Shoemaker Certification
Diane Parks, APRN-NP
May 4, 2020

Chronic Inflammatory Response Syndrome (CIRS) Understanding, Diagnosing and Treating

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History

Chronic Inflammatory Response Syndrome (CIRS) is a multi-system, multi-symptom illness associated with exposure to biotoxins or neurotoxins. It is usually present in a subset of the population with genetic susceptibility characterized by a grouping of symptoms, proteometrics, genomic abnormalities, specific brain changes and abnormal visual contrast sensitivity. (1) This is not only an inflammatory disorder, but also an immune mechanism dysfunction caused by toxins, and depending on genetic profile, can affect up to 24% of the population. These patients are often seen multiple practitioners presenting with a long list of misdiagnoses having spent thousands of dollars resulting in little or no symptomatic improvement. The list of diagnoses may include - but not limited to - dementia, autoimmune disease, chronic fatigue, fibromyalgia, ADD/ADHD, depression, panic disorder, general anxiety disorder, bipolar disorder, insomnia, cardiovascular/respiratory disease, asthma, exercise intolerance, obesity (suggestive of indifference to the consequences), allergies, irritable bowel disorder, and somatization. Typically, their quality of life is greatly diminished as they experience dysfunction within the neurological, immune, endocrine, circulatory, respiratory, muscular skeletal and psychological systems.

Most of the credit for the recognition, evaluation, and treatment of CIRS belongs to Dr. Ritchie Shoemaker, who in 1997 as a family practitioner in Pocomoke, Maryland first noted the signs and symptoms of this syndrome in local fishermen. These fishermen began presenting with striking physical and neurologic symptoms after exposure to environmental factors that were also causing fish to die in large numbers in conjunction with Pfiesteria bloom outbreaks in the Pocomoke River. Focused investigation by him, in collaboration with other noted colleagues, led to the evolving foundation, research, and formulation of the Shoemaker Protocol for management of this previously unrecognized syndrome. With time, Dr. Shoemaker and his colleagues began to recognize striking similarities in other patients with similar symptoms exposed to other toxins, such as mold from water damaged buildings (WDB), tick borne microbes (Borrelia burgdoferi and Babesia microti), recluse spiders (brown and Mediterranean), ciguatera from ingestion of contaminated fish, and inhalation or contact with algae blooms containing cyanobacteria. Since the initial recognition of a chronic immune response syndrome, research based strategies developed by Dr. Shoemaker has resulted in the diagnosis and treatment of over 10,000 patients worldwide.

Inflammatory and Immune Cascade

In a healthy, non-genetically susceptible person, the removal of toxins is accomplished by the interplay between the innate and adaptive immune systems. The innate system is the primary

and first responder to invading antigens. By activation of cytokines and TGF (Transforming Growth Factor) Beta-1 for the recruitment of immune cells to the area of insult, it initiates activation of the complement system to assist in removing the invading antigens. The innate system then communicates with the adaptive immune system (or second line of defense) to destroy the toxins by presenting them to inflammatory T cell lymphocytes by which induction of antibodies by B cells occurs. Natural killer T cells are also activated to produce, among other factors, cytokines, including IL-2 and TNF-alpha, and lend support to B cell antibody production. When the adaptive system is intact and working appropriately, (i.e. without a defective HLA system), it provides long-lasting immunity and return to homeostasis. These two systems are quite effective in providing an adequate defense from foreign toxins in approximately 75% of the population with a normal histocompatibility gene group, an entity that provides instruction for making Human Leukocyte Antigens. The HLA complex helps the immune system distinguish the body's own proteins from other foreign invader proteins such as those made by viruses and bacteria. In biotoxin illness, the HLA challenged individual is incapable of mounting an adequate response and thus unable to clear the toxin. This leads to chronic activation of the innate system in which inflammatory cytokines are left in place resulting in dysregulation of multiple body systems. **(2)** If this individual is not properly evaluated for prompt treatment by one experienced in CIRS management, toxins can remain in the body for months and years leading to extraordinary damage, expensive misdiagnoses by providers not aware of the etiology, and ultimately a major interference in the patient's quality of life.

INSTIGATORS OF CIRS

Listed below are examples of known sources of biotoxins found to initiate CIRS. They are responsible for triggering the innate and adaptive immune systems causing systemic inflammation.

- CIRS-WDB (Water Damaged Building): Examples - Chaetomium globosum, Aspergillus penicillioides, Aspergillus versicolor, Stachybotrys chartarum, Wallemia sebi, Actinomycetes, bacteria and inflammagens. A WDB has been called a "toxic stew" as at least 30 potentially toxic entities have been identified and all can set off an innate immune response. **(Appendix 1)**
- CIRS-Post Lyme Syndrome (PLS): Borrelia species
- CIRS-possible estuarine associated syndrome (PEAS): Pfiesteria (dinoflagellate)
- CIRS-Ciguateria: Gambierdiscus (dinoflagellate)
- CIRS-Arachnids: Recluse spiders (brown and Mediterranean)
- CIRS-Apicomplexans: Babesia Spp., Sarcocystis
- CIRS-Cyanobacteria: Microcystis, Lyngbya, Cylindrospermopsis, Anabaenopsis

Diagnosis of CIRS

An accurate diagnosis of CIRS requires a detailed assessment of the many signs and symptoms

presented by the patient. By its very nature, CIRS is a complex conglomeration of many dysfunctional processes that can mimic many other diseases; therefore, it is helpful to formulate a concerted plan to differentiate it from these other these diseases. A detailed long term history is required which would include a specific CIRS cluster of symptoms questionnaire (see below). In addition, visual contrast sensitivity testing and a comprehensive physical exam are necessary elements of the initial assessment. **(3)**

A two-tiered system case definition was introduced by Dr. Shoemaker in 2005 to more definitively establish the diagnosis. Its focus was to make an objective model to allow a tool for accurate diagnosis. A standardized process was then implemented in which all of the criteria for Tier One had to be met and three out of six measures in Tier Two had to be met to make the diagnosis. Furthermore, in 2008, the Government Accountability Office (GAO) reviewing 54 studies from US agencies involved with consequences to exposure to WDB, noted no significant coordination with these agencies, and as a result, proposed a federal case definition requiring the inclusion of criteria for CIRS-WDB. **(4)** Subsequently, a third tier was added for the evaluation of success of treatment. In coordination with this review, the elements for diagnosis of CIRS was expanded. The following lists the requirements of Tier One, Tier Two, and Tier Three criteria:

Tier 1 (All of the following criteria must be met)

1) Potential for exposure to toxins in a water damage/damp indoor space. This includes visual mold growth, musty smells or abnormal ERMI test (MSQPCR), tick or spider bite, eating fish that feeds on a barrier reef, exposure to Pfiesteria or Cyanobacteria
2) Presence of a multisystem, multi-symptom illness with specific symptoms mirroring those outlined in published studies. A Cluster of Symptoms Questionnaire has been developed for ease in identifying these symptoms. A score of 8 of 13 symptoms indicates 92% likely hood of CIRS, 6 of 13 is suspicious. In children, 5 of 13 is significant and warrants further evaluation. **(Appendix 2)**
3) Absence of pertinent differential diagnoses after a thorough evaluation **(3)**

Tier 2 - (At least 3 of 6 criteria)

- Failed Visual Contrast Sensitivity Test (VCS) – Neurotoxic illness
- HLA DR/DQ Mutations – Genetic susceptibility
- Increase in at least 1 of 3 inflammatory markers: Matrix Metalloproteinase-9 (MMP-9), Transforming Growth Factor Beta-1 (TGF-beta 1), C4a - Cytokine activation
- Decreased alpha Melanocyte Stimulating Hormone (MSH) – Hypothalamic impairment
- Dysregulation ADH or Copeptin/Osmolality – Pituitary and peripheral endocrine dysregulation
- Dysregulation of ACTH/Cortisol – Pituitary and peripheral endocrine dysregulation **(7)**

