Chronic Inflammatory Response Syndrome
The Shoemaker Protocol

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The phenomenon of “Mold Ilness” has gained increased attention in the past year, but the condition is not new. Dr. Richie Shoemaker, pioneer and visionary in the field of Chronic Inflammatory Response Syndrome (CIRS), has been researching the subject for 18 years. He has identified and documented the etiology, physiological dysregulation, objective clinical manifestations, specific laboratory markers, and effective treatment of this previously elusive syndrome.

The following protocol has evolved from experience with more than 10,000 patients. Compelling scientific data has been meticulously measured, documented and published in peer-reviewed journals, to shed light on a phenomenon that may potentially impact up to 25% of the population.

Patients are encouraged to partner with Shoemaker Certified Physicians or Nurse Practitioners who are experts at diagnosing and treating them systematically according to this evidence based protocol. With appropriate diagnosis, education, treatment and support, CIRS patients can not only survive, but also THRIVE as they recover their health.

The process requires serious commitment and dedication of both patient and practitioner. The reward, for the vast majority of CIRS patients, is a quality of life that they have not experienced for years, and that many had lost hope of seeing again. The roadmap to success has been validated and will continue to evolve with new scientific discovery and understanding.

1. Differential Diagnosis is the first step on the road to recovery. Many CIRS patients are misdiagnosed multiple times due to lack of a comprehensive and meticulous history, physical exam, and laboratory assessment. Labels like CFS, fibromyalgia, depression, MS or “somatization” are meaningless without a differential diagnosis that includes CIRS.

A systematic and detailed history is often the key to recognizing CIRS. The standardized Symptom Cluster Analysis is used as a format for interviewing the patient. 37 distinct symptoms, grouped in 13 clusters are carefully explored with the patient. Positive findings in 8 of the 13 clusters suggest the

presence of CIRS. This instrument is NOT to be given to the patient for independent completion, as nuances of symptoms may be missed.

A comprehensive medical history includes previous medical diagnoses, medications, supplements, surgeries, major injuries, hospitalizations, and allergies. A developmental and behavioral assessment includes pregnancy complications, school performance, behavioral anomalies and mood volatility.

A thorough environmental history is critical. Any potential (past or present) exposure to Water Damaged Buildings (WDB), molds, herbicides, pesticides, petrochemicals, known toxins or other volatile organic compounds are documented. Any known tick bite or high-risk activities such as hiking, camping, gardening, especially in endemic areas, is noted. History of exposure to toxin-carrying fish or algae blooms is also questioned.

Family medical history and pertinent symptoms are also elicited. It is helpful to have a family member present for this interview. The patient may have limited recall due to cognitive effects of CIRS. The triggering event for CIRS may be recent, or may have occurred years previously. Once triggered, the toxins will remain, in genetically susceptible individuals, until properly treated.

A complete physical exam is conducted to assess for any confounding illness. Specific physical findings common in CIRS include pallor, cool hands or feet, dermatographia, weakness of shoulder anti-gravity muscles with normal grip and shrug strength, malar rash, mild dehydration, postural hypotension, bilateral conjunctival injection and tearing, resting tremor, abnormal gait, and a particular sub-set will be tall and thin with hyper-flexibility.

Visual Contrast Sensitivity (VCS) testing, a scientific tool for evaluating neurotoxicity caused by biotoxins, is conducted to establish a baseline and repeated after each step of the protocol to monitor clinical progress. (see manual for VCS Procedure). A regression in VCS is evidence of re-exposure to a biotoxin.

An extensive blood profile is drawn to look for HLA-DR and characteristic inflammatory markers that are unique to CIRS. These include HLA-DRB 1,3,4,5 and DQB1, C3a, C4a, MMP-9, TGF beta-1, ADH/Osmolality, VEGF, and VIP. Additional labs, to rule out potential confounding conditions, are also obtained. These generally include anti-gliadin antibodies, anti-cardiolipin

antibodies, Cortisol, DHEA, CMP, CBC, CRP, ACTH, TSH, Testosterone, Lipid Profile, Vitamin D3, Leptin, CD4/CD25, and von Willebrand factor. If Lyme disease is part of the differential diagnosis, a Western Blot is drawn. Biomarkers including C4a, TGF beta-1, MMP9, VEGF and VIP are measured repeatedly as the patient progresses through the sequential steps of the Protocol in order to objectively measure and document clinical progress.

An MRI with NeuroQuant is utilized to demonstrate predictable brain changes that are caused the disruption in blood brain barrier that occurs in CIRS. NeuroQuant is a volumetric computer program applied to the brain MRI. Mold exposure is reflected by the unique “fingerprint” of microscopic interstitial edema of white matter in the forebrain and cerebellum as well as gray matter atrophy and decrease in volume of the caudate nucleus.

Spirometry is performed as part of the initial evaluation. FVC, FEV1, O2 saturation, and FEV1/FVC % are measured. Restrictive lung disease is commonly seen in CIRS. FVC will be reduced and FEV1 to FVC ratio will be normal or elevated in restrictive pulmonary disease. Spirometry is re-evaluated as biomarkers are corrected. A deep nasal culture for multiple antibiotic resistant coagulase negative staph (MARCoNS) is also obtained at the first visit if CIRS is suspected.

