

# **Chronic Inflammatory Response Syndrome (CIRS)**

## **Evaluation and Treatment**

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# Introduction

When a patient presents to a doctor with many symptoms, has seen many doctors, and has not improved despite many attempts by the most well meaning practitioners, both traditional and alternative/integrative/functional, it is time to consider whether a diagnosis of CIRS may be playing a role in his presentation. However, this decision can be complex. Unless a specific roadmap is followed and a process of deductive reasoning applied to a differential diagnosis, one may find oneself in a quagmire of conflicting information.

What will follow in this essay is a step by step map for health care practitioners to follow in the process of deductive reasoning in the consideration of whether CIRS may be underlying the patient's presentation. Unless a practitioner follows an evidence-based protocol of carefully developed steps as outlined by Dr Shoemaker and others, one may be tempted to omit or skip specific steps in the diagnostic process thereby reaching conclusions that are not in keeping with the published research. Thus, it is vital to follow the steps exactly so to support or refute the evidence.

Health care practitioners must precede a diagnostic workup for CIRS with the normal workup one employs for chronically ill patients: present history, presenting symptoms, past history, family history, medications, allergies, supplements, surgeries, dental history, toxin exposure, review of systems. A cognitive and mood history is also essential. As a certified functional medicine practitioner, I am most interested in the timeline of illness presentation, as well as any antecedents, mediators, and triggers that may fall outside of the CIRS presentation.

However, if the patient's symptom clusters point towards a possible diagnosis of CIRS, the diagnosis of CIRS must be included in the differential diagnosis. It is then incumbent upon the practitioner to enquire as to whether or not there have been any exposures to the possible agents and/or biotoxins that are responsible for initiating this potential diagnosis and if so, to then follow the rest of the diagnostic criteria to establish the diagnosis.

Questions to ask patients who have been exposed to water damaged buildings include: Do you/did you live in a building with obvious mold visible? Has your home ever been flooded? Is there any obvious water intrusion? Do you smell musty odors? Does your home have condensation on the windows? Are there any water stains around your light fixtures in the ceilings? Did you feel worse after you moved homes, school, and work place? Has conventional air quality testing revealed mold spores present?

Further questioning includes: Have you had a tick bite, EM rash, severe flu-like illness that persisted after visiting Lyme endemic areas? Have you been exposed or swam in a body of water with an algae bloom? Have you ever been in waters/estuaries where sudden fish kills were reported through direct contact or inhalation of aerosolized or volatized toxins? Have you eaten reef fish and felt ill soon afterwards? Have you ever had a spider bite (brown recluse spider)?

# Background Information prior to engaging in the diagnostic criteria

## Immune System

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The immune system is composed of two major subdivisions: the innate or nonspecific and the adaptive or specific immune system (found only in vertebrates). We are born with innate immune responses intact; we develop adaptive immune systems after birth.

The innate immune system is the body's primary defense mechanism against invading antigens: the adaptive immune system is summonsed by the innate immune system as a second line of defense provided there are no HLA genetic defects in the individual (74% of the population).

26 % (1 in 4) of the population has an aberrant HLA system that leads to upregulation of the innate immune system with an inability to adequately notify and summons the adaptive immune system.

This defective setup informs the basic underlying issue with CIRS; an aberrant upregulation of the innate immune system due to biotoxin inducing triggers, with a defective adaptive immune response to these inflammatory signals

## Innate System

- Acts almost immediately to infection, the adaptive takes longer to respond
- Is not specific to a particular antigen and reacts the same way to a variety of infectious agents and inflammagens.
- Recognizes toxins with pattern recognition receptors
- Does not provide long-lasting immunity to the host
- Communicates with the adaptive immune system via macrophages/monocytes and dendritic cells as antigen-presenting cells, the first responders of the innate immune system
- Recruits immune cells to the site of infection via the use of cytokines and TGF beta-1
- Activates the complement cascade system to assist in removing antigens
- Presents toxins to the adaptive immune system naïve lymphocytes called T cells, the lead cells of the adaptive immune system. These inflammatory molecules do not have a specific target and they do not remove biotoxins. Trichothecenes, the biotoxins released from *Stachybotrys* and *Fusarium* mold species can slow the maturation rate of dendritic cells,<sup>1</sup> resulting in defective antigen presentation to the adaptive immune system

Both aspects of the immune system have cellular and humoral components.