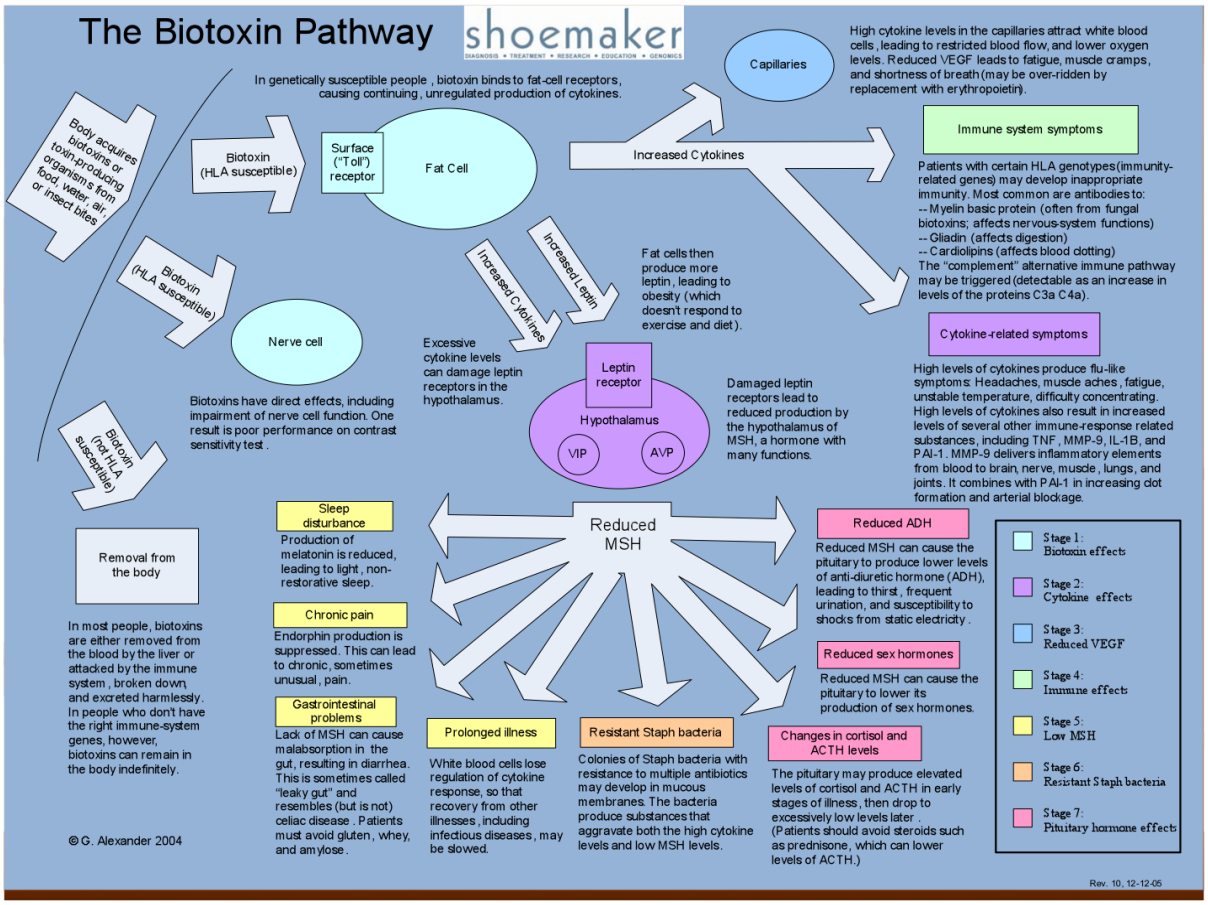
Tier 3 – (Improvement in at least 2 of 3 markers)

- Cholestyramine or Welchol/Colesevelam – resolution of symptoms

- Reduced Leptin, if increased prior to treatment
- Reduced MMP-9, if increased prior to treatment **(3, 6, 30)**

The Biotoxin Pathway

For a better understanding of chronic inflammatory response syndrome, Dr. Shoemaker has provided a pathway chart depicting the effects of biotoxins on genetically susceptible people and the varied responses the body may engender to combat the insult. In this population, the normal response of the immune system for removing the insult is altered; therefore, unregulated and exaggerated defense mechanisms are left unchecked. This leads to a cascade of detrimental symptoms and pathology. Exposures triggering the pathway include, but are not limited to, toxins from WDB, infected tick borne bacteria/parasites (Borrelia, Babesia, Ehrlichia), inhaled, ingested, or skin absorbed dinoflagellates (Pfiesteria, Ciguatera), locally injected venom (Loxosceles species), and inhaled or absorbed Cyanobacteria toxin. The degree of symptom and system response to any of these insults may depend on the amount of exposure and the toxin involved. **(5)**



Confirming Diagnosis of CIRS

After meeting the system criteria in Tier One outlined previously, the next step is to confirm the diagnosis. Many tests have been listed in Tier Two and are described below in further detail. It is important to note there are many tests that will most likely not be abnormal including CBC, metabolic profile, ESR, CRP, TSH, ANA, Immunoglobulins IgG, IgM, IgE), Lipid profiles, Antibody profiles, all complement except for anaphylatoxins, all genetic testing except for HLA DR/DQ, LH, FSH, SHBG, estradiol, estrone, prolactin, normal EKG, viral studies. **(3, 6)**

1) VCS test – Positive test means deficiency in contrasting ability

Visual contrast is a measure of neurological function by the ability to differentiate between visual patterns of grey, black, and white. Dr. Ken Hudnell, a neurotoxicologist for the EPA, was the first to use VCS testing for biotoxin illness. Chemicals, toxins, and medications have all been implicated in negatively affecting the visual nervous system. Specifically, capillary hypo-perfusion caused by inflammation from toxins compromise the optic nerve and retina such that the visual contrast delineation is decreased as opposed to visual acuity (the sharpness of retinal focus) which is left largely unaffected. According to Dr. Shoemaker, 92% of CIRS patients will fail VCS testing: however, 8% will falsely pass if they possess outstanding visual acuity despite severe inflammation.

If the patient fails the VCS test and symptom clusters are positive, the likelihood of CIRS exceeds 98.5%. **(7)** There are two methods of taking a VCS test: 1) an online version found on the home page of www.survivingmold.com and 2) a recommended hand held version purchased at https://www.survivingmold.com/store1/vcs-aptitude-handheld-kits. Careful adherence to directions is necessary for accurate assessment. Determination of a passing score occurs when a patient, using one eye at a time, is able to see beyond row 6 in column C and beyond row 5 in Column D. Column E is used to monitor treatment success as well as monitor possible intensification reaction in patterns with Lyme disease. **(3)** In regards to improvement, Dr. Shoemaker states, "a rise in one block in one column is not significant, but a rise of one block from each of five columns is significant. A rise of two blocks (or a fall in two blocks) for any one column is significant. **(8)**

2) HLA DR/DQ Test (Human Leukocyte Antigen) – (LabCorp test #167120)

This test determines if a patient is genetically susceptible for the development of CIRS. In the susceptible population, the innate immune system recognizes the biotoxins sending signals to the adaptive immune system to respond. Unfortunately, the adaptive immune system does not recognize the biotoxins and therefore cannot make antibodies against them. Without the help of the adaptive immune system, the innate system is constantly triggered (upregulated) creating high levels of inflammation. This incites a multi-system, multi-symptom illness known as CIRS.