2. Perform MSQCPR (mold-specific quantitative polymerase chain reaction) fungal DNA testing to ensure there is no ongoing exposure to water damaged buildings. The QPSR is an objective, standardized DNA based method of identifying and quantifying molds. **ERMI (Environmental Relative Moldiness Index) Testing** tests for 36 species and is currently the best predictor of total mold burden. ERMI should be <2 if the patient’s C4a less than 20,000. If the C4a is more than 20,000, the ERMI must be a negative 1. The “HERTSMI-2″ score looks at 5 organisms from group I in ERMI and assigns weight to the values. Any score over 10 is a problem. NOTE: These numbers are general guidelines. Some patients will remain symptomatic even once these values are obtained. Building performance must be evaluated and optimized as an integral part of this process, in order for patients to obtain and continue clinical success.

3. Remove from exposure to Water Damaged Buildings. Continued exposure to a WDB (home, work, school, etc.) will sabotage patient recovery. This must be stressed to patients and families. Toxins cannot be removed efficiently and physiology corrected if biotoxin exposure is ongoing. Patients

who have been dealing with the illness for a longer period, and have been triggered numerous times by WDB, may exhibit a “sicker quicker” phenomenon. Auto activation of MASP-2 results in increased C4a with profound diffuse inflammation and capillary hypoperfusion. As little as 10 minutes exposure is capable of activating innate immunity & unleashing a predictable cascade of potentially devastating inflammatory substances. Vigilant environmental monitoring and appropriate avoidance is critical to clinical recovery. If the patient is considering moving to a new building, temporarily or permanently, it is essential to do a QPCR evaluation on the new structure prior to relocating. Proper decontamination of non-porous contents is critical. Porous items such as mattresses, upholstered furniture, and paper items will invariably need to be replaced.

4. Reduce biotoxin load in the body with Cholestryamine 4 grams on an empty stomach QID (may need to ramp up gradually). Patients are given an instruction sheet on proper use and timing of CSM in relation to medications, supplements and food (See Appendix A). Use Welchol 2 tablets tid, with food, for those who do not tolerate CSM. Welchol is only ¼ as effective in binding capacity. Compliance may be facilitated by using CSM in the morning and at bedtime, with Welchol taken at lunch and dinner. In very sensitive individuals, CSM may be preceded by 1 week of high-dose fish oils and a low amylose diet. Low amylose diet handout is given (See Appendix B). This therapy is continued for at least 5 days after CSM is started. Monitor progress with VCS vision test. Once the patient has passed the VCS test, the next step of the protocol begins. NOTE: At the end of the protocol, patients are instructed in the prophylactic use of CSM or Welchol for potential re-exposure.

5. Eradicate biofilm forming Multiple Antibiotic Resistant Coagulase Negative Staphylococcus (MARCoNS), detected by deep nasal culture. (See manual for nasal culture procedure). If the API-Staph culture (specific for coagulase negative staph) shows resistance to two or more distinct classes of antibiotics, give BEG Spray (Bactroban, EDTA, Gentamicin) 2 sprays in each nostril tid for 1 month. A repeat culture is taken 1 week after completing BEG spray. Persistent MARCoNS is treated with plain EDTA, 2 sprays in each nostril tid for 6-8 weeks, to dissolve stubborn biofilms. Re-culture is performed after 1 week off the spray. If MARCoNS persists after the above steps, consider canine exposure, close contact with another person with low MSH or ongoing environmental exposure. MARCoNS exists in the presence of a low MSH. Once MSH is levels are corrected, the opportunistic organisms should not return unless there is re-exposure and relapse.

6. Correct anti-gliadin antibodies (AGA) by avoiding gluten-containing foods for at least 3 months. Low MSH causes dysregulation of T-reg cells with the potential development of autoimmune disorders. Re-check AGA after 3 months and, if negative, the patient may cautiously and gradually re-introduce gluten into the diet, while documenting re-emergence of any symptoms. If AGA is still positive, celiac disease must be ruled out. If Tissue Transglutaminase (TTG) antibodies are elevated, gluten is permanently eliminated. NOTE: Many patients will feel better without gluten, even when the TTG antibodies are normal.

7. Correct androgens. Abnormal androgens are commonly caused by up-regulation of aromatase. If DHEA is low, supplement DHEA, up to 25 mg. tid for 1 month. Estradiol levels are checked after two weeks on DHEA. Excess aromatase activity will be corrected by VIP later in the protocol. Treatment with testosterone is contraindicated, at this stage, as up-regulated aromatase activity will promote conversion of testosterone to estrogen.

