Chronic Fatiguing Illnesses:
Entering the era of new biomarkers and therapies

Ritchie C. Shoemaker[1,4]*, Andrew Heyman[2], Annalaura Mancia[3] and James C Ryan[4]

[1]Center for Research on Biotoxin-Associated Illnesses, Pocomoke, MD, USA

[2] George Washington University, Washington DC, USA

[3]University of Ferrara, Ferrara, Italy

[4]ProgeneDX, LLC, Deerfield Beach, FL USA

* Corresponding author ritchieshoemaker@msn.com

Section 20
CIRS Treatment Protocol

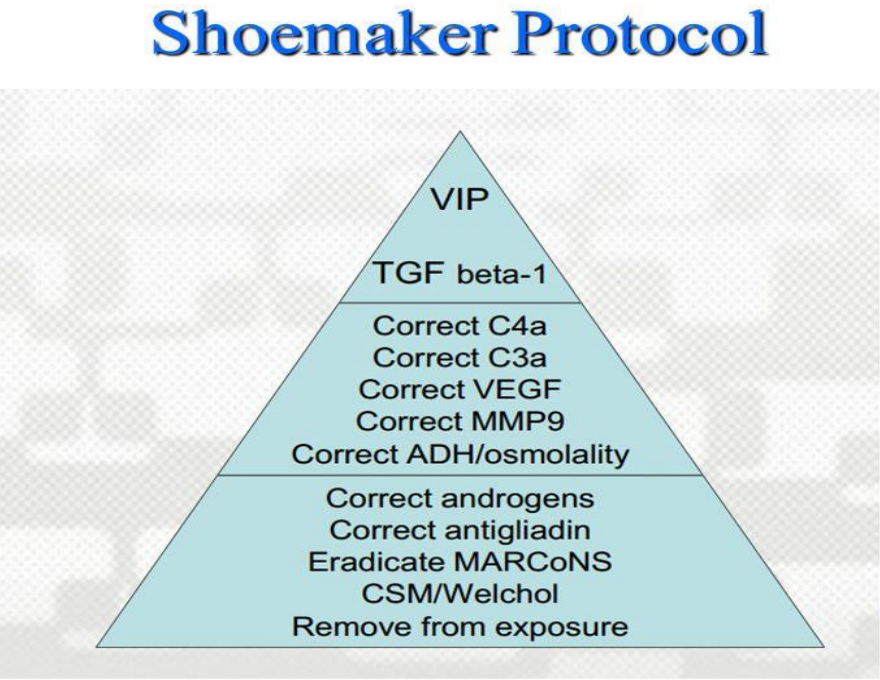
Treatment for CIRS is a lengthy process designed to (i) first remove the patient from the exposure(s); (ii) modulate both stress responses and inflammatory responses; (iii) decrease the inflammatory burden and allostatic load; (iv) repair damage to organs systems.

Allostatic load is defined by McEwen (41) as "wear and tear" or overload in response to being in a chronic state of allostasis (change). Sleep deprivation, maladaptation, poor nutrition, and exercise habits contribute to this weathering effect. Initial increase in stress and change is good for the body and the brain, but chronic stimulation and increased allostatic load can be detrimental. Patients with CIRS have an increased allostatic load due to the chronicity of the inflammatory response and consequent metabolic derangements. Reduction of internal metabolic resources leads to loss of physiologic and psychologic resiliency as a result, and creates vulnerability for more permanent injury to the brain, organ and microvascular systems.

An 11-step treatment protocol for CIRS has been developed over the last two decades. Proper diagnosis relies on a combination of detailed history, physical examination and diagnostic data highlighted throughout. Evaluation needs to include determining the potential biotoxin exposure, length of exposure / re-exposure and co-morbid conditions.

The treatment process is staged and progressive. Detailed patient education and encouragement are paramount. CIRS is a complex immunological disorder resulting from uncontrolled inflammation involving primarily the innate immune system. Some patients move quickly through the protocol while others do not. Some individuals can "get stuck" in one treatment step or often even "backslide" into an already completed step. Treatment is highly individualized

depending on exposure and concurrent disease states but in each patient the basic format of the protocol is invariant. Therefore, the CIRS treatment protocol will take time and requires a significant amount of patient education and support.



