitant treatment of family dogs with treatment of patient(s) may help determine if dogs are the nidus of infection or if they are the unhappy victim in MARCoNS colonization, as well as determine the best form of treatment and evaluation in dogs.

**Detoxification**

Detoxification pathways through the liver are essential for health. Glutathione (GSH), a powerful antioxidant in the body is a sulfur-based molecule that is recycled through the methylation cycle. Reduced in the process of anti-oxidation, GSH must be converted to its original un-reduced form in order to be used again. It has been reported that the enzymes required for this process are genetically downregulated by mycotoxins. Treatment with GSH, either orally via a lipospheric formulation, or intravenously, might improve the intensification symptoms of CIRS treatment and reduce the length of time of treatment. Evaluation of GSH levels, and trials of oral or IV GSH versus placebo could determine the possible efficacy of this antioxidant.

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