Dr. Shoemaker has conducted an extensive gene registry and found that approximately 24% of the population is "mold" susceptible and 21% is Lyme susceptible. (9) Lyme susceptible patients do not always respond well to antibiotics and may need CIRS treatment to help enable clearance of the toxin. Lyme patients also tend to have an increased risk of developing CIRS - WDB. (4)

Dr. Shoemaker developed the Rosetta Stone Index which was designed as a scoring method based upon a compilation of HLA haplotypes to assess the risk of susceptibility to several toxins. (10) A caveat: Not all online automatic interpretation of results is completely accurate, therefore, there is the need for provider adeptness for accurate interpretation. **(Appendix 3)**

3) *α*MSH (alpha melanocyte stimulating hormone) (LabCorp test # 10421)
Reference range: 35-81 pg/mL

Alpha MSH is a neuro-regulatory hormone instrumental in ensuring optimal immune system response. It also has powerful anti-inflammatory actions. (7) In CIRS patients, MSH is usually low causing abnormal regulation of cytokines, endorphins, melatonin, sex hormones, cortisol, and ACTH. Contributing symptoms include chronic fatigue, unusual pain features, sleep disturbance, headaches, temperature instability, muscle aches, and decreased concentration. In addition, physiologic disturbances with gluten intolerance, ADH/osmolality imbalance, and leptin resistant weight gain have been demonstrated.

4) MARCoNS (multiple antibiotic resistant coagulase negative staph) (Mycobiology DX)
Reference Range: Positive with or without biofilms or Negative

MARCoNS is found deep within the nasal passages and is extremely common in those with CIRS-WDB as well as patients with post Lyme Syndrome who have been treated with antibiotics for a prolonged period of time. In the past, MARCoNS was presumed to be benign colonizers of the nose and skin, but with the increase use of antibiotics, these bacteria have shown resistance to two or more antibiotics. They have now become pathogens able to produce biofilms allowing the bacteria to live undetected and act like multicellular organisms. The biofilm hinders penetration of antibiotics for treatment. MSH and MARCoNS have a bidirectional relationship. Nasal membranes are protected from colonization by adequate MSH levels; however, with declining MSH, the protective layer is reduced leading to the development of MARCoNS. It has been shown that 80% of MSH-deficient patients will have MARCoNS and with this presence, MSH continues to decline. Initially, it was thought MARCoNS was confined to the nose, but recently MARCoNS has been cultured from dental cavities. Most patients with MARCoNS do not experience nasal congestion, rhinitis, or sinusitis, but do have cognitive concerns describing symptoms as "brain fog", decline in memory, attention and concentration.

A MARCoNS test should be part of the initial work-up for CIRS. It is done with a API-STAPH nasal culture obtained from the nasopharynx. Only one side of the nose needs be tested inserting the swab deep within the nasal pathway or approximately 3-4 inches. It is important to go slowly, taking care to following the angle of the passage and once in the correct area, twirl the swab for 3-5 seconds. MicobiologyDX provides test kits and sampling: http://www.microbiologydx.com. **(3)**

5) MMP-9 (matrix metalloproteinase-9) (LabCorp test # 500124)
Reference range: 0-322 ng/mL – Per Dr. Shoemaker LabCorp current reference range of 85-332 is incorrect as they still use Esoterix range that combines controls and cases **(6)**

MMP-9 is an enzyme of the innate immune system produced by blood vessel endothelium. Expression of MMP-9 is triggered by high levels of cytokines. Once elevated, increased vascular permeability occurs thus delivering inflammatory products to local tissues including the lungs, nervous and muscular systems. Symptoms include headaches, muscle pain, cognitive issues, altered lung function, static shocks, and neurological issues. **(11)**

6) C4a (complement 4a) (National Jewish ONLY)
Reference range: < 2830 ng/mL - NOTE: Because Jewish National is the only reliable source of testing, it may be very difficult for patients to obtain this test.

This marker is of great significance in CIRS-WDB diagnosis and is also usually elevated with exposure to dinoflagellates, cyanobacteria, and persistent Lyme disease. It is a complement split anaphylatoxin which mediates chemotaxis, contraction of smooth muscle, histamine release from mast cells, capillary hypoperfusion and increases vascular permeability. Exposure to a biotoxin activates the mannose binding lectin associated enzymes (MASP-1 and MASP-2) producing C4a. Symptoms related to an elevated C4a include fatigue, respiratory concerns and can also play a role in changes of six executive functions: decreased concentration, difficulty with word finding, decreased assimilation of new knowledge, confusion, and disorientation. It potentially plays a role in Alzheimer's disease as a decrease in C4a seems to be associated with improved symptoms. This test is not only used for assessment of current exposure, but also for re-exposure in that an increase in C4a can occur within 10 minutes of exposure. It is therefore a good screening tool for both current and recurrent exposure trials. Clinical severity often correlates with higher levels of C4a. It is therefore a good screening tool for both current exposure and re-exposure trials. Often times, clinical severity correlates with higher levels of C4a. **(6)**

7) C3a (National Jewish ONLY)
Reference range: < 940 ng/mL - NOTE: This test is also very difficult to obtain.

C3a is an anaphylatoxin which stimulates histamine release from mast cells causing contraction of smooth muscle, capillary hypoperfusion, and increased vascular permeability. C3a stimulates

the adaptive immune system, induces and modulates T and B cell production and proliferation. It is found in the lung, kidney, and brain. The presence of bacterial membranes may elevate C3a exemplified by activation in many active Lyme patients. **(3)**

8) Leptin (Quest Test # 90367 or LabCorp Test # 146712)
Reference range: Male: 0.5-13.8 ng/mL; Female: 1.1-27.5 ng/mL

Leptin is produced in adipocytes and links the neuroendocrine and immune systems acting as both a hormone and cytokine. Cytokines such as TNFalpha, IL-6, and IL-1 are unregulated resulting in heightened inflammation and in some patients, elevated plasminogen activator inhibitor-1 (PAI), abnormal von Willebrand factor's (VWF), and Factor VIII resulting in coagulopathies. These inflammatory cytokines block leptin hypothalamic receptors creating leptin resistance. Leptin resistance decreases the body's ability to use fat stores as energy giving rise to dramatic weight gain despite calorie restriction and exercise. Leptin links the hormone system by affecting MSH, ACTH, and endorphin production. For instance, symptoms associated with a lower MSH might include temperature instability, headaches, muscle aches, and decreased ability to concentrate. **(7)**

9) Transforming Growth Factor beta-1 (TEG beta-1) (Quest only – Test # 91238: performed at Cambridge Medical)
Reference range: < 2382 pg/mL

TGF beta-1 is a protein playing an important role in the regulatory properties of the immune system especially in regard to tissue repair and fibrosis. It is produced by lymphocytes, macrophages, and dendritic cells and controls growth, differentiation, activation, and death of immune cells. It has been associated with autoimmune diseases specifically SLE, rheumatoid arthritis, dermatomyositis, scleroderma, ulcerative colitis. In addition, lung fibrosis, vocal cord polyps, GI dysfunction and an increased incidence of opportunistic infection has been linked to elevated levels of TGF beta-1. One example of its effects is on lung performance noted by an increased incidence of pulmonary systolic pressure and possible progression to pulmonary hypertension. In conjunction with elevated production of MMP-9 and VEGF, TGF beta-1 has also been implicated with increased blood brain barrier permeability resulting in inflammatory consequences such as learning disabilities and cognitive dysfunction. **(3)**

10) Vascular Endothelial Growth Factor (VEGF - plasma) (Quest – Test # 14512 or LabCorp – Test # 117006)
Reference range: 31-86 pm/mL

VEGF is a growth factor, which in health people, dilates blood vessels in response to hypoxia inducible factor (HIF). Hypoxia occurs when inflammatory cytokine bound to the endothelium release chemicals narrowing the capillaries. Regulatory cells then produce HIF which induces an increase VEGF. Low VEGF may be an indicator of capillary hypoperfusion leading to fatigue and

cognitive decline, and if present in skeletal muscle, decreased muscle endurance. Treatment is necessary for levels < 31; however, in CIRS patients, levels can be over 100 indicating activation of the innate immune response as the body compensates for low oxygen delivery. Very high VEGF can also occur with renal failure and rarely cancer. **(2, 6)**

11) Anti-Gliadin Antibody (AGA – IgG, IgA)
(Quest – Test # 8889 or Labcorp – Test # 161646/161647)
Reference range: 0-19 U

Though elevated AGA does not necessarily indicate celiac disease, it does strongly suggest an inflammatory response to gluten. In gluten sensitive patients, the adaptive immune response mediated by the antigen-specific T regulatory lymphocytes incites autoimmune dysregulation. In CIRS patients, who often have low MSH levels, this dysregulation can be enhanced. AGA IgG and IgA are antibodies against gliadin found in gluten, a protein present in wheat, barley, and rye. Oats, too, can be an instigator of the response if cross contamination occurs in processing with gliadin containing foods. NOTE: If a patient is strictly gluten free, it is still necessary to test AGA. **(2)**

12) Androgen Deficiency – Total testosterone and DHEA-sulfate (Quest or LabCorp)
Reference range: Varies by sex and age
NOTE: Optimally, a more sensitive assay is performed in menopausal women to assure the most accurate result.

