



TREATMENT OF CHRONIC INFLAMMATORY RESPONSE SYNDROME IN THE PACIFIC NORTHWEST

Linda S Goggin MD
Feel Good Functional Medicine
1815 C St. Ste. K-37
Bellingham, WA 98225
(360) 739-3611
www.feelgoodfunctionalmed.com

TREATMENT OF CHRONIC INFLAMMATORY RESPONSE SYNDROME IN THE PACIFIC NORTHWEST

INTRODUCTION

Practicing as a family physician in Washington State, one learns to love rain. While I enjoy the Pacific Northwest, it took me a few years to understand that the drizzle I loved could create significant health issues in my clients. Over the years I have found a subset of patients challenging to diagnose and adequately treat, often returning with a myriad of symptoms, both cognitive and physical, generally presenting with normal standard laboratory exams such as complete blood count, complete metabolic panel, c-reactive protein, sedimentation rate, urinalysis, and thyroid evaluation. These folks appeared to be “worried well”. In attempting to develop a treatment plan with these patients, I could sense the frustration of a person who felt terrible and was not being given clear answers.

Often in conventional medicine, when a physician sees no clear diagnosis to explain a person's symptoms, the patient is given a descriptive label like fibromyalgia, anxiety or depression, and a prescription for an antidepressant. Being seriously ill and being told you're fine will certainly lead to a symptom complex that is consistent with depression or anxiety! When I developed multiple symptoms and felt bad (knowing that something was drastically wrong in my body) and my physician suggested that I go on an antidepressant, I understood the frustration of others who have had similar experiences.

At that time in my career, I had not yet heard about chronic inflammatory response syndrome (CIRS). Now, reflecting back on all the years and all the patients, I can see that this unique subset of people (who I would try desperately to treat) simply came to my practice a little too early, before I was able to order the correct lab tests, ask the right questions, diagnose and treat this ubiquitous, under-the-radar syndrome which causes so much unnecessary suffering.

UNDERSTANDING CHRONIC INFLAMMATORY RESPONSE SYNDROME

We owe much of our understanding of Chronic Inflammatory Response Syndrome (CIRS) to Dr Ritchie Shoemaker, MD, a family doctor in Pocomoke, MD, devoted clinician researcher, advocate, and public servant, who continues to connect complex clinical dots from bench to bedside, furthering our current understanding of (CIRS), also known as “biotoxin illness” or “sick building syndrome.”

In 1997, Dr. Shoemaker recognized the connection between a symptom complex seen in his patients and exposure to a biotoxin-producing fish-killing dinoflagellate called pfiesteria¹. This discovery opened the door to the recognition of illness-causing biotoxins, similar in size, shape and character, that cause comparable multi-system, multi-symptom illness, recognizable with the right labs, and treatable with the right protocol.

HOW CAN A PERSON BE EXPOSED TO BIOTOXINS?

INHALATION: The air in water-damaged buildings contains a mix of inflammatory particles that include mold, bacteria, toxic metabolic products, cell wall fragments, and other organic compounds that make a susceptible person sick. Not just one thing in the air, the “brew” -- when inhaled by a susceptible person-- causes illness.

TICK OR RECLUSE SPIDER BITE: A patient may not remember being bitten by a tick and still may contract an infection that creates biotoxins such as Lyme Disease (*Borrelia Burgdorferi*) or Babesiosis (*Babesia Microtia*). Most people do remember the bite of a brown recluse or Mediterranean Recluse spider! Ouch!

INGESTION: If a susceptible person eats reef fish contaminated with dinoflagellates (which make Ciguatoxin) they may get sick. These larger reef fish eat smaller reef fish which have dined on the dinoflagellates.

CONTACT WITH CONTAMINATED WATER: Swimming, drinking or inhaling aerosolized particles while in water contaminated with cyanobacteria or other biotoxin producing organisms may cause illness.

A large enough dose of these biotoxins may make anyone sick in the short term, but for those with a genetic susceptibility, who can't break down and remove the biotoxins, it may create a long-lasting illness that worsens with each exposure.

WHEN TO CONSIDER THE DIAGNOSIS

CIRS needs to be considered in any patient who has seen multiple providers trying to understand the source of fatigue along with many symptoms. CIRS patients have out-of-control immune response to biotoxins within their body, giving many symptoms. Many have waxing and waning symptoms, both physical and psychological, throughout their whole lives. Improvement in symptoms may be associated with moves from one place to another, with a presumption that reduction in symptoms after a move are because they're "in a better phase of their life". Sometimes true, other times the improvement is due to moving out of an environment with inhaled toxicants that made them sick, anxious, and depressed. Commonly misdiagnosed with Chronic Fatigue Syndrome, Attention Deficit Disorder, Hypochondriasis, Irritable Bowel Syndrome, PTSD, Allergies, Fibromyalgia, Anxiety, Depression, or "faking it;" the CIRS patient may feel desperate.

Suspecting the diagnosis requires being aware of CIRS, which has broadly made its appearance in the literature of mainstream medicine but is still little known to providers in clinics. With more than 1,700 publications in the literature concerning and related to this illness, aware providers remain hopeful that word will spread-- now that medical schools are beginning to offer courses in CIRS-- and physicians and other health care givers will include this in their differential diagnosis.

CIRS IN PEDIATRICS

The recognition of symptoms due to Chronic Inflammatory Response Syndrome in kids can dramatically change their lives. Identifying early stage CIRS in children proves trickier, as the provider must consider it at an earlier stage, as any multi system multi-symptom illness begins with a single symptom in a single system. Therefore, suspecting chronic inflammatory response syndrome in children who present with symptoms such as headaches, fatigue, gut troubles, respiratory and sinus issues, mood disorders and behavioral problems, could potentially change their whole lives. Identifying CIRS before it blossoms into an extensive syndrome can allow parents and caregivers to make sure the living environment is safe and inform choices throughout the life. Prevalence data from Dr Scott McMahon, a leading CIRS expert and practicing pediatrician, found that CIRS beats out asthma in frequency in the pediatric population with a prevalence rate of 7% compared to 5% for asthma². Identifying affected children, getting them into safe environments and moving them through the Shoemaker Protocol for CIRS can open the door to a remarkably different life for a susceptible child.

WHAT MAKES A PERSON SUSCEPTIBLE TO CIRTS?

Let's begin with a basic explanation of how your immune system works: There are two divisions of your immune system that work together to protect you: the **“non-specific” (innate) immune system** and the **“specific” (adaptive) immune system**.

The nonspecific (innate) immune system is composed of cells that act like sentries of your body. Always on the lookout, they remain ready to mount a general attack when they see invaders. When the cells of the innate immune system identify danger signals or invaders, they send a message to your **specific (adaptive) immune system**, ordering a specialized attack with antibodies to eliminate invaders who might make you sick. Some people's immune systems are great at this; others have a built-in glitch within their HLA genes that creates a breakdown in communication.