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<sup>1</sup> Hymery N, Sibiril Y, Parent-Massin D. In vitro effects of trichothecenes on human dendritic cells. *Toxicol In Vitro*. 2006 Sep; 20 (6): 899-909. PMID: 16517116

## Adaptive System

- Provides long term immunity by creating immunological memory after the initial exposure to a specific pathogen or biotoxin
- Adaptive immunity involves the destruction of foreign pathogens and presentation of their peptide remains to T cells to begin process of antibody production by B cells, and NK cells and cytotoxic T cells.<sup>2</sup> The T cells teach the B cells to recognize and respond to invading toxins so that, in the future, if re-exposed, antibodies produced by the B cells can mount an appropriate antibody response
- In biotoxin illness, due to specific genetic HLA susceptibilities, the adaptive system cannot see the biotoxins presented to them by the innate system and thus cannot produce antibodies to neutralize them. The toxin isn't recognized as foreign.<sup>3</sup> These toxins have a unique structure called "ionophores" that prevent them being metabolized or excreted. The innate immune system continues to create inflammatory cytokines, leading to dysregulation of multiple systems and thus the CIRS diagnosis
- Patients with CIRS have dysfunction of T reg cells which are converted into pathogenic T lymphocytes via the inflammatory cytokine TGF beta-1
- B cells, the cells of TH 2 immunity, tend to fight infections and inflammagens outside of the cell and produce antibodies
- T cells, the cells of TH 1 immunity, tend to fight infections and inflammagens within the cell and produce transfer factors. Transfer factors are made in a similar fashion to B cells antibodies<sup>4</sup>

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<sup>2</sup> Ryan J, 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 Medical Genomics 2015 8:15

<sup>3</sup> Shoemaker R. Mold Warriors . Otter Bay Books Baltimore pg. 63

<sup>4</sup> Rappaport S. The Evaluation and Treatment of Chronic Inflammatory Response Syndrome. Pg 16

## Case Definition of CIRS

Chronic Inflammatory Response Syndrome (CIRS) is a syndrome which was originally described and expanded upon by Dr Ritchie Shoemaker in the late 90s. To date, there are over 1700 scientific articles on this condition.

CIRS is defined as a multi-symptom, multisystem illness caused by exposure to biotoxins or neurotoxins derived from a biological source.<sup>5</sup> It is associated with a well-defined set of abnormal biochemical disorders and test results in genetically susceptible individuals.

In a 2013 paper, CIRS was described as a chronic, progressive, multi-system, multi-symptom syndrome characterized by exposure to biotoxins, HLA genetic predisposition, altered innate and adaptive immunity, peripheral hypoperfusion at multiple sites and multiple hypothalamic-pituitary-end organ dysregulations.<sup>6</sup> This inflammatory dysregulation can affect every organ in the body and if left untreated, can become debilitating. Diagnosis begins with a history of symptoms suggestive of CIRS plus a history of exposure to a known trigger. Once these criteria are established, a set of specific diagnostic biomarkers is undertaken to establish the diagnosis.

**Biotoxins** are extremely small, fat soluble molecules capable of going from cell to cell through membranes without being carried directly in the blood stream rendering them impossible to find in the blood stream. Biotoxins can enter through inhalation, direct contact with contaminated water, ingestion, tick bites and spider bites. These biotoxins, in genetically susceptible people whose immune system (antibodies) do not recognize and tag them, lead to chronic inflammation and long lasting chronic illness. Biotoxins bind to certain surface receptors, particularly those on white blood cells (macrophages, monocytes and dendritic cells) called antigen presenting cells.

Pattern recognition receptors (PRRs) are a primitive part of the immune system. They are proteins expressed by cells of the innate immune system to identify two classes of molecules: pathogen-associated molecular patterns (PAMPs), which are associated with microbial pathogens, and damage-associated molecular patterns (DAMPs), which are associated with cell components that are released during cell damage or death.

The microbe-specific molecules that are recognized by a given PRR are called pathogen-associated molecular patterns (PAMPs) and include bacterial carbohydrates (such as lipopolysaccharide or LPS, mannose), nucleic acids (such as bacterial or viral DNA or RNA), bacterial peptides (flagellin,

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<sup>5</sup> Shoemaker RC, House D, Ryan J, Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. *Health*, 2013;5 (3): 396-401

<sup>6</sup> Shoemaker R.C. Ryan JC Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. *Health* 5 (3), 396-401

microtubule elongation factors), peptidoglycans and lipoteichoic acids (from Gram-positive bacteria), *N*-formylmethionine, lipoproteins and fungal glucans, mannans, and chitin.