- **Testosterone (Female: sensitive) – Quest Test # 15983, LabCorp Test # 500159**
- **Testosterone (Male: regular) – Quest Test #36170, LabCorp Test #4226**
- **DHEA-sulfate – Quest Test #402, LabCorp Test # 4020**
- **Estrone – Quest Test #23244, Labcorp Test #4564**
- **Estradiol – sensitive (menopause women and men) – Quest Test #30289, LabCorp Test #140244**
- **Estradiol – regular (Non-menopausal women) – Quest Test #4021, LabCorp Test #4515**

Androgen levels can become abnormally low due to upregulation in the aromatase enzyme. DHEA-s may also be low. Inflammation causes more rapid conversion of testosterone into estrogen resulting in high estrogen and low testosterone. Testosterone therapy is contraindicated in these patients. DHEA-s may be used in its place, but it necessitates monitoring estrogen levels so they are not elevated as opposed to the intended normalization of testosterone. For this reason, both estrone and estradiol should be tested to insure proper conversion. Symptoms of hormonal dysregulation include fatigue, muscle wasting, low libido and sexual dysfunction, high hematocrit/hemoglobin, mid abdominal weight gain, gynecomastia, water retention, PMS complaints such as anxiety and irritability. **(12)**

13) von Willebrand's Comprehensive Panel (Quest only – Test #19790)

Reference Range: < 50 or > 150 IU for Factor VIII, von Willebrand's antigen, or Ristocetin associated cofactor

Von Willebrand's Disease is typically an inherited disorder characterized by excessive or prolonged bleeding. In CIRS patients, however, the condition can be acquired as a result of increased C4a which may paradoxically result in both bleeding tendencies and hyper-coagulation. Symptoms related to bleeding tendencies include recurrent, sometimes profuse nose bleeds, generalized bleeding, and heavy menstrual periods. Conversely, others with the acquired disorder may be at significant risk for intravascular clotting resulting in pulmonary embolism, deep vein thrombosis or micro-emboli in the brain. If hyper-coagulation occurs, cognitive decline may be a presenting symptom due to the decreased oxygen delivery distal to emboli though patients often are asymptomatic to the inciting event. If acquired von Willebrand's disease is present, other pertinent labs to consider include: PT, PTT, Sed rate, D-dimer, fibrinogen. Other than avoidance of exposure to inciting factors, treatment with desmopressin (DDAVP) may be warranted for episodes of profuse bleeding. **(2)**

14) Plasminogen Activator Inhibitor-1 (PAI-1) (Quest Test # 36555, LabCorp #146787) (Reference Range: 4-43 ng/mL)

PAI-1 is an acute phase reactant that can become elevated with infection, pregnancy, inflammation and trauma. It can increase risk of hypercoagulation. **(3)**

15) Anticardiolipin Antibodies (IgA, IgG, IgM) (Quest Test #, LabcCorp Test #161950)
Reference range: Negative = ACA IgA < 11 APL; ACA IgG < 14 GPL; ACA IgM < 12 MPL

Anticardiolipin antibodies attack the cardiolipin cellular membrane and can cause abnormal bleeding tendencies including increased blood clotting. These antibodies are found in patients with lupus, scleroderma autoimmune thrombocytopenia, pulmonary embolism, deep vein thrombosis, and endocarditis from clot formation on heart valves. In pregnancy, they may also increase the risk of spontaneous abortion.

16) Antidiuretic Hormone (ADH) (LabCorp only, Test # 10447) (Quest now Substitutes Copeptin in its place, Test #37740) Quest makes the assumption that Copeptin is a more reliable marker. (13) Currently a review of results is underway in the CIRS professional community to determine an optimal CIRS reference range. CIRS competent providers have reported a normal range between 3 - 4 pmol/L as an equal correlation to a normal range of ADH < 0.8 pg/ml.

Serum Osmolality (Quest Test #677, LabCorp Test #2071)
Reference range: 280-300 mOsm/L

Antidiuretic hormone (ADH), also known as vasopressin (AVP), is a hormone secreted by the pituitary gland in response to extracelluar fluid hypertonicity. It regulates fluid balance by increasing solute-free water reabsorption back into circulation from the kidney and secondly causes constriction of arterioles increasing peripheral vascular resistance. By these mechanisms, it helps to maintain blood pressure, blood volume, and tissue water content. Osmolality is a measure of the concentration of dissolved solutes such as sodium, potassium, chloride, and glucose**.** **(9)** ADH/osmolality dysregulation occurs in 60% of CIRS patients contributing to symptoms of frequent urination, dehydration, excessive thirst, and headaches. Excessive salt on the skin acts a conduit for electrical static shocks. **(3)**

17) Adrenocorticotropin Hormone (ACTH)/Cortisol (ACTH: Quest Test #211, LabCorp #4440) (Cortisol: Quest Test #4212, LabCorp #4051)

Normal Reference Range:
ACTH: 8-77 pg/mL (Must be drawn between 7-10 am)
Cortisol: AM 4.3-22.4 ncg//dL (drawn between 7-9 am)
PM 3.1-16.7 ncg/dL (drawn between 4-5 pm) (9)

ACTH Dysregulation:

1) **Absolute high: ACTH > 45 or Cortisol > 21**
2) **Absolute low: ACTH < 5 or Cortisol < 4**
3) **Relative: ACTH was < 10 when cortisol was < 7**
4) **Relative: ACTH was > 15 when cortisol was > 16 (2)**

The hypothalamic-pituitary-adrenal (HPA) axis is a feedback response to incoming stress from many body systems. ACTH is released by the pituitary gland and signals the adrenal gland to produce cortisol. Cortisol has many functions among which include stimulating gluconeogenesis, regulating glycogen stores in the liver, immune regulation, and the physiological response of "flight or fight". In the body's reaction to acute illness, stress, inflammation, fever, bacterial or viral infections, cortisol secretion initially rises (if the adrenal gland's capability is intact) to modulate the stress response; however, with chronic exposure to adverse stimuli, typical in CIRS patients, cortisol levels may decrease due to adrenal gland diminution in its ability to maintain an adequate response. As a result of this diminished response, ACTH production is adjusted by the hypothalamic sensitivity to these signals resulting in a subsequent "instruction" to the pituitary gland for the release of the appropriate secretion of ACTH. Unfortunately, in CIRS patients, the capacity to perform this function may not be adequate and symptoms such as daytime fatigue, sleep disturbance, insomnia, dizziness, and fluctuating blood sugar levels may result. **(9)** Dr. Shoemaker has also reported that 60% of CIRS patients with low MSH will experience loss of cortisol regulation. **(7)**

18) **Vasoactive Intestinal Peptide (VIP) – important but no longer measured as testing has been found to be unnecessary**