GENETIC SUSCEPTIBILITY AND HLA BLOOD TYPES

Specific genetic traits on an area of the sixth chromosome make **1 in 4 people at risk** for illness with exposure to biotoxins. Each person has their own version of HLA complex (human leukocyte antigen), and individual variations affect immune response. It is estimated that 24% of people have one of a group of HLA types in their blood that makes certain biotoxins unrecognizable to the “specific” or adaptable immune system.

Biotoxins enter the body by inhalation, direct contact with contaminated water, ingestion, or through some bites (tick or recluse species spider bite). Exposure of a susceptible person to biotoxins allows these invaders to waltz around scot-free; wreaking havoc in a person's body. These patients' nonspecific immune system attempts to send up the alarm, which the specific immune system does not hear. The persistent alarm affects multiple areas of the body, disrupting the immune system, dysregulating key neurohormonal systems and leading to a host of symptoms. (Figure 1)

When the nonspecific immune system “ramps itself up” (revealing this through easily checked blood markers) it creates a cascade of events in the body that lead to the symptoms of CIRTS. Measuring the biotoxins themselves is not possible because they can travel easily across the membranes of the body, Biomarkers leave a telltale trail of the effects of these biotoxins.

Primary care physicians generally do not know about ordering and interpretation of these markers; that explains why your family doctor can't identify this in your body. Labs commonly ordered by CIRTS specialists include: MSH, MMP9, VEGF, TGF beta-1, AVP/osmolality, ACTH/cortisol, and Visual Contrast Sensitivity testing. A 2017 publication in Internal Medicine Review³ explains current understanding of critical concepts linking the physiology to the biomarkers of CIRTS. Imagine the relief someone feels who

has been told their symptoms are “all in their head” when lab work clearly shows that their symptoms have a real cause **and** an effective treatment.

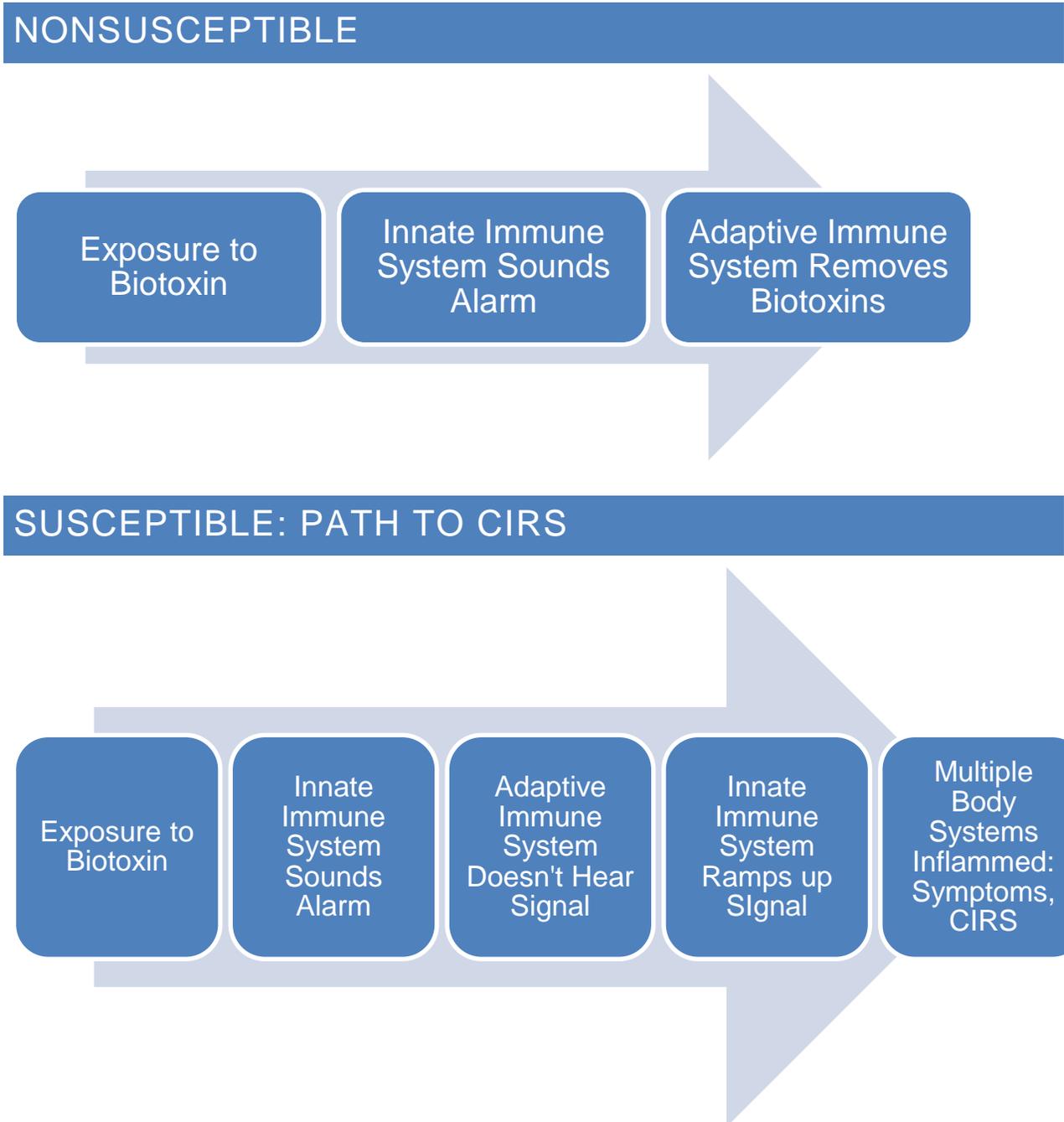


Figure 1

INITIAL EVALUATION

When evaluating a patient with a multi-system multi-symptom presentation, CIRS must be considered. As with any patient that comes in to see a primary care provider, a typical evaluation for commonly identified chronic illness must precede workup for chronic inflammatory response syndrome. Initial evaluation must be thorough and include:

Complete History: Including chart review of all previous medical records.

- Current symptom complex

- Timeline of previous symptoms (including both physical and cognitive symptoms),

- Exposures throughout the lifetime (see below more about significant exposures)

- Past medical, surgical, family, dental history

- Prior treatment with record review

- Medications and supplements,

Complete physical and laboratory evaluation:

Looking for all the common problems we see in our society such as diabetes, cardiovascular disorders, rheumatological disorders, and cancers.

If symptoms persist with medical management of identified problems and a history of exposure exists, the diagnosis of CIRS must be considered. Determining that CIRS is contributing to a person's symptoms can be exceptionally complex, requiring detailed investigation, history taking, interpretation of data. This sort of evaluation is virtually impossible in a primary care physician's office due to time constraints of a busy practice. When a health care provider recognizes this as a potential issue, the patient should be referred to a specialist who sees this frequently or should themselves take the time to become certified in diagnosis and treatment of CIRS.