Endogenous stress signals are called damage-associated molecular patterns (DAMPs) and include uric acid and extracellular ATP, among many other compounds.<sup>7</sup>

This binding releases specific amounts of inflammatory molecules, cytokines, complement and TGF beta-1- the innate immune system activation sequence. This inflammation is not specific and cannot remove the biotoxins but result in persistent inflammation and a syndrome now known as CIRS.

Unlike bacterial or viral pathogens, which can be identified in blood work, biotoxins cannot be identified by routine blood tests and therefore one needs to rely on identifying them via the damage they inflict on the immune system, neuropeptide hormones and end-organ hormone systems.

Keith Berndtson MD, describes the structure of biotoxins in his Chronic Inflammatory Response Syndrome essay.<sup>8</sup> For example, cell membranes depend on ion channels to transport potassium, sodium and calcium ions in and out of cells. Biotoxins show the structural forms of amphipathic ionophores, creating ion channels that disrupt cell electrodynamics and hence the battery-like charge, rendering the cell incapable of performing its energy producing functions derived from the ion pumps. They also behave as “rogue” ion channels.

Biotoxins have both water and fat soluble capacities. Biotoxins nestle on the inner fat soluble membrane of cells, thus showing a predilection for fatty tissue like the brain, nervous tissue and the autonomic nervous system. Thus, they disrupt cell function without destroying the cell; as opposed to pore-forming toxins which create large holes in cell membranes, which are enough to kill the cell itself.

Cell-signaling is disrupted inside the cell by the disruption in the ion movement. The cell then triggers a defensive response by activating genes that code for inflammatory cytokines, on top of the already overworked innate immune system driven by CIRS. Elevated TGF beta-1 is a sign that the body is over revving from both an innate and an adaptive immune system T cell response.

CIRS biotoxins are first and foremost neurotoxins due to the fatty acid predilection with the brain being a common site, especially if there is porous blood-brain barrier. Cardiovascular and GI sites are also common organ sites due to the rich nervous innervation and the fact that these biotoxins reside intracellularly in the fatty acid membrane, not accessible in the blood stream. They are difficult to dislodge particularly when the adaptive immune system is not adequately working.

Originally, the case definition criteria included Tier One and Tier Two criteria. All tier-one criteria had to be met and three of the six tier- two criteria had to be met to confirm the condition. As research progressed and deeper insights were gained, Dr Shoemaker updated his case definition in 2006 by including Tier-Three criteria which described the response to successful treatment.

In 2008, the Government Accountability Office (GAO) issued their case definition, which was largely reliant on the published work of Dr. Shoemaker. It is the definition commonly used today. Dr. Scott McMahon at the 2016 Surviving Mold Conference at Irving, California, recommended that the GAO case definition be used in clinical practice.

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<sup>7</sup> [https://en.wikipedia.org/wiki/Pattern\\_recognition\\_receptor](https://en.wikipedia.org/wiki/Pattern_recognition_receptor)

<sup>8</sup> Berndtson K. Chronic Inflammatory Response Syndrome, 2013

## TIER ONE CRITERIA – all three must be met

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**1. Exposure** The patient must have a story of an exposure to a biotoxin causing illness.

- **Mold** – water damaged buildings (due to faulty construction, defects in ventilation, condensation issues, high humidity, leaky pipes, poor basement designs, flat roofs without adequate ventilation, fake stucco, faulty appliances, poorly ventilated bathrooms, front end loading washing machines) host microbial growth (bacteria, fungi, mycobacteria and actinomycetes) and produce over 30 different toxins and inflammagens (including mannans, beta glucans, hemolysins and proteinases). Toxic metabolic fragments and cell wall fragments from these filamentous molds are the major source of these biotoxins.

Mold is a specific biotoxin producing component of many water damaged buildings. In 2011, the National Institute for Occupational Safety and Health reported that 50 % of buildings have sustained water damage. Indoor fungi such as *Stachybotrys*, *Aspergillus*, *Acremonium*, *Penicillium* and *Chaetomium* have been implicated.

The Center for Disease Control (CDC) agrees with these findings, stating in a paper published after Hurricane Katrina and Rita in New Orleans, “Mold, endotoxins and fungal glucans were detected in the environment after Hurricanes Katrina and Rita in New Orleans at concentrations that have been previously associated with health effects.”<sup>9</sup> Among the sources of biotoxins that can produce CIRS, biotoxins from molds known to grow in water damaged buildings (WDB) account for some 80% of the CIRS-related illness burden.<sup>10</sup>

- **Lyme disease**- *Borrelia burgdorferi* infections produce a biotoxin (Bbtox1).<sup>11</sup> A history of a tick-bite, an EM rash, followed by a flu-like illness and the use of suitable testing (Elisa plus confirmatory Western Blot) is required to make the diagnosis. Lyme disease and post Lyme treatment syndrome remains a highly contentious area of investigation. Dr Shoemaker’s research showed that up to 21 % of the population is genetically Lyme susceptible, more likely to develop post-Lyme syndrome and less responsive to antibiotics for Lyme disease. They will be more likely to have an upregulated, persistent, inflammatory immune response due to the circulating neurotoxins, in spite of the bacteria being adequately killed by antibiotics.