Step 1: The initial step of this protocol requires the individual to remove himself from exposure to habitat containing biotoxins/inflammagens. Treatment is designed to remove biotoxins from carriage in the body, so stopping addition of biotoxin burden to the body comes first. A baseline VCS test is performed. Step 1 is often the most overwhelming part of the protocol as it involves a change in lifestyle. Biotoxins, and inflammagens too, if not removed, will continue to adversely affect the immune, neurologic and gastrointestinal systems (and more: this illness is systemic). While no one body system works in isolation, CIRS patients have a dysregulation of multiple body systems requiring a detail-oriented approach to healing. Proper emotional and dietary support is essential for many to reach successful completion of this protocol and return to health. Dietary considerations may include elimination of inflammatory foods such as gluten, especially when MSH is low and anti-gliadin antibodies are high. A low-amylose diet is suggested for some to help reduce or eliminate a naturally occurring starch (example: wheat, rice, oats, banana and potato) and foods containing added sugars/corn syrups, as they may contribute to elevated MMP9.

Step 2: Cholestyramine (CSM) is a prescription bile acid sequestrant originally designed to lower cholesterol. An anion binding resin, CSM has a quaternary ammonium side chain which creates a localized, net positive charge which enables CSM to hold on to net negative charges from biotoxins that have an anion ring in water solutions. Acting like a sponge to assist in elimination of these biotoxins, CSM will also bind to food, medications and supplements.

Therefore, the drug is administered 30 minutes before food and medications; or 60 minutes after. If a patient has low MSH, this patient may "intensify," or begin to feel worse with initiation of treatment. In this instance, encouragement of a low amylose diet and pretreatment with ten days of Omega-3 fatty acids in substantial doses serve to prevent most intensification reactions. CSM is the drug of choice in the CIRS protocol since it contains four times as many electrically active sites than the only other binder confirmed to produce benefit, colesevelam (Welchol). If the patient is unable to tolerate CSM, has multiple food allergies or chemical sensitivities, Welchol usually is far easier to take as it may be better tolerated. CSM remains the drug of choice in the CIRS protocol, but Welchol, taken with food, is far better tolerated.

Recheck VCS after 4 weeks on CSM/Welchol. If patient fails the VCS test after 1 month, consider repeat exposure or poor compliance with CSM. Continue with CSM/Welchol until patient has passed the VCS test.

Step 3: Eradication of multiple antibiotic resistant coagulase negative staphylococcus (MARCoNS) from the nasopharynx. This type of bacteria secretes both biofilm and extracellular products, possibly including a neurotoxin that easily penetrates the olfactory nerve and further inflames the central nervous system. Biofilm production is a marvelous defense mechanism making it difficult for antibiotics to penetrate and eradicate. Be aware that MARCoNS are called "commensal," they do not cause an infection. Patients won't know they have MARCoNS; headaches, runny nose and sinus congestion do not mean presence of MARCoNS. These interesting staphylococci live on mucus membranes suppressing normal host inflammatory responses that would otherwise destroy the organisms. Unfortunately, MARCoNS are resistant to the vast majority of "natural" agents. Use of a specially compounded spray that contains EDTA and antibiotic coverage for both positive and negative-gram bacteria needs to be prescribed. Never use anti-fungal medications, (i) as the CIRS-WDB problem is not fungal infection; and (ii) antibiotic resistance is rapidly transferred to MARCoNS, creating unheard of levels of resistance to gentamicin and vancomycin.

Testing and treatment of MARCoNS typically begins after one month on a Step 2 binder and passing the VCS test. If a patient continues to feel worse while on the antibiotic spray, check for re-exposure, retesting VCS and MMP-9. Recheck MARCoNS nasal swab for pathogen eradication and VCS prior to moving to step 4.