CIRS DIAGNOSIS: ADVANCES IN UNDERSTANDING

Diagnosing CIRS requires an extensive history and a deep dive into symptom complexes throughout the patient's life. With expansion in research into the pathophysiology and treatment of this illness comes development of ever improving guidelines to help providers identify and treat CIRS.

A landmark paper in the Internal Medicine Review in 2018⁴ provides the current diagnostic process for CIRS, introducing the concept of genomic expression to further characterize both initial abnormalities stemming from nuclear-directed down regulation of mitochondrial processes^{5 6} as well as modulation towards normal with use of the most well-articulated and researched treatment for CIRS illness: the Shoemaker Protocol.

DIAGNOSTIC REQUIREMENTS FOR CIRS

1. Documented clear potential for exposure to biotoxins.
2. Exclusion of other causes.
3. Multi-system, Multi-symptom illness as described in the published literature
 - a. Adults require 8 of 13 CIRS Symptom Cluster Positivity
 - b. Pediatrics require 6 of 13 Symptom Cluster Positivity
4. Documentation of response to therapy. (4)

EXPOSURE: CLEARLY IDENTIFIED POTENTIAL FOR EXPOSURE

Current understanding of CIRS attributes most of these cases to those exposed to water-damaged buildings (WDB). Care must be taken to explore this possibility with people, as even a minor leak could set up the appropriate environment for toxigenic mold and bacteria to grow, creating a hidden source of inhaled toxicants that will affect a susceptible person.

Clues could include:

1. Water stains on ceilings or around light fixtures
2. Condensation around windows and doors
3. History of a prior roof leak or plumbing problem
4. Visible mold in attic, crawl spaces, bathroom, kitchens
5. Change in physical symptoms with a move to or from any certain building.

Additionally, questioning the person about their work and or school buildings can be revealing. It is estimated that 50% of buildings have a history of water damage⁷ and there have been cases in which lawsuits have been brought against schools for emergence of illness and students exposed to the toxic soup emitted by toxigenic bacteria, fungi, and mold growth fueled by water damaged buildings.

There are other routes of exposure to biotoxins, and because an exposure can be in the distant past, it is important to take a thorough history.

Other Potential Biotoxin Exposures:

1. Post-Lyme syndrome. A client with symptom persistence, even after antibiotics.
2. Illness while living in or after visiting Lyme disease endemic areas. (Even without a tick bite, as many do not know they have been bitten by a tick)
3. Brown recluse spider bite
4. Significant illness after eating reef fish (ciguatoxin)
5. Swimming in a body of water (could be saltwater, brackish, or fresh) where recent “fish kill” occurred (pfiesteria), or there is a bloom of toxic algae or cyanobacteria.
 - a. Note: this is not always visible or obvious. It is more important to ask if someone got sick after a swim with gastrointestinal, respiratory, skin problems or cognitive symptoms.

EXCLUSION OF OTHER CAUSES

A thorough history, physical and laboratory examination ruling out other diagnoses, with the understanding that “descriptive” diseases and “symptom complex” disorders with no confirmatory lab exam do not rule out CIRS. This includes diagnoses such as anxiety, depression, mood disorders, Alzheimer's, Chronic fatigue syndrome, ADD/ADHD, fibromyalgia, among others.

SYMPTOM CLUSTER ANALYSIS: AS REPORTED IN PUBLISHED LITERATURE

There must be a multi-system, multi-symptom illness presenting with symptoms similar to those seen in peer reviewed publications. Symptoms from at least 6 of the 13 Symptom Clusters shown below requires investigation into CIRS. In adults, symptoms from 8 of the 13 Clusters make the diagnosis of biotoxin illness with 95% accuracy; in children, 6 out of 13 clusters are adequate to support a diagnosis.(4) (Fig. 2)



Figure 2

ANCILLARY TESTING

Ancillary testing supports the CIRS diagnosis, guides treatment and provides final diagnostic confirmation by showing improvement with treatment.

- Genetic susceptibility using HLA DR/DQ haplotyping
- Environmental Evaluation using ERMI/HERTSMI-2
- Transcriptomic biotoxin effects (DNA effects)
 - PAX Gene Tube Analysis identifies nuclear-directed downregulation of mitochondrial energy production reversible with treatment.
- Proteomic biotoxin effects (blood work -markers)
 - Down regulation of regulatory neuropeptides including Melanocyte Stimulation Hormone (MSH), Vasoactive Intestinal Peptide (VIP) and its receptor
 - Dysregulation of primary hormonal systems in the body including the ACTH/cortisol axis, ADH/osmolality control, and altered levels of sex hormones-low testosterone in particular.
 - Elevation of at least 1 of 3 inflammatory markers required: MMP9, TGF beta-1, C4a
 - Patients diagnosed with CIRS show abnormalities in at least 4 of the 8 objective markers traditionally evaluated including: TGF Beta-1, VIP, C4a, C3a, VEGF, MSH, MMP9, ACTH/Cortisol, and AVP/osmolality, HLA, and VCS.
- Physical biotoxin effects in the body.
 - Neurotoxic: Visual Contrast Sensitivity and NeuroQuant Brain MRI
 - Cardiopulmonary: Echocardiogram and VO2Max Testing
 - Sinopulmonary: MARCoNS growth in the nasal passages correlated with low MSH

GENETIC SUSCEPTIBILITY: HLA BLOOD TYPING

HLA DR/DQ testing identifies those with certain haplotypes that prevent people from effectively removing biotoxins. Through a review of international genetic registries, Dr Shoemaker recognized that 24% of the population has a genetic predisposition to biotoxin illness⁸. Most patients with CIRS have a genetic predisposition; a small percentage (5%) of people with CIRS who do not have a susceptible haplotype.

ENVIRONMENTAL EVALUATION

ERMI OR HERTSMI-2 TESTING TO EVALUATE SAFETY OF THE HOME ENVIRONMENT.

Developed by the EPA, ERMI (Environmental Relative Moldiness Index) testing uses a dust sampling method to identify and quantify molds that have been shown statistically to have significant impact on indoor air quality, evaluating these relative to the quantity of collected mold species in the same sample which are commonly found outside.⁹ This gives an idea of building safety from an air quality standpoint.

The HERTSMI-2 is a scoring system based on the concentration of the five mold species that have clearly shown causation in human illness. This scoring may use data from the ERMI test or be done in isolation as a way to follow building health after remediation.

TRANSCRIPTOMIC BIOTOXIN EFFECTS

Pax Genomics measures mRNA and miRNA and can show aberrant nuclear DNA regulation of innate immune function, ribosomal and mitochondrial gene expression at the cellular level. Additionally, serial testing after treatment has been shown to show improvement at the cellular level with The Shoemaker Protocol using VIP (6). The advent of the availability of transcriptomic evaluation, which lays out the underlying reversible genetic abnormalities that cause proteomic abnormalities, marks the dawn of a new era in diagnosing CIRS. Specific diagnosis, differentiating patterns between biotoxin illness caused by different exposures could be possible with the development of this technology.