A 2010 paper showed that *Borrelia* antigens may bind to pattern recognition receptors of the innate immune system and result in decreased CD 38 and thus decreased dendritic cell activation.<sup>12</sup> Individuals thus have genetically determined defective protective antibody production and upregulated innate immune systems; they fail to respond to antibiotics, the definition of post-treatment Lyme syndrome (PTLS).

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<sup>9</sup> Rao C, Brown C, et al. *Applied and Environmental Micro* 2007; 73 (5); 1630-1634

<sup>10</sup> Berndtson K. *Chronic Inflammatory Response Syndrome*. 2013. Pg 3

<sup>11</sup> Cartwright MJ, Martin SE, Donta ST. A novel neurotoxin (Bbtox1) of *Borrelia burgdorferi*. Meeting of the American Society for Microbiology. 1999 May: Chicago.

<sup>12</sup> Hartiala P, Hytonen J, et al. TLR2 utilization of *Borrelia* does not induce p38 and IFN-beta autocrine loop-dependent expression of CD38, resulting in poor migration and weak IL-12 secretion of dendritic cells. *Journal of Immunology* 2010 May 2015;184 (10): 5732 -42.

- Invertebrate species producing neurotoxins including dinoflagellates (ciguatera and red tide), Pfiesteria (PEAS), and cyanobacteria- (freshwater blue-green algae *Cylindrospermopsis* and *Microcystis* - a genus of freshwater cyanobacteria) exposure. Ciguatera fish poisoning is the most common marine toxin poisoning worldwide with an estimated 50,000-500,000 cases annually.<sup>13</sup> Ciguatoxins are dinoflagellates of the genus *Gambierdiscus* found in numerous (over 400) reef fish such as barracuda, grouper and snapper with larger and older fish higher up the fish chain being the most toxic.
- Poisonous spiders like Brown Recluse and Mediterranean Recluse spiders.

**2. Other Diseases** are ruled out via a thorough differential diagnosis workup. Patients with CIRS are often misdiagnosed as having depression, anxiety, PTSD, somatization, Alzheimer's, Parkinsonism, allergy, ADD/ADHD, fibromyalgia and Chronic Fatigue Syndrome. If treated for these underlying conditions, it will make no difference to their underlying CIRS diagnosis.<sup>14</sup>

**3. Symptoms** must be allied with the clinical picture as outlined by Dr. Shoemaker in numerous publications.

Symptoms associated with CIRS (37 in number) are grouped into 8 organ system categories. Symptoms in at least 4 out of the 8 organ system categories (below) are considered diagnostic.

The symptoms categories are listed in the table below:

- 1) General fatigue and weakness
- 2) Muscles – aches, cramps (claw-like cramping of hands and feet), joint pains, morning stiffness, ice-pick pains
- 3) General – headache, frequent urination and increased thirst, night sweats, static electricity or shocks, appetite swings.
- 4) Eyes - light sensitivity, red eyes, blurred vision, tearing
- 5) Respiratory – sinus congestion, cough, shortness of breath
- 6) Gastrointestinal – abdominal pain, diarrhoea
- 7) Neurological – numbness, tingling, metallic taste, vertigo, temperature regulation, dizziness, tics, atypical seizures, fine motor skill problems
- 8) Cognitive - memory loss, concentration difficulties, confusion, learning difficulties, difficulty finding words, disorientation, mood swings, anxiety, panic

These 8 categories are further organized in a questionnaire (below) into 13 symptom clusters. Each cluster has between 1-5 symptoms. The clusters were selected by statisticians in order to maximize predictive capabilities. A patient presenting with at least 1 symptom in at least 6 of

<sup>13</sup> Ryan J, 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 Medical Genomics* 2015 8:15

<sup>14</sup> Ryan J, Shoemaker RC, 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 fluctuations that coincide with healing. *Medical Research Archives* Vol 4 Issue 7 2016.

the 13 clusters for more than two weeks, needs to be considered as having the CIRS diagnosis and should have a thorough diagnostic workup. In adults, if symptoms are present in at least 8 symptom clusters, this is considered consistent with biotoxin illness. In children, if symptoms are in 6 symptom clusters, these results are considered positive.