VIP is a neuro/endocrine peptide possessing diverse cardiovascular effects that include vasodilatation of the cerebral and coronary arteries, stimulation of myocardial contractility, relaxation of smooth muscle in the trachea, stomach, and gall bladder. It is produced by immunoreactive nerve fibers originating from many tissues including the gut, pancreas, and hypothalamus. Often diminished in CIRS patients, resulting symptoms include shortness of breath (especially with exercise), increased inflammatory cytokine release, androgen deficiency, and cognitive impairment. Intranasal administration of VIP has been shown to significantly improve all of the above symptoms and in addition, help correct proteomics, transcriptomics, and grey matter nuclear atrophy. **(7)**

19) Transcriptomics – Gene Expression: Inflammation Explained (GENIE)

GENIE is a relatively new test that is revolutionizing diagnosis and treatment in CIRS patients. It contains 175 reporter genes covering areas such as mitochondrial ATP synthase, toll like receptors, apoptosis, caspases, and more. First conceived 10 years ago, followed by more than 3 years of development and validation, the test became available. CIRS patients are in a state of hypometabolism manifested by pathologic suppression of ribosomal and nuclear encoded mitochondrial genes. **(15)** In 2016, Dr. Shoemaker and James Ryan PhD published research showing the sequencing of RNA in patients with CIRS treated with VIP. The results showed VIP down regulated gene expression which correlated with resolution of symptoms **(3, 31)** These findings suggest a powerful potential for treatment in patients with chronic fatigue, fibromyalgia, and the illnesses with unknown etiologies. **(15)** GENIE can be ordered by patient or provider: www.survivingmold.com/store1/progene-dx**.**

20) Other important tests/procedures to consider

- Pulmonary Function Tests – Baseline on everyone and then as needed (Asthma is associated with obstructive, but if restrictive consider interstitial lung changes associated with CIRS.
- EKG – baseline on everyone and then as needed
- Pulmonary artery systolic pressure (PASP) – Consider this test on any patient who becomes short of breath with exercise or walking up steps that resolves with rest. Inquire if there was a diagnosis of asthma, coronary artery disease, labeled as overweight and out of shape". Echocardiogram is done to evaluate pulmonary artery systolic pressure (tricuspid regurgitation), which should not rise more than 8 Hg during exercise. Elevated PASP, often found in CIRS, can cause palpitations and dyspnea which does not respond to beta 2 antagonists. **(3)**
- VO2 max – consider if fatigue takes days to recover. This "push-crash" syndrome is caused from capillary hypoperfusion and abnormal nuclear encoded mitochondrial genes. Low VO2 max will most likely show decreased ability to perform maximum exercise for more than one to two minutes. **(32)**

21) MRI of the brain without contrast with NeuroQuant

NeuroQuant is an addition to an MRI to determine the volume of 11 regions of the brain and stratified to age. It was developed by CorTechs Labs and cleared by the FDA in 2007. NeuroQuant has been used to evaluate Alzheimer's, epilepsy, traumatic brain injury and PTSD. Additionally, due to high rate of neurocognitive deficits in CIRS patients, studies have demonstrated brain changes and patterns specific to CIRS using NeuroQuant. **(3)** These patterns include:

CIRS-WBD (mold)

- Increased forebrain parenchyma
- Increased cortical gray
- Decreased caudate

CIRS-PLS

- Increased thalamus
- Decreased putamen

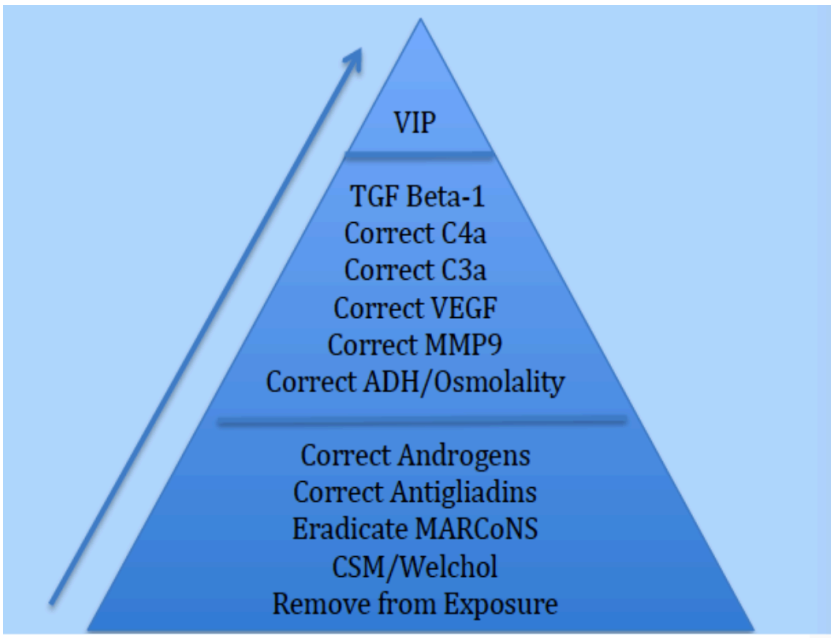
Dr. Shoemaker has developed online software analysis as a scoring system of NeuroQuant (General Morphometry Report) specific to areas of atrophy, asymmetry as well as determining mold vs Lyme. This report is very helpful in determining treatment strategies. This online analysis can be found at https://www.survivingmold.com/store1/online-neuroquant-test **(16)**

Shoemaker 12-step Protocol for CIRS

The Shoemaker protocol involves 12 steps done in specific order and begins with the most important step, removal of exposure. In genetically susceptible individuals, simply removing the exposure will often not be sufficient to correct other associated maladies such as immune dysregulation, neuroendocrine and hormonal abnormalities, inflammation, brain atrophy, coagulation disorders, all contributors to this multi-system, multi-symptom illness.

Removal from exposure is the first and most important step laying the foundation for future treatment success. In determining the source, the practitioner must focus on a deliberate, painstaking, sometimes expensive process which requires extensive knowledge for all conditions in the differential diagnoses that may contribute to the illness. While WDB and PLS are frontrunners in CIRS illness, dinoflagellate (Pfiesteria), food poisoning, Ciguatera, Cyanobacteria, Babesia and spider bite poison have to be considered. Once the source(s) of disease are identified, aggressive measures must be implemented to remove this source of exposure.

The Shoemaker Protocol Pyramid (4)



Step 1: Removal from Exposure

Since WDB is by far the greatest contributor of CIRS, the focus of discussion will center on this. It has been shown that up to 50% of all homes in the United States have water damage allowing for mold proliferation and its associated endotoxins and inflammagens. At times the patient can easily recall past exposure such as a vivid memory of multiple leaks in the childhood home, splotches of black growth on a college dorm wall, dusky smells in previous living quarters, visual presence of mold on a damp area around a toilet or in a crawl space, etc. At other times, however, there is no history of a problem creating doubt in the patient's mind as to how they could possibly be affected. Strong denial of exposure results and stiff resistance to the effort and expense of investigating the cause makes successful management of the illness a challenge.

The practitioner must be diligent in clearly laying the foundation for a regimented process, based on research and laboratory findings, to confirm the diagnosis of CIRS-WDB. It takes compassion and patience to help the patient determine appropriate individual, family, and financial decisions. From the beginning, the patient should be informed about potential length of treatment, approximate cost of testing and office visits, and the need for mandatory encounters with the practitioner every 4-6 weeks to monitor symptoms and insure efficacy of treatment. Even after detailed explanation, the patient often denies that their home, work or school environment could be the cause of such a complex health issue. (3)

Ideally, the patient will be referred to a CIRS trained Indoor Environmental Professional (IEP) to perform an in-depth inspection and necessary testing to adequately assess the home. While

may locations in the US do not have availability of IEP inspectors, many now have remote inspection and testing available, a tremendous advantage for those with limited resources. But in cases when this assessment is not possible, the patient can test their home using a MSQPCR (Mold Specific Quantitative Polymerase Chain Reaction) also known as Environmental Relative Mold Index test (ERMI) and Health Effects Roster of Type-Specific Formers of Mycotoxins and Inflammagens test (HERTSMI-2), both of which offer predictors of whether a building is safe from significant harmful mold exposure. Surface rather than air samples are obtained because surface dust provides historical data as to toxin concentration associated with WDB and air samples only give a snapshot of a 10-15 minute window. **(4)** ERMI and HERTSMI-2 can be obtained through Mycometrics at www.mycometrics.com. ERMI, HERTMI-2, Actinomycetes, and Endotoxins can all be obtained through Environmetrics at www.environmetrics.com. Both provide detailed instruction for collection of samples.