8. Correct elevated MMP9. Matrix Metalloproteinase 9 is an enzyme that disrupts the basement membrane of endothelial cells, increasing vascular permeability and allowing inflammatory compounds to enter the brain, nerves, muscles, joints and lungs. This enzyme significantly weakens the blood brain barrier and may cause debilitating neurological symptoms, seen in the most compromised CIRS patients. If MMP9 is elevated (over 332ng/ml) it is treated with a low amylose diet and high dose fish oil (2.4 gm. EPA and 1.8 gm. DHA total daily dose).

9. Correct ADH / Osmolality. Biotoxin patients often experience a low ADH and an increased serum osmolality due to the inability of the kidneys to hold on to free water. Symptoms include polydipsia, polyuria, postural hypotension, migraine-like headaches, and frequent static shocks. Low ADH/high osmolality may mimic Postural Orthostatic Tachycardia Syndrome (POTS). Low ADH is treated with desmopressin (DDAVP) 0.2 mg every other day, at hs, for 2 weeks. Serum sodium is checked in 5 days and again at 10 days to monitor for hyponatremia. Daily weights and weekly electrolyte monitoring is indicated if DDAVP therapy is potentially required longer than 2 weeks.

10. Correct VEGF. Vascular Endothelial Growth Factor stimulates angiogenesis in response to Hypoxia Inducible Factor and promotes capillary

vasodilatation. VEGF is often suppressed (less than 31 pg/ml) in patients with CIRS. This results in capillary hypoperfusion and diffuse tissue hypoxia. Symptoms of “brain fog”, fatigue, muscle pain, dyspnea on exertion and post-exercise exhaustion are often associated with a low VEGF. It is treated with a low amylose diet and high dose fish oil (see Step 8 above).

11. Correct elevated Complement C3a. This split product of complement activation is elevated in the presence of bacterial membranes, such as Borrelia. If elevated, the bacterial infection is first treated with antibiotics. If C3a remains elevated, a statin can be used to lower the level. Zocor 80 mg/day is given along with CoQ10 150 mg/day. 10 days of CoQ10 therapy, prior to starting Zocor, is suggested to minimize side effects due to reduced levels of ubiquinone. Liver enzymes are evaluated prior to starting statins and repeated in 1 month.

12. Correct elevated Complement C4a if levels are greater than 2830 ng/ml. C4a is also a split product of complement activation and a potent anaphylatoxin. Elevation is due to the diffuse inflammation caused by CIRS-WDB. C4a is a critical marker that indicates the acute severity of the syndrome. VIP (Vasoactive Intestinal Polypeptide) is the treatment of choice. It is a nasal spray, dosed at 50 mcg/ml, 1 spray qid. (See Step #14 for guidelines.) Older treatment regimens that employed mini-dose erythropoietin are no longer recommended.

13. Correct elevated TGF-B1. Transforming Growth Factor Beta-1 causes dysfunctional tissue remodeling. It down-regulates VEGF and influences T-reg cells to induce autoimmunity. A CIRS specific T-Reg Cell Panel (CD4+CD25++CD127 lo/-) may be ordered to evaluate pathologic immune response. If TGF-B1 is elevated (over 2380 pg/ml), treat with losartan, beginning at 12.5 to 25 mg daily. Once blood pressure is stabilized, increase to 25 mg bid for 30 days. A metabolite, specific to losartan, (exp 3179), lowers TGF-B1 levels. Blood pressure monitoring is important during therapy, especially for patients already on anti-hypertensive agents.

14. Correct low Vasoactive Intestinal Polypeptide (VIP) if the patient is still symptomatic after the above steps. The fundamental goal of CIRS Treatment is to restore the regulation of the innate immune system. Some patients will achieve this goal before completing all the sequential steps of the Protocol. For those who are still symptomatic at this stage, VIP offers real hope. The nasal spray is dosed at 50 mcg/ml, 1 spray qid. The first dose is given in the office. A TGF-B1 level is drawn prior to the VIP administration and again 15 minutes later.

If there is a rise in TGF-B1, it is an indication of hidden mold exposure. It is critical that there be no continued mold exposure, that MARCoNS culture be negative and VCS testing is normal before starting VIP. When those conditions are met, VIP has the ability to correct C4a, TGF-B1, VEGF, MMP9, estradiol, testosterone, Vitamin D3 and Pulmonary Artery Systolic Pressure. It can dramatically improve quality of life. Serum lipase is tested prior to beginning VIP, and monthly during VIP therapy. If there is a significant rise in lipase, determine the cause as this may require the cessation of VIP therapy.

15. Monitor stability of clinical symptoms & laboratory tests off of medications. Vigilance concerning re-exposure is essential. Patients are instructed in prophylactic use of CSM or Welchol for potential re-exposure.

Dr. Shoemaker's depiction of the Biotoxin Pathway has given us a previously unappreciated view of innate immunity and the cascade of dysregulation caused by biotoxins and other inflammagens in genetically susceptible individuals. Ongoing research on the genomics of CIRS, by Shoemaker and Ryan, continues to expand our understanding of this very prevalent syndrome and its successful clinical management.

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Appendix A: 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

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Appendix B: No Amylose Diet

FORBIDDEN 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.
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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.
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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.