PROTEOMIC BIOTOXIN EFFECTS

Proteomics is the evaluation of blood markers typically altered in CIRS. Patients diagnosed with CIRS show abnormalities in at least 4 of the 8 objective serum markers traditionally evaluated including: TGF Beta-1, VIP, C4a, C3a, VEGF, MSH, MMP9, ACTH/Cortisol, and AVP/osmolality. These markers are followed throughout the protocol. Measurement of proteomics has paved the way to a deeper understanding of the underlying physiology.

The Biotoxin Pathway as illustrated below (fig. 3) gives an excellent visual explanation of the cascade of events stemming from the persistent effect of biotoxins in the body.

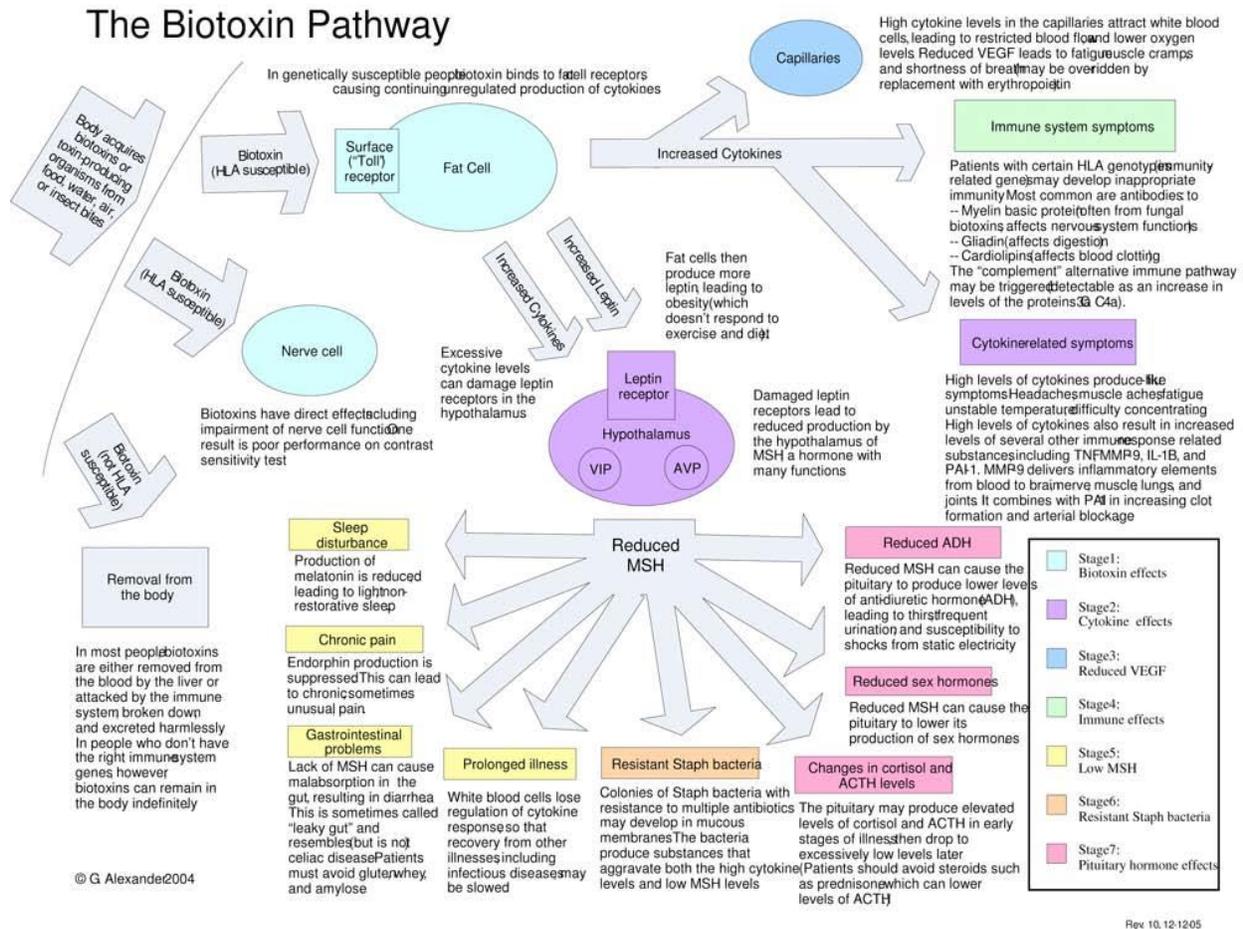


Figure 3. from www.survivingmold.com

LOW MELANOCYTE STIMULATING HORMONE NORMAL RANGE 35-81PG/ML

Release of this neuroendocrine hormone is controlled by leptin in the pituitary. With biotoxin illness, disruption of the leptin receptor due to an increase in cytokines causes a drop in MSH, a master controller of many functions in the body. Low levels of MSH lead to dysregulation of multiple processes causing:

- Problems with sleep patterns and melatonin, leading to disturbed sleep
- Problems with salt and water balance through interaction with ADH/AVP and serum osmolality, leading to increased thirst and urination, palpitations and POTS
- Dysregulation of the immune system with increased inflammatory cytokines, T cell abnormalities, and increase in autoimmunity.
- Increased pain due to decreased endorphin production

- Issues with increased gut permeability
- Reduction in androgens/low testosterone
- Colonization of the nose with MARCoNS
- Weight gain unresponsive to changes in diet and exercise

ABNORMALITIES IN CORTISOL/ ACTH

ACTH stimulates the release of cortisol from the pituitary, and elevation of cortisol normally feeds back to turn down production of ACTH. Dysregulation of this normal feedback loop is common in CIRS.

Normal ranges are as follows:

ACTH: 8-37 pg/mL; 1.76-8.14pmol/L

Cortisol: AM 4.3-22.4 ug/dL; 3.07-15.99umol/L

PM 3.1-16.7 ug/dL; 2.21-11.92 umol/L

Absolute or relative abnormalities, as these two work in concert in the body.

High: ACTH>45 or cortisol >21

Low: ACTH <5 or cortisol <4

Relative: ACTH <10 when cortisol <7

Relative ACTH >15 when cortisol >16

ABNORMALITIES IN ADH/AVP AND SERUM OSMOLALITY

Shifting in response to reduced MSH production, ADH/AVP and osmolality work hand in hand to maintain salt and water balance in the body. When levels are abnormal, patients may experience dizziness, postural orthostatic hypotension, racing heart, static shocks (due to increased chloride on the skin), low blood pressure, thirst, and increased urination.