The guidelines below for ERMI should be followed if an individual has genetic susceptibility:

- When the ERMI score is < 2 and the MSH < 35 with a C4a < 20,000, the patient is most likely able to tolerate the environment: however, if the MSH score is < 35 and the C4a is > 20,000, then an ERMI of < 1 is required. **(3, 17)**

A HERTSMI-2 score can be derived either individually or calculated from the ERMI report. It tests for five toxic mold species associated with indoor air: Aspergillus penicilloides, Aspergillus versicolor, Chaetomium globosum, Stachybotyrs chartarum and Wallemia sebi.

- A HERTSMI-2 ≤ 10 is generally consider safe for all, but the most sensitive patients may require a score ≤ 8 for it to be considered a safe environment. **(3, 17)**

Once the presence of elevated toxigenic mold species has been identified, remediation by a highly skilled professional with a clear understanding of the intricacies of biotoxin remediation should be used. After remediation, this should be followed by small particle cleaning again by a skilled professional. This step is most often omitted, a costly error because continued mold exposure from pre-remediated dust may still be present. Assuming remediation and post-remediation small particle cleaning have been successful, a repeat HERTSMI-2 will verify safe entry with a score ≤ 10. Once this confirmation has been achieved, proceeding to Step 2 is permissible.

Step 2: Reducing Biotoxin Carriage with Cholestyramine (CSM) or Welchol

CSM is a non-absorbable medication used to treat elevated cholesterol first approved by the FDA in 1973. It has also been used off label to treat secretory diarrhea cause by Clostridium difficile. **(4, 18)** In 1997, Dr. Shoemaker discovered its benefit in mitigating symptoms associated with a Pfiesteria outbreak in Maryland. Its success in alleviating biotoxin-related symptoms in Pfiesteria exposure led to off label use in other biotoxin illnesses and the development of the

Shoemaker protocol. **(4, 19, 20)** Because CSM has strong toxin binding properties, is non-absorbable and eliminated in the stool, it is an ideal vehicle for removal of these biotoxins. It is therefore considered a first line therapy. Side effects are mostly related to GI symptoms such as constipation, nausea, reflux, and bloating.

CSM can be prescribed through traditional pharmacies readily available under the trade name, Questran or Questran Light. The latter contains aspartame, a component that should not be used in patients with a history of depression, anxiety, or heightened sensitivities to chemicals, dyes, fillers, or sucrose. An alternative might be the compounded version mixed with Stevia. **(4, 18, 21)**

CSM is prescribed four times a day with timing to avoid binding nutrients in food, vitamins, or other medications. It is recommended to begin at a low dose, slowly titrating to full dosing as tolerated. At times, one might experience an "intensification reaction", sometimes confused with the Jarisch-Herxheimer reaction to antibiotics. The intensity of the reaction can be managed by preloading with high dose Omega 3 Fatty Acids (EPA 2.4g and DHA 1.8g/day) a week or two prior to the first dose of CSM. In addition, a low amylose diet is recommended. **(Appendix 4)**

When CSM is not tolerated, Welchol, taken with meals, may be a satisfactory alternative. Unfortunately, it has only 25% binding capacity as compared to CSM. A hybrid therapy has also been proposed: CSM taken prior to breakfast and at bedtime and Welchol taken with lunch and dinner.

Dosing and timing of Medication (Appendix 5)

1) Cholestyramine dosing
Adults: > 120 lbs or > 18
Questran: 9 grams (1 scoop) mixed in 6 oz of water up to four times daily, following guidelines Appendix 5.

Compounding Cholestyramine (CSM): 4 grams mixed with 6 oz water up to four times daily, following guidelines in Table 6

Pediatrics: < 120 or < 18
Questran or Compounded CSM: 60 mg/kg/dose mixed with 6 oz of water, up to three times daily, following guidelines Appendix 5.

2) Welchol dosing
Adults: Welchol 625 mg: Take 2 tablets up to 3 times daily with meals

Pediatrics: Welchol 625 mg: Take 1 tablet up to 3 times daily with meals

Guidelines once treatment begins:

- Repeat VCS test every 30 days after starting CSM
- Consider GENIE testing prior to initiating CSM and then at least every 6 months
- Baseline labs have already been obtained and are repeated with each step of the protocol or at the discretion of practitioner: TGF-beta1, MMP-9, VEGF, MSH, ADH/osmolality and ACTH/Cortisol, Testosterone, DHEA-s, Leptin
- Once VCS test has been passed and confirmation is obtained that home/school/work is free from exposure, discontinue CSM and begin maintenance dose of Welchol 625 mg 1 tablet twice daily
- Should re-exposure occur, have the patient take a VCS test, increase Welchol 625 mg 2 tablets three times per day with meals or preferably CSM 4 g three to four times per day or as tolerated per guidelines and continue for a minimum of 3 days to decrease biotoxin burden and inflammation
- Treatment failure occurs from continued or new exposure, poor compliance or failure to eradicate MARCoNS. **(3)**

Step 3: Eradicate MARCoNS

If MARCoNS testing is positive, begin treatment 30 days after initiation of CSM/Welchol with the compounded medication EDTA. MARCoNS can be resistant to treatment, sometimes requiring up to one year. Dr. Shoemaker reports the surge of overuse of antifungal medications has caused increased resistance to multiple antibiotics making eradication more difficult. Typically, CIRS improvement will not occur until MARCoNS is eradicated. **(22)**

Medication
Adults: EDTA 0.2% - Instill 2 sprays each nostril three times daily. Blow nose first

Pediatrics: EDTA 0.2% - Instill 1 spray alternate nostril three times daily – Rarely needed

Guidelines once treatment begins:

- Initial treatment may cause the patient to feel worse due to "die off", but when starting at a low dose and slowly titrating up, in conjunction with a low amylose diet and high dose Omega 3 Fatty Acids, the incidence of this should decline.
- If "die off" symptoms persist, consider re-exposure and check a VCS test. Row D and E will fall and MMP-9 will increase.
- Retest after 1 month, but rarely is MARCoNS eradicated so quickly. If positive, continue treating for 2 additional months and then retest. May need 6-12 months of treatment. **(2)**
- GENIE can be an invaluable tool to guide length of treatment as two weeks of EDTA has been shown to improve ribosomal suppression. **(23, 24)** VIP can be initiated after 2 weeks on EDTA nasal spray.

Step 4: Eliminate Gluten in AGA Positive Patients

AGA is not celiac disease, but does indicate an inflammatory response to gluten. If positive, initiate a strict gluten free diet for 3 months. This will reduce GI inflammation.