Step 4: Anti-gliadin antibodies (AGA) can develop in the presence of low MSH, signaling an emerging gluten sensitivity, associated with dysregulation of T regulatory cells. An autoimmune disease may result as immune dysfunction progresses, associated with a mounting antigenic burden from repeated gluten exposure in the diet. A strict avoidance of gluten containing food and beverages should be recommended for a period of 3 months followed by repeat blood testing. Any patient with a (+) AGA must then be tested for celiac disease, with TTG-IgA the most straightforward test.

If AGA is negative, the patient can choose to gradually reintroduce gluten into the diet while documenting problematic signs and symptoms. Many patients feel better eliminating gluten completely on an ongoing basis.

Step 5: Abnormal androgens are commonly caused by an unregulated, overexpressed aromatase enzyme leading to a dysregulation of androgenic hormones. If DHEA, testosterone and estrogen are low, supplementation is recommended, understanding that all of these hormones are indirectly regulated by MSH. Continued monitoring of hormone levels are recommended.

Inflammation and low MSH levels can cause testosterone to rapidly convert into estrogens via aromatase, which further decreases testosterone while elevating estrogen levels. Do not give testosterone replacement as this will potentially further suppress testosterone. Following a gluten-free, low amylose diet is key in reducing all sources of inflammation in the CIRS patient.

Always determine DHEA blood level prior to prescribing DHEA. After two weeks of treatment, verify estrogens are not rising. Dysregulation of aromatase in CIRS patients is common. Vasoactive intestinal polypeptide (VIP) nasal spray can also stabilize aromatase at this step and rebalance androgens. Never prescribe VIP if the patient (i) is exposed to mold; (ii) fails the VCS test; (iii) has MARCoNS; and (iv) has an elevated lipase.

Step 6: Dehydration, with excessive urinary wasting of free water stemming from impaired production of antidiuretic hormone (ADH) is a common reason for elevated serum osmolality. Osmolality measures the concentration of electrolytes and other chemicals in the serum. ADH is a pituitary hormone, also made in the hypothalamus that controls free water in the body by inducing the kidneys to resorb water in the collecting ducts. When we drink water, our kidneys work to remove the water while ADH helps us retain it. A high osmolality suggests the blood is concentrated while a low osmolality suggests there is more water in the blood than needed. Common symptoms of hypothalamic dysfunction and low ADH in CIRS include polydipsia, polyuria, headache, static shock, dizziness upon standing (postural hypotension) and Postural Orthostatic Tachycardia Syndrome (POTS). Additional diagnostic tests affected include VIP and MSH.

Treatment of low ADH and high osmolality includes low dose desmopressin (DDAVP). Correction of ADH can result in edema and weight gain due to fluid retention.

⇑⇑ serum osmolality - ⇑⇑ ADH = Normal
⇓⇓ serum osmolality - ⇓⇓ ADH = Normal
⇑⇑ serum osmolality - ⇓⇓ ADH = consider DDAVP

DDAVP can precipitously drop serum sodium, so careful, cautious use of DDAVP protocols are required.

Step 7: Correction of matrix metalloproteinase 9 (MMP-9) will help resolve many symptoms in the cluster of symptoms of CIRS. MMP9 is an enzyme released into the system when cytokines activate specific receptors, particularly on endothelial cells and macrophages. This activation results in increased vascular permeability causing a breakdown of the endothelial basement membrane which provides a barrier between blood contents and the tissues.

Prior to initiating step 7, a thorough examination of diagnostic markers, to include leptin, is warranted. If MMP9 is elevated (over 332 ng/ml, drawn in a chilled SST tube and spun

immediately), encourage low amylose diet coupled with supplementation of high dose fish oil (total dose: EPA 2.4gm and DHA 1.8gm) in divided doses daily.

Step 8: Elevated C3a is associated with smooth muscle constriction and the release of oxidants, leukotrienes and enzymes from the immune system. Hypo-perfusion and vascular permeability also result. An elevated C3a is identified in an active Lyme disease. Therefore, this co-morbid condition should be ruled out.