Normal range: ADH: 1-13.3 pg/ML; 0.9-12.28 pmol/L

Osmol: 280-300mOsm/kg

High serum osmolality and high ADH are normal; Low serum osmolality and low ADH are normal

Absolute or relative abnormalities may be seen:

Absolute High: ADH greater than 13 or osmolality greater than 300

Absolute low: ADH less than 5 or osmolality less than 275

Relative: ADH was less than 2.2 when osmolality was 292-300

Relative: ADH was greater than four when is molality was 275-278

Matrix Metalloproteinase 9 (MMP) NORMAL 85-332NG/ML

White blood cells (activated macrophages) activate the enzyme MMP9 which creates holes in the basement membranes of endothelial cells, allowing inflammatory compounds to penetrate into tissues. This is an important normal function of the immune system so that inflammatory “helpers” can get to sites of inflammation; however with a continuous stimulus like biotoxins, this becomes destructive.

VASCULAR ENDOTHELIAL GROWTH FACTOR NORMAL 31-86 PG/ML

Vascular Endothelial Growth Factor, lowered in CIRS, is a marker for capillary hypoperfusion. (low blood flow in the smallest of vessels). It serves to stimulate blood vessel growth in response to Hypoxia Inducible Factor (HIF). The cells lining blood vessels release HIF when they need more oxygen. CIRS disturbs this system, and poor muscle endurance and fatigue results. This marker may also be elevated in renal failure and Bartonella infections¹⁰.

TRANSFORMING GROWTH FACTOR BETA-1 NORMAL <2380 PG/ML

Elevated TGF beta-1 indicates an over-active immune response and is a key marker for severity in CIRS. It can change regulatory T cells into pathologic T cells, which then drive further inflammation. It also may cause tissue remodeling in multiple tissues in the body. Lowering TGF Beta-1 is critically important due to the potential for long term tissue changes due to the remodeling capacity of this cytokine.

The Complement System:C4a and C3a

The complement system is part of the innate immune system that is triggered by exposure to pathogens. It helps to rid the body of invaders using a complex cascade of inflammatory and immune messengers. Overactivity of this system can lead to anaphylaxis and tissue damage. With CIRS, one sees measurable change in two components of the system: C4a and C3a due to activation of the complement cascade by biotoxins.

In those exposed to water damaged buildings, C4a is very important marker. More commonly elevated in CIRS, it correlates with illness severity and results from activation of the classical or Mannose-binding lectin pathway of complement activation. When a susceptible person is exposed to biotoxins, including toxigenic fungi and inflammagens associated with water damaged buildings, activation of this pathway may cause a rise in the levels of C4a within minutes.

C3a is released in response to a bacterial cell membranes and is elevated in Lyme Disease. When elevated, both may cause constriction of smooth muscle, poor blood flow in capillaries, and increased inflammatory products from white blood cells.

Normal ranges 0-2930 ng/mL C3a 55-486 ng/mL

ANDROGENS

Lower levels found in CIRS. (Important to resist the urge to correct with replacement, as this can create problems with feedback regulation and establishment of internal hormonal balance.)

VON WILLEBRAND'S PROFILE

Von Willebrand's Disease is a clotting disorder that may be inborn or acquired through the lifetime. Some people with CIRS develop clotting disorders manifest as nose bleeds, heavy periods, bleeding gums, or bleeding of other membrane surfaces. These individuals should be evaluated with a panel for von Willebrand's Disease.

MEASUREMENT OF AUTOIMMUNITY

Antibodies such as anti-gliadin AB and anti-cardiolipin AB will show as the immune system is further dysregulated. CIRS increases autoimmunity due to changes in the regulatory T cell populations.

LEPTIN

Leptin Resistance is seen due to disruption of receptors from bombardment with cytokine. This causes dysregulation of MSH and stubborn weight gain.

T CELL POPULATION MEASUREMENT

CD4+CD25+ to identify abnormalities in regulatory T cells which is acquired due to CIRS.

VIP/VIP RECEPTOR-2

Neuroregulatory peptide which can down regulate inflammation and interacts with MSH and ADH. Vasoactive Intestinal Peptide is produced in the suprachiasmatic nucleus of the hypothalamus, in the gut and pancreas. Responsible for many functions in the body, VIP helps regulate blood flow and modulate inflammation, acting as a key integrator of communication among cells. Low levels of VIP and disruption of the receptor for VIP leads to a significant proportion of the symptoms seen with biotoxin illness. Shortness of breath and altered pulmonary artery pressure, cognitive impairment, exercise intolerance, hormonal imbalances, even atrophy of brain structures has been shown to improve in patients with replacement of VIP using an intranasal solution (6).

PHYSICAL BIOTOXIN EFFECTS IN THE BODY

NEUROLOGICAL BIOTOXIN EFFECTS:

ABNORMAL VISUAL CONTRAST SENSITIVITY

Abnormal Visual Contrast Sensitivity, when combined with a positive result on symptom cluster review with an experienced physician, gives 98% accuracy, confirming the diagnosis of CIRS. This test measures the ability of the eyes to differentiate light gray from white. Biotoxins affect nerves, and VCS testing identifies subtle changes in neurologic function of the optic nerve that indicate biotoxin illness (1). This is a simple test that patients can do at home on their computer. Good light and 20/50 vision are required for accurate results. At the Surviving Mold website <https://www.survivingmold.com/store1/online-screening-test> one may sign in, perform the test, and get results very quickly to determine if they have been affected.

NEUROLOGICAL BIOTOXIN EFFECTS:

BRAIN MRI WITH NEUROQUANT EVALUATION

Specific quantitative changes in brain volume have been identified in CIRS as compared to controls, those with exposure to water-damage buildings showing an increase in forebrain parenchyma, pallidum and cortical gray, and a decrease in caudate volume¹¹. Those with CIRS due to Lyme show reduction in forebrain parenchymal and putamen volume, with an enlarged thalamus¹². Aging creates challenges in MRI interpretation due to volume shifts in the aging brain, and these measurements may be helpful in determining diagnosis with cognitive symptoms.

SINOPULMONARY BIOTOXIN EFFECTS: MARCONS CULTURE

Low levels of MSH due to biotoxin effects or genetic susceptibility leads to potential for growth of MARCoNS (Multiple Antibiotic Resistant Coagulase Negative Staph) in the nasal passages. MSH has a protective effect on the nasal mucosa; MARCONS is not found in those with normal level of MSH. MARCONS creates a biofilm and blocks effective treatment of CIRS, and therefore must be recognized and treated. Identified with a nasal swab, these bacteria create endotoxins, hemolysins, and a slimy film that protects themselves from treatment. MARCoNS further decrease MSH, worsening all of the issues that go along with low MSH, and they must be eradicated.

CARDIOPULMONARY EFFECTS: ECHOCARDIOGRAM AND VO2MAX

Pulmonary Function Testing, VO2Max, and Stress Echocardiogram. Determines cardiopulmonary function, as many with CIRS have reduced cardiopulmonary reserve similar to that seen in heart failure.