Guidelines once treatment begins:

- If a no amylose diet was initiated during the first step of CIRS treatment, continue for an additional 3 months.
- After 3 months, retest AGA and if negative, slowly reinitiate gluten and monitor for symptoms
- If symptoms return or a patient feels better off gluten, remove for life. **(2)**

Step 5: Correct Androgens: Testosterone/DHEA-s

Androgens (Testosterone and DHEA) may become abnormal due to upregulation in aromatase enzyme. Inflammation causes more rapid conversion of testosterone into estrogen resulting in high estrogen and low testosterone. It is contraindicated to treat with testosterone in these patients. Instead, treating with DHEA will slowly increase testosterone as well as DHEA, with less risk of increasing estradiol, estrone, hematocrit and hemoglobin as often seen in testosterone therapy. **(12)**

Medication
Adults: Men– DHEA 25-75 mg daily, Women 5-25 mg daily

Pediatrics: Not indicated

Guidelines once treatment begins:

- Obtain pre-treatment DHEA-s, Total and Free Testosterone, Estradiol, Estrone, CBC, CMP and at least every 2-3 months
- Do not use aromatase inhibitors with a *α*MSH < 35, as this could cause deterioration
- DHEA can be reduced or discontinued once DHEA-s and Testosterone levels normalize

Step 6: Correct ADH/Osmolality

ADH/Osmolality dysregulation occurs in 80% of CIRS patient's contributing to symptoms of frequent urination, dehydration, excessive thirst, headaches. Excessive salt on the skin acts as a conduit for electricity contributing to static shocks. Desmopressin Acetate (DDAVP) is an exogenous replacement for ADH and is started when osmolality is high > 295. **(2)**

Medication
Adults: Initially one 0.2 mg tablet every other night for 10 nights. Monitor carefully for side effects, specifically weight gain and edema. **(2, 4, 26)**

Pediatrics: 1 -4 sprays per night based on weight and age

Guidelines once treatment begins:

- After 5 doses check ADH, osmolality, electrolytes to ensure normal sodium and potassium
- If on "off days" symptoms persist, consider DDVAP 0.2 mg daily and check electrolytes ADH and osmolality after 10 days.
- Medication taper is required once ADH/Osmolality have normalized
- For patients with POTS, daily DDVAP may be beneficial on a long-term basis, taking care to regularly monitor electrolytes, ADH and osmolality
- May correct acquired von Willebrand's syndrome and reduce MMP-9. Patient's need to carry DDAVP to stop hemorrhage.
- DDVAP is off label use for this purpose **(2)**

Step 7: Correction of MMP-9

As previously mentioned, elevated MMP-9 is often corrected with high dose Omega 3 Fatty Acids – EPA 2.4 g and DHA 1.8 g daily, which may have been initiated prior to starting CSM/Welchol to prevent intensification reaction. Actos 45 mg daily is rarely used in current treatment protocols due to black box warning for bladder cancer.

Step 8: Correction of VEGF

VEGF is a growth factor which in healthy people dilates blood vessels in response to hypoxia inducible factor (HIF). Hypoxia occurs when inflammatory cytokines bound to the endothelium release chemicals narrowing the capillaries. Hypoxia causes symptoms of decreased muscle endurance, poor endurance, fatigue and cognitive decline.

Often Steps 1-7 will have corrected VEGF, but exercise can be added to optimize levels. VEGF is secreted in response to exercise; however, this is a double-edged sword as many patients are noncompliant with exercise recommendations due to significant loss of endurance experienced during exercise. Start with high intensity exercise lasting from seconds to several minutes and with time transitioning to anerobic conditioning for optimal response. **(26)** Consistency is key to provide ongoing signaling for the body to produce VEGF. Once VEGF has normalized, treat capillary hypoperfusion, low V02 and post exercise malaise. Dr. Shoemaker recommends graded exercise started in the following way:

- Start with cardio exercises for 5 min daily working up to 15 minutes daily
- Then add floor exercises 5 minutes daily working up to 15 minutes daily
- Then add free weights 5 minutes daily working up to 15 minutes daily
- After one month, go back to each exercise and add intensity **(27)**

Step 9: Correction of C3a

C3a is an anaphylatoxin which stimulates histamine release from mast cells, causes contraction of smooth muscle, capillary hypoperfusion and increased vascular permeability. The presence of bacterial membranes elevates C3a and an example of activation of C3a would be active Lyme disease. **(4)**

Medication
Adults: High dose Statins 80 mg daily to reduce C3a. **(26)**

Guidelines once treatment begins:

- Obtain pre-treatment liver enzymes and monthly while on treatment
- Statins lower CoQ10 so add 100-150 mg daily while on treatment

Step 10: Correction of C4a

This marker is of great significance to CIRS-WDB and will also be elevated with exposure to dinoflagellates, cyanobacteria and persistent Lyme disease. Additionally, increased C4a can play a role in changes of six executive functions: decreased concentration, difficulty with word finding, decreased assimilation of new knowledge, confusion and disorientation. It potentially also plays a role in Alzheimer's disease and with a decrease in C4a cognitive symptoms can improve. **(3)**

Medication
Adults: VIP Nasal spray 50 mcg/ml – 4 sprays daily **(26)**

Guidelines once treatment begins:

- Rarely need to treat if < 5000, but if > 10,000 will cause adverse effects **(25)**
- Obtain pre-treatment C4a, liver enzymes, lipase, amylase and monthly while on treatment
- This test is not only used for assessment of current exposure but also re-exposure as well as an increase in C4a can occur within 10 minutes of exposure
- Procrit was previously used but no longer recommended due to black box warning for risk of blood clotting **(3)**

Step 11: Reduction of TGF beta-1

TGF beta-1 is a very important protein playing an important role in the regulatory properties of the immune system especially with regard to tissue repair and fibrosis.

Medication
Adults: Losartan 1-2 times daily for 30 days **(26)**
For patient with low blood pressure or unable to tolerate Losartan, use VIP 50 mcg/ml intranasally 4 spays daily **(3)**

Pediatrics: Losartan 0.6/0.7 mg/kg/day in divided doses twice daily

Guidelines once treatment begins:

- Monitor blood pressure twice daily during first month of treatment
- Obtain pre-treatment lipase, GGTP, TGF beta-1 and then monthly while on treatment

Step 12: VIP (Vasoactive Intestinal Polypeptide)

This final step is without a doubt the most impressive and beneficial for those with sustained or severe illness**.** Exogenous VIP given intranasally can reverse SOB with exercise, downregulating cytokines (decrease inflammation), normalize TGF beta-1, androgen deficiency, improve cognition, correct proteomics, transcriptomics and improve grey matter nuclear atrophy in CIRS. **(7)**

Adults: Full strength VIP 500 mcg/ml – Instill 1 spray (50 mcg) intransally four times daily – alternating nostrils with each application. Higher doses have been used depending on severity of symptoms and atrophy.

Pediatrics: VIP has not been well established in pediatric patients

Guidelines before initiating VIP: (2, 3, 23, 28, 29)

- Thoroughly educate patient and family regarding risks, benefits, alternative, side effects, importance of following protocol and consider written consent.
- Proof of lack of exposure to biotoxins (ERMI < 2 or HERTSMI-2 ≤ 10.
- Must pass VCS test.
- Negative MARCoNS – this is often very difficult to achieve due to persistent nature of MARCoNS; however, with the increased use of GENIE, there is some indication that the genes associated with MARCoNS are downregulated within two weeks. In the future, this may become part of the VIP protocol as more data is obtained.
- Normal lipase, GGTP

- Consider obtaining a stress echocardiogram to evaluate pulmonary artery systolic pressure (tricuspid regurgitation), which should not rise more than 8 Hg during exercise. Elevated PASP often found in CIRS can cause palpitations and dyspnea which does not respond to beta 2 antagonists. **(3)**
- Office visit for Pre-VIP Vital Signs and physical exam: (BP, pulse), examination of skin and abdomen. Have patient instill 1 spray in one nostril. Then check VS Q 5 minutes X3 and assess for occurrence of rashes. Ask patient if breathing or joint pain has improved or if there is the presence of abdominal pain.
- Ideally TGF beta-1 and C4a would be done at baseline and again 15-minutes post VIP. If a two-fold increase, consider continued exposure. This is difficult for practices without lab facilities. **(2)**

Guidelines once treatment begins:

- Monthly lipase, GGTP and abdominal exam. VIP must be discontinued with elevated lipase, consider gallbladder disease and/or pancreatitis, or with abdominal pain or rash.
- VIP duration ranges from 6 months to 18 months.
- Regularly assess symptom improvement, CIRS biomarkers, VCS test, cognition, and when normal consider tapering down to 2 sprays daily for 30 days, followed by 1 spray daily for 30 days, and then discontinue. **(3)**
- Repeat NeuroQuant MRI after 9-12 months of VIP. VIP has been shown to correct CIRS-WDB and improve or reverse CIRS-WDB related atrophy noted on NeuroQuant MRI. **(30)**
- Follow up at 6-months post VIP to ensure stability, VCS and labs remain normal **(3)**