High dose statin therapy taken for 30 days will reduce T cell activation, macrophage infiltration, vascular wall inflammation and lower C3a. Inhibiting HMG-CoA with drugs like Lipitor or Zocor will reduce the amount of cholesterol produced. Unfortunately, while down regulating the immune system with these products, the important anti-oxidant co-enzyme Q (CoQ10 is one of many Co-Qs) is also depleted. CoQ10 is necessary for the mitochondria of the cells to make energy from carbohydrates and fatty acids. When CoQ10 is low, muscle pain may result.

HMG-CoA medications have side effects, drug and food interactions. Patient education and understanding is necessary prior to initiating therapy.

Step 9: The split product of the mannose binding lectin (MBL) pathway of the complement system is a key determinant of severity for CIRS illness. After C4 is cleaved, complement 4a (C4a) will activate mast cells, basal cells and cause the release of chemotactic factors. C4a will also increase smooth muscle contraction and vascular permeability.

Low dose, short term use of erythropoietin will reduce C4a, but given the FDA Black Box Warning associated with this is prescription product, this drug is now rarely used.

Step 10: Transforming growth factor beta 1 (TGFβ-1) is a critical immune regulator that is often elevated in CIRS patients. Affecting autoimmunity through gene activation, TGFβ-1 turns on Treg cells which regulate Th1, Th2, Th17 cells. Elevated TGFβ-1 has been identified in connective tissue disorders and remodeling of smooth muscle lung cells turning them into fibroblastic cells.

Elevated TGFβ-1 and low MSH contribute to gastrointestinal dysfunction. To normalize, initiate a short course of an angiotensin II receptor antagonist, losartan (Cozaar). Communication with primary care provider is encouraged if patient is on multiple medications of for hypertension.

If the patient has evidence of fibrosis in tissues, especially skin, lung, liver and kidney, think of TGF beta-1. A user's guide to TGF beta-1 follows:

<2,380 Normal
>5,000 multiple symptoms present
>10,000 Restrictive lung disease, tremor, joint and cognitive problems.

Step 11: The final step of this protocol involves administration of VIP nasal spray, which has been shown to reduce vascular constriction and improve blood flow to the brain (thus healing areas of interstitial edema and nuclear atrophy) while inducing regulation of genomic activity

through binding to cell surface membrane receptors. An instructive module regarding use of VIP is found at www.survivingmold.com.

Frequent monitoring and repeating specific diagnostics to include: CIRS biomarkers, ERMI home mold test (Environmental Relative Moldiness Index; the lesser cost of HERTSMI-2 is noted), MARCoNS, and VCS. Until these criteria are met, VIP cannot be prescribed.

MARCoNS, if present, must be eradicated with test of cure documentation

VCS must be normalized

Home and work/school must be cleared of WDB inflammagens and mold with an ERMI score of less than or equal to 2; or HERTSMI-2 must be less than or equal to 10.

Once the decision to initiate treatment with VIP is made, pre-treatment vital signs and biomarkers are to be completed:

TGF β-1

C4a by Quest / National Jewish Center located in Denver, Colorado

VEGF, MMP-9, Vitamin D OH 25, estradiol, total testosterone and lipase

A test dose of one spray is given into each nostril. The patient should be observed for any symptom improvement with vital signs taken every 5 minutes for fifteen minutes. Initial improvement could be described as reduced shortness of breath, relief from joint pain or improved brain cognition. A second set of biomarkers is then drawn to include TGFβ-1.

If there is a twofold increase or more at the second measure of TGFβ-1, 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 offered (Hopkinton Drug, 800-439-4441). Initial dosing is one spray four times a day for 30 days. After a month, the dosage is adjusted based on symptoms.

VIP downregulates MASP2 which is an auto-activating receptor in C4a production that can cause patients to deteriorate rapidly with re-exposure. As VIP normalizes MASP-2, the so-called "sicker-quicker" phenomenon may end even if the patient is re-exposed.

Prescription VIP may cause pancreatitis and increase lipase levels. For this reason, lipase 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 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 removal of the gallbladder may be indicated if VIP needs to be continued.