DOCUMENTATION OF RESPONSE TO THERAPY

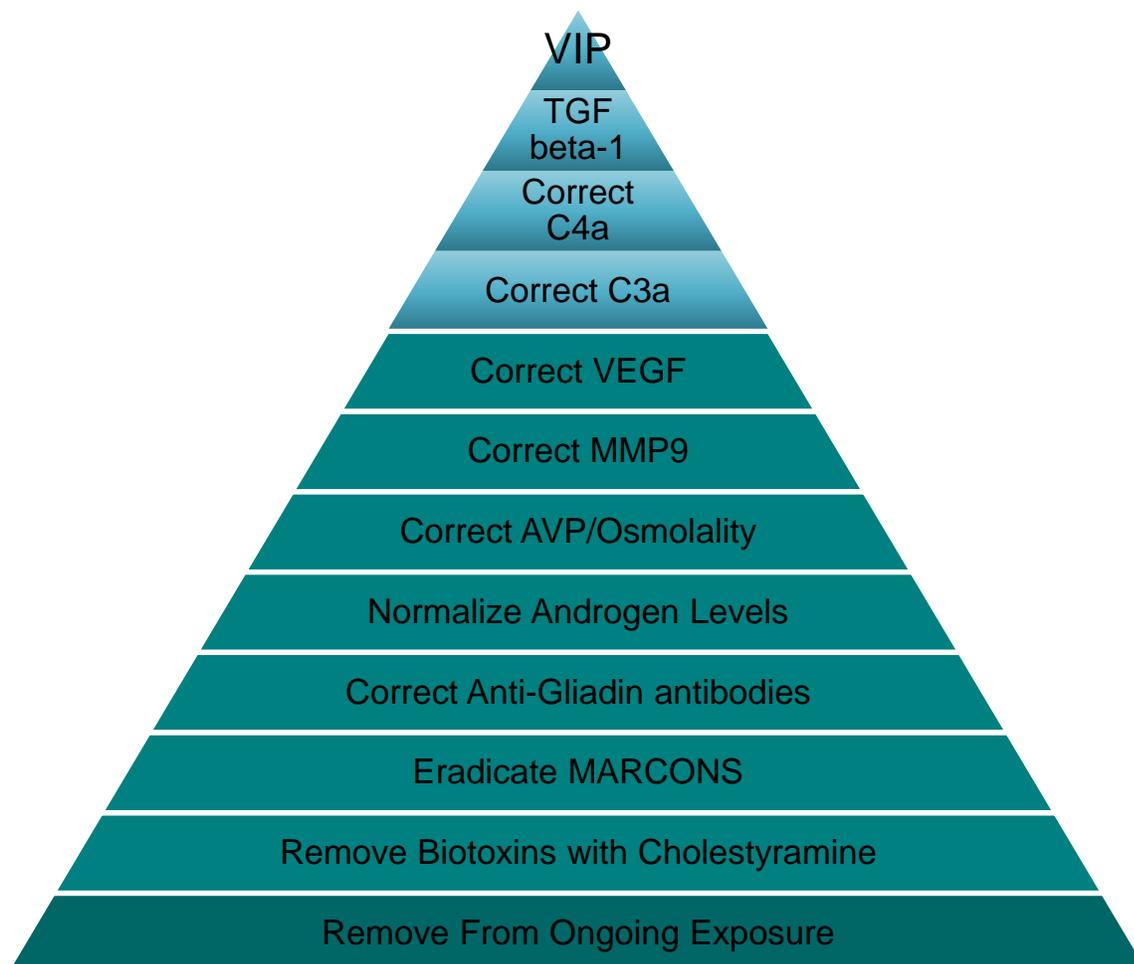
Validation of diagnosis requires that the patient show improvement in the following areas:

- Improvement in symptoms and Visual Contrast Sensitivity.
- Lab Markers return to normal levels.

Management of Chronic Inflammatory Response Syndrome

Treating CIRS requires a stepwise approach that begins with complete removal from the trigger(s) causing the immune system upregulation. Validated, research-based treatment requires that subsequent steps be followed in a stepwise fashion, as each step sets the stage for the following step.

The Shoemaker Protocol Treatment Plan



STEP 1: REMOVE FROM ONGOING EXPOSURE

The first step of the Shoemaker Protocol can be the most difficult. After establishing the diagnosis, the source of biotoxin exposure must be identified and removed. Considering past exposures such as food poisoning from eating reef fish, tick bites, spider bites, as well as mold or water-damaged building exposure and carefully eliminating these is necessary for treatment to be successful. If untreated Lyme disease is possible, antibiotics may be required.

Up to 50% of all homes in the United States have had water intrusion events at some point in their history. Checking air quality, even if the home appears to be in excellent condition, using ERMI (Environmental Relative Moldiness Index) or HERTSMI-2 (Health Effects Roster of Type Specific Formers of Mycotoxins and Inflammagens-2) dust testing is essential. Having a visual inspection by an Indoor Environmental Professional (IEP) with knowledge of the specific needs of CIRS patients gives critical input regarding home safety with regards to previous and potential for new water damage.

An excellent resource for remediation is the Indoor Environmental Professionals Panel of Surviving Mold CONSENSUS STATEMENT¹³ as well as the book *Mold Illness: Surviving and Thriving; A Recovery Manual for Patients and Families Impacted by CIRS* by Paula Vetter, Laura Rossi and Cindy Edwards.

Remediation must achieve an ERMI below 2 or a HERTSMI-2 score of <10 for safe re-occupancy of the structure. If the patient has a measurement above 20,000 then ERMI score should be <-1. Sometimes a workplace may be the source of exposure; people have had to leave their jobs because of susceptibility to severe illness when being in a water-damaged building-- even for a short period of time.

Many times personal belongings must be let go; this is one of the tough parts of biotoxin illness. Non-porous items must be thoroughly wiped down and cleaned. Porous items or furniture that cannot be wiped down such as paper and personal effects must generally be discarded. Photographing memorabilia can preserve memories.

STEP 2: REMOVAL OF TOXINS FROM THE BODY

Cholestyramine is a drug that has been used for many years to reduce cholesterol. Use of this medication to remove biotoxins is an “off-label” use. It has been shown in clinical trials studying the Shoemaker protocol to be effective in treating biotoxin illness^{14 15}It has a unique structure that allows it to find biotoxins and eliminate them in the stool.