Re-exposure instructions

It is almost inevitable a CIRS patient will experience re-exposure and it is imperative that a plan is in place to quickly mitigate damage to prevent full blown CIRS relapse. The following are guidelines for Sequential Activation of Innate Immune Elements – SAIIE)

- Treat with CSM or Welchol to re-establish control lab values
- Patient must stay in a safe environment and stop all biotoxin medication
- After 3 days, measure VCS, C4a, Leptin, MMP-9, TGF beta-1, VEGF, Factor VIIi
- Patient continues to stay off all biotoxin meds
- Re-expose patient to the problematic building for 8 hours
- Retest labs the morning after, then re-expose patient to the building for another 8 hours
- Retest labs the morning after and have patient stay in the building for another 8 hours (3rd exposure to problematic building)
- Retest labs for the 3rd time since baseline
- After labs, restart CSM or Welchol if patient is experiencing symptoms of CIRS **(3, 18)**

Predictive lab changes with re-exposure

- C4a increases in 4 hours
- Leptin increases on day 2
- MMP-9 increased on day 2-3
- VEGF increases on day 1 and crashes day 3 **(6)**

Summary

It does not matter if your area of expertise is primary care, pediatrics, OB/GYN, pulmonology, rheumatology or endocrinology, a patient experiencing CIRS will present on a regular basis. These are the most complicated, often times misunderstood patients whose quality of life has been severely impacted by this little recognized, but very dramatic illness. Many CIRS patients have seen 10-15 or more practitioners, often given diagnosis of chronic fatigue, fibromyalgia, anxiety, depression, bipolar disorder and OCD. They may have spent hundreds, if not thousands of dollars on their healthcare without benefit.

As a practitioner, becoming proficient in the management of CIRS illness, has been a professional game changer and an intellectual challenge like no other aspect of my education endeavors. It is truly impossible to turn a blind eye to an illness that once learned, smacks you in the face on a regular basis. This patient population is intellectually and emotionally challenging; yet the rewards are great. It is helpful to keep in mind that despite great efforts on the part of the provider, not all patients have the will, sheer determination or financial means to do the work it takes to get better.

I stand in amazement each and every day that as a family doc in rural Maryland treating a strange and unforgiving illness, Dr. Shoemaker extrapolated this experience into a research driven, self-made “university” mentoring and educating hundreds of medical practitioners and professionals throughout the world, and in doing so, saving thousands of lives. The professionals who have surrounded him are determined, smart, and dedicated to spreading information about CIRS. Thank you, Dr. Shoemaker.

The amount of research and study that goes into the journey towards certification in the Shoemaker protocol is intense. Not only did I rely on vast research articles, books and slide presentations, but the certification papers of other practitioners obtaining certification were invaluable to organizing the protocol in a succinct and straight-forward manner. I would like to acknowledge the excellent work by Drs. Thomas, Smith, Hoffman, Berry, Lawson and advanced nurse practitioner’s Beshara, Meinhardt. Thank you! Also, a big thank you to Deb Waidner for always “being there” to answer millions of questions, offer encouragement and motivation. She is counselor extraordinaire, extremely dedicated and a lot of fun! Thank you, Deb! Finally, my sincere thanks to my physician husband who is intrigued by CIRS and has learned so much as he expertly edited this paper to make it “presentable” to others!

For all those CIRS professionals, I love this quote: “Those who danced were thought to be quite insane by those who could not hear the music” (Angela Monet). CIRS is the dance and we are the dancers.

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Appendices

Appendix 1: Toxic Stew of a Water Damaged Building (Toxins, Inflammagens, Microbes)

Fungi	Aspergillus penicillodies, Asperigillus versicolor, Wallemia sebi, Stachybotyrs chartarum, Chaetomium globosum
Bacteria	Mycotoxins, hyphal fragments, conidia, mannans, spirocyclic drimanes, Chitinases
Bacteria fragments	Endotoxins, Lipopolysaccharides, Actinomycetes, Nocardia, Hemolysins
Protozoa	Protozoa and amoebas
Inflammagens	Siderophores, Beta glucans, Cell wall component, cell fragments, proteinases
VOCs	Microbial VOC's, building material VOC's, Inorganic xenobiotics
Particulates	Bioaerosols, Course particulates, Fine particulates, Ultrafine particulates, Mano-sized particulates

Appendix 2: Cluster of Symptoms (Yes or No) – Highest score 13

Diarrhea Abdominal pain Numbness	Impaired memory Difficulty with word finding
Disorientation Metallic taste Watery eyes	Unusual skin sensitivity Tingling Tremors Unusual pain
Congested sinuses Shortness of breath	Blurred vision Night sweats Mood swings Ice-pick pain Red or bloodshot eyes
Muscle weakness Body aches Headache Sensitivity to light Trouble learning new info	Excessive thirst Confusion Cough
Vertigo Static shocks	Joint pain Morning Stiffness Muscle cramps
Trouble regulating body temperature Increased urinary frequency Appetite swings	Trouble concentrating
Persistent fatigue	Score: / Date:

Appendix 3: Rosetta Stone (Appendix of Surviving Mold)

	DRB1	DQ	DRB3	DRB4	DRB5
Multisusceptible	4	3		53	
	11/12	3	52B		
	14	5	52B		
Mold susceptible	7	2/3		53	
	13	6	52A, B, C		
	17	2	52A		
	18*	4	52A		
Borrelia, Post Lyme Syndrome	15	6			51
	16	5			51
Dinoflagellates	4	7/8		53	
MARCoNS – Multi Antibiotic Resistant Coagulase Negative Staph Aureus	11	7	52B		
No recognized significance	8	3, 4, 6			
Low risk Mold	7	9		53	
	12	7	52B		
	9	9		53	

Appendix 4: Low or No Amylose Diet (www.survivingmold.com)

FORBIDEN FOODS

- Roots and tubers including white and sweet potatoes, beets, peanuts, carrots, and other vegetables which grow underground. Onions and garlic are permitted.
- Bananas (the only forbidden fruit).
- Wheat and wheat-based products including bread, pasta, cakes, crackers, cookies.
  Rice
- Oats
- Barley
- Rye
  Foods with added sugar, sucrose, corn syrup, or maltodextrin

ALLOWED FOODS: Allowed foods include basically anything that is not on the list of forbidden foods including:

- Corn
- Onions
- Garlic
- All vegetables that grow above the ground: including lettuce, tomatoes, beans of all types, peas, cucumbers, and celery
- All fruits except bananas.
- Meat, fish, and poultry
- Condiments (avoid low-fat varieties as they usually contain added sugar)
- Spices
- Eggs
- Dairy (avoid sugar-laden products)
- Nuts
- Sunflower, pumpkin, and squash seeds
- If you have been advised to be on a gluten-free diet, no changes need to be made in order for you to eat gluten-free. This diet does not allow rice while gluten-free products often use rice as a substitute for wheat

Appendix 5: Cholestyramine (CSM) Protocol (www.survivingmold.com)

Cholestyramine (CSM) Protocol

1. On an empty stomach, take 4 gms of CSM mixed with 4-6 oz. water, or juice.
2. Stir well and swallow. Add more liquid, if necessary, to consume full amount of powder
3. Drink an extra 4-6 oz of liquid.
4. After 30 minutes, you may eat or take meds (wait at least 2 hours before taking thyroxine, digitalis, theophylline, Coumadin and others; ask your doctor for information).
5. Take CSM 4 times a day!
6. If you eat first, wait at least 60 minutes before taking your next CSM.
7. Reflux, constipation, bloating and bowel distress are not unusual.
8. Use acid blocking medications if needed. Talk to your doctor about this.
9. Use Miralax to relieve constipation