- CSM Needs to be taken at least 30 minutes before or one hour after meals, medications and supplements. Medications such as thyroid medicine, digitalis, coumadin, and theophylline should be separated by at least 2 hours from your dose of cholestyramine.
- Generally, CSM should be started slowly, because reflux, belching, nausea, constipation and bloating may be side effects.
- It is important to avoid constipation, this can be done by using a combination of dietary fiber, increasing veggies, adequate water intake, magnesium or other means such as MiraLAX.
- CSM dosing is 4-9 grams four times a day mixed with 4-6 oz of water or juice.
- Welchol may be substituted, as it is better tolerated, but it takes longer to remove the biotoxins. Welchol dosing is 625 mg 2 tablets 3 times a day with meals.
- One option for easier dosing is to combine cholestyramine and Welchol, taking the cholestyramine morning and bedtime and the Welchol at lunch and dinner.
- Treatment length is determined by following Visual Contrast Sensitivity.
- Some patients, particularly those with biotoxin illness due to Lyme disease may have a release of cytokines that causes increase of symptoms. This may be ameliorated by pretreating with EPA 2.4gm / DHA 1.8gm (fish oil) daily in divided or using Actos15-45mg daily.
- When VCS has normalized, Welchol 625mg twice daily can be used to prevent flares with incidental exposures.
- Pediatric Dosing of CSM for those under 18 or less than 120 lbs. is 60mg/kg/dose three times daily.
- Using omega 3s (EPA/DHA) and a low amylose diet can make CSM more tolerable. A low amylose diet eliminates:
 - wheat, rice, barley, oats, and rye
 - Bananas (other fruits are allowed)
 - root vegetables (except garlic and onions)
 - Foods with added sugar, corn syrup, maltodextrin, sucrose

STEP 3 ERADICATE MARCONS

Eliminating MARCONS is critical for the effective treatment of biotoxin illness.

- Treat with nasal spray combining EDTA and Silver
- Treat for 30 days using two sprays in each nostril three times a day in adults

- Repeat nasal culture to confirm effective eradication.
- If culture still positive consider exposure to mold, a partner with MARCONS or possibly from the nose of the family dog.
- If symptoms worsen, evaluate Visual Contrast Sensitivity and MMP-9 levels to check for a re-exposure. Ensure the patient is eating a low amylose diet, taking fish oil, and consider Actos.

STEP 4 ELIMINATE GLUTEN IN ANTI-GLIADIN ANTIBODY POSITIVE PATIENTS

For those with antigliadin antibodies, it is important that they eliminate gluten from their diet.

- At least 3 months of gluten-free diet. then recheck antigliadin antibodies. If these are negative may do trial back on gluten, monitoring for GI symptoms.
- Recommend periodic evaluation for anti-gliadin antibodies; if these are positive, rule out celiac disease.

STEP 5: CORRECT ANDROGENS

Treatment: DHEA

Levels of androgens may decrease with chronic inflammatory response syndrome due to an up-regulated aromatase enzyme. This can cause low testosterone and elevated estrogen. It is important to avoid simple replacement of testosterone in men as this can create problems later when trying to balance systems after treatment, suppressing natural production of testosterone. Women may present with menstrual problems such as heavy periods, clotting, ovarian cysts, painful periods and interstitial cystitis.

- DHEA 25mg -75 mg
- VIP spray: 4 sprays intranasally, alternating nostrils up to 4 times a day can reduce aromatase enzyme activity and improve testosterone production.

STEP 6: CORRECT OSMOLALITY/ADH IMBALANCE

Treatment: desmopressin acetate (DDAVP)

- Indicated when osmolality is above 295 and ADH is $<.08$
- Begin with DDAVP 0.2 mg tablet every other night for 5 doses.
- After dose 5, recheck labs including serum osmolality and electrolytes to ensure osmolality and sodium is normal.
- DDAVP can cause edema and weight gain due to fluid retention.

- May increase dose to daily if symptoms (such as frequent urination, thirst, orthostatic hypotension, headaches or static shocks) persist.
- Recheck labs at day 10
- Those with continuing symptoms may need to be on this for an indeterminate basis.
- Pediatric dosing is 1-4 sprays of DDAVP based on child's weight and age.
- This treatment may also correct acquired von Willebrand's syndrome. Those who have acquired von Willebrand's syndrome may carry DDAVP spray with them for as needed dosing in case of nose bleeds.
- Dosing will need to be tapered as ADH abnormalities normalize with continue treatment.

STEP 7: CORRECT ELEVATED MMP-9

Treatment: Fish Oil and Actos

Correction of elevated Matrix Metalloproteinase 9 happens as one turns up production of a receptor in the nucleus called PPAR-gamma. This in turn will regulate production of chemical messengers in the body that are keeping the symptom cycle running in CIRS, reducing Tumor Necrosis Factor, Leptin, plasminogen activator inhibitor - 1 and raising low VEGF.

- Actos should only be used in adults with leptin levels above 7. Dosing at 45 mg daily for 30 days.
- High-dose fish oil of at least EPA 2.4 grams/ DHA 1.8 grams daily in divided doses may be used in those who cannot tolerate Actos, or for whom it is contraindicated.
- The metabolic panel should be followed to ensure adequate kidney function as well as monitoring for hypoglycemia.
- Actos has a black box warning for bladder cancer with long-term use.

STEP EIGHT: CORRECTION OF LOW VEGF

A similar treatment protocol as for MMP-9, using Actos, or high dose fish oil and a low amylose diet is recommended for addressing low VEGF.

STEP 9 CORRECT ELEVATED C3A

Treatment: high dose statins.

- Begin CoQ10 150 mg for 10 days prior to beginning a statin medication at high dose levels.

- Statin medications are metabolized by cytochrome p450 384 and it is important to watch for interactions with medications or food (grapefruit) that increase or decrease activity of this enzyme.
- Monitor metabolic panel to you ensure adequate kidney and liver function.
- Statin treatment continues until C3a Level is normal, generally for 1 month. If elevation persists, this suggests that there is continued ongoing stimulation of the complement system by a bacterial membrane, and warrants further investigation, particularly for tick borne infection such as Lyme disease.
- With statins there is a reduction in overactive immune responses associated with the complement cascade.

STEP 10: CORRECTION OF C4A

Treatment: Procrit (Original Protocol) or VIP Nasal Spray

- Erythropoietin is also called Procrit, and it is used by subcutaneous injection 8000 units twice-weekly for 5-8 doses with baby aspirin.
- Most practitioners are using VIP spray instead of Procrit because of issues with the black box warning of thrombosis with Procrit.
- Requires informed consent as this is an off-label use.
- Procrit is only used in adults.
- Intranasal VIP spray: 4 Sprays daily may be used as a potentially safer option.

STEP 11: REDUCE ELEVATED TGF BETA-1

Treatment: Losartan

- Losartan is a blood pressure medication that creates a breakdown product in the body that lowers TGF beta-1.
- Dose losartan at 12.5 mg twice daily for adults, maximum dose 50 mg daily.
- Pediatric dosing is 62.7mg per kilogram per day bid
- Follow TGF beta-1 to evaluate for improvement
- If blood pressure is low, preventing the use of losartan, VIP nasal spray may be used to lower TGF beta-1.
- Indications for use include TGF beta-1 above 2380. Blood pressure should be monitored daily during use. If blood pressure drops too low losartan must be discontinued.

STEP 12 REPLACE LOW VASOACTIVE INTESTINAL PEPTIDE RECEPTOR 2 (VIP)

Treatment: Intranasal VIP

For those with persistent symptoms who have moved through the protocol, a trial of Vasoactive Intestinal Peptide can significantly improve symptoms. Following NeuroQuant MRI measurements may also be helpful in evaluating efficacy of intranasal VIP.

BEGINNING VASOACTIVE INTESTINAL PEPTIDE INTRANASALLY REQUIRES:

- Normal Visual Contrast Sensitivity
- Eradication of MARCoNS
- ERMI score of less than or equal to 2 or HERTSMI-2 score of less than or equal to 10
- Normal lipase and GGT
- Baseline labs need to be checked including VIP, MSH, TGF beta-1, C4a, VEGF, MMP-9, vitamin D, total testosterone, estradiol, CD4+/CD25++
- Consider baseline stress echo to measure tricuspid regurgitation and pulmonary artery systolic pressure to verify it does not rise over 8 millimeters during exercise.
- Initial dose must be given in the office.

IN-OFFICE ADMINISTRATION OF INITIAL DOSE

- Test dose of 50 micrograms in single nostril and observe patient for changes and symptoms, rash, reduction in shortness of breath, reduction in joint pain and or improve cognition.
- Check blood pressure and pulse 5 minutes x 3.
- Fifteen minutes after VIP is administered, redraw TGF beta-1 and C4a levels. If a 33% increase is noted, hidden mold exposure may be ongoing.

HOME DOSING AND MONITORING

- Follow lipase levels monthly, if elevated, VIP must be discontinued. Other monthly labs that should be followed are C4a TGF beta-1 as well as any other labs which have been abnormal.
- If limited Improvement in symptoms, may increase dosing up to 8 sprays daily.
- If the patient develops new onset of abdominal pain, rash, changes in blood pressure, or elevation in lipase VIP must be discontinued.

- Recheck echocardiogram after 30 days as well as lab work including lipase, C4a, TGF beta-1, and VCS.
- When VCS and lab work are stable, and symptoms are improving, VIP may be tapered to twice-daily for 30 days and then discontinued.
- Recheck Labs 6 months off VIP.

STEP 13 IMPROVING EXERCISE TOLERANCE

- Graded exercise starting with low intensity cardio such as walking or biking five minutes a day and gradually working up to 15 minutes per day.
- Must be done 7 days a week.
- After the client has worked up to 15 minutes a day then floor exercises are added such as sit-ups and leg lifts beginning with five minutes a day and working up to 15 minutes per day.
- When tolerating 15 minutes of cardio and 15 minutes of floor exercises, then free weights may be added in the same manner, beginning with 5 minutes per day and working up to 15 minutes per day.
- After one month increase intensity, following the same sequence.

POST-TREATMENT

After completion of treatment there will be times when the determination that a building is safe for occupancy must be made. One can do this with formal re-exposure trial. This involves discontinuing treatment medications and staying away from the building for three days, checking initials lab work and returning to the building in question for 8 hours. Symptoms and labs and VCS testing is followed over a three-day period with daily return to the building. Using a scoring system (SAEIIIE)⁸ one can identify if the client has had an upregulation of the innate immune responses representing exposure to inhaled inflammatory substances in that building.

Some clients need to continue treatment with different parts of the protocol for extended period. That said, by following this protocol carefully, in order, most patients can achieve gradual return to excellent health. This takes time and patience, and it is worth the effort in the end.

ENDNOTES

- ¹ Shoemaker RC, Hudnell HK. Possible estuary-associated syndrome: symptoms, vision, and treatment. *Environ Health Perspect.* 2001 May;109(5):539-45.
- ² McMahon SW. An Evaluation of Alternate Means to Diagnose Chronic Inflammatory Response Syndrome and Determine Prevalence. *Medical Research Archives*, [S.I.], v. 5, n. 3, mar. 2017. ISSN 2375-1924.
- ³ Shoemaker, RC et al. Inflammation Induced Chronic Fatiguing Illnesses A steady march towards understanding mechanisms and identifying new biomarkers and therapies. *Internal Medicine Review*: Oct 2017; Vol. 3 (11).
- ⁴ Ritchie Shoemaker MD¹ Karen Johnson MD¹ Lysander Jim MD¹ Yvonne Berry MD¹ Ming Dooley¹ James Ryan PhD² Scott McMahon MD. Diagnostic Process for Chronic Inflammatory Response Syndrome (CIRS): A Consensus Statement Report of the Consensus Committee of Surviving Mold. *Internal Medicine Review*: May 2018; Vol. 4 (5).
- ⁵ Ryan J, Wu Q, Shoemaker R. Transcriptomic signatures in whole blood of patients who acquire a chronic inflammatory response syndrome (CIRS) following an exposure to the marine toxin ciguatoxin. *BMC Med Genomics.* 2015; 8:15
- ⁶ . Ryan, J, Shoemaker R. RNA-Seq on patients with chronic inflammatory response syndrome (CIRS) treated with vasoactive intestinal polypeptide (VIP) shows a shift in metabolic state and innate immune functions that coincide with healing. *Med Res Arch* 2016; 4(7): 1-11.
- ⁷ Spengler J, Neas L, Nakai S, Dockery D, Speizer F, Ware J, and Raizenne, (1994) Respiratory symptoms and housing characteristics. *Indoor Air*, 4:72-82.
- ⁸ Hoffman, B. Chronic Inflammatory Response Syndrome (CIRS) Evaluation and Treatment. (2018) www.survivingmold.com
- ⁹ Lin K-T, Shoemaker R.C. *Inside Air Quality Filtration News* (2007) Vol 26, No 3, pg. 32.
- ¹⁰ Kempf VA, Volkmann B, Schaller M, Sander, CA, Alitalo K, Riess T, Autenrieth IB. Evidence of a leading role for VEGF in Bartonella henselae-induced endothelial cell proliferations. *Cell Microbio.* 2001 Sep;3(9); 623-32.
- ¹¹ Shoemaker R, House, D, Ryan J. Structural brain abnormalities in patients with inflammatory illness acquired following exposure to water damaged buildings: A volumetric MRI study using NeuroQuant. *Neurotoxicology and Teratology* 2014 June.
- ¹² Shoemaker, R. *Proceedings of Surviving Mold Conference.* 2018
- ¹³ Schwartz L, Weatherman G, Schrantz M, Spates W, Charlton J, Berndtson K, Shoemaker R, Medically sound investigation and remediation of water-damaged Buildings in cases of CIRS-WDB. (2016) *Indoor Environmental Professionals Panel of Surviving Mold.*

¹⁴ Shoemaker RC¹, House DE. Neurotoxicol Teratol. 2006 Sep-Oct;28(5):573-88. Epub 2006 Aug 7. Sick building syndrome (SBS) and exposure to water-damaged buildings: time series study, clinical trial and mechanisms.

¹⁵ Hudnell, K. Neurotoxicol Teratol. 2005 Sep-Oct;27(5):733-43. Epub 2005 Aug 15. Chronic biotoxin-associated illness: multiple system symptoms, a vision deficit, and effective treatment.