Chronic Inflammatory Response System	Clinical Questionnaire					
Symptom Checklist						
Please answer YES or NO for each symptom						
	Date	Date	Date	Date	Date	Date
Fatigue						
<b>Subtotal</b>						
Weakness						
Decreased Assimilation of New Knowledge						
Aches						
Headache						
Light Sensitivity						
<b>Subtotal</b>						
Memory Impairment						
Decreased Word Finding						
<b>Subtotal</b>						
Difficulty Concentrating						
<b>Subtotal</b>						
Joint Pain						
A.M. Stiffness						
Cramps						
<b>Subtotal</b>						
Tingling						
Tremors						
Unusual Pain						
Unusual Skin Sensitivity						
<b>Subtotal</b>						
Shortness of breath						
Sinus Congestion						
<b>Subtotal</b>						
Cough						
Excessive thirst						
Confusion						
<b>Subtotal</b>						
Appetite swings						
Difficulty Regulating Body Temperature						
Increased Urinary Function						
<b>Subtotal</b>						
Red Eyes						
Blurred Vision						
Sweats (night)						
Mood Swings						
Ice-pick Pain						
<b>Subtotal</b>						
Abdominal Pain						
Diarrhea						
Numbness						
<b>Subtotal</b>						
Tearing of Eyes						
Disorientation						
Metallic Taste						
<b>Subtotal</b>						
Static Shocks						
Vertigo						
<b>Subtotal</b>						
<b>TOTAL</b>						
Reference: Ritchie Shoemaker - April 2012						

## Signs

Signs were not included in the Three Tier categories.

There are many possible clues on physical examination as to the possibility of a CIRS diagnosis:

- 1) Red eyes
- 2) Tremor – resting.
- 3) Cool hands and feet
- 4) Discolored hands and feet
- 5) Pallor
- 6) Weakness in the shoulder extensor muscles
- 7) Decreased muscle strength in the arms and forearms
- 8) Grip strength and shrugging of shoulders against resistance
- 9) Hyper flexibility - Flexibility is tested
- 10) A full examination of all systems is to be done, including thyroid, cardiac and respiratory systems<sup>15</sup>

## **TIER TWO CRITERIA – at least three of the following six criteria must be met**

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### **1. Abnormal Visual Contrast Sensitivity (VCS)**

<http://www.survivingmold.com/store1/online-screening-test>

- In 1997, Dr. Shoemaker and Ken Hudnell published a study demonstrating that patients with exposure to biotoxins showed abnormal VCS results consistent with biotoxin illness. The visual contrast test measures the neurologic function of the optic nerve from the retina to the cortex by measuring the least amount (threshold) of luminescence difference between adjacent areas (contrast) necessary for an observer to detect a visual pattern.
- The test measures contrast sensitivity for five sizes (spatial frequencies) of light, gray and dark bar patterns (sinusoidal gratings). The VCS eliminates near, far, color, motion and peripheral vision variables.
- There are spatial frequencies measured amongst healthy individuals which is the curve formed by the highest level of contrast the patient will see, versus the CIRS patients who will have lower contrast sensitivities and their curves will fall below the healthy control line. Higher contrast sensitivity is better.

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<sup>15</sup> Shoemaker R. Biotoxin Illness Treatment Protocol Pg. 1

- In the presence of biotoxin illness, visual contrast sensitivity decreases. Only rows C and D count for scoring pass or fail. One must see 7 in each eye on C and 6 in each eye on D. Rows D and C show improvement with clearing of biotoxins. With an intensification reaction to cholestyramine, there will be a fall in column E followed by a fall in column D.<sup>16</sup> A fail in 1 eye and not the other eye, still constitutes a fail.
- VCS appears to be an early, persistent, highly sensitive, inexpensive and easily measured indicator for biotoxin illness.<sup>17</sup> Only 8 % of people with CIRS will have a normal VCS. Thus, 92 % of people with biotoxin illness will fail the VCS. However, 98 % of patients who fail the VCS test and who have 8 of the symptom clusters will have biotoxin illness.
- A few people will pass the VCS but still show signs, symptoms, and inflammatory markers suggestive of biotoxin illness such as artists and professional baseball players with extra keen vision.<sup>18</sup> Occupational exposure to solvents, hydrocarbons and petrochemicals can cause a person to fail the VCS test but not have biotoxin illness. This phenomenon is rare.
- The test can be done online (reference above) as well as in the office with a specific hand-held chart. <http://www.survivingmold.com/store1/vcs-aptitude-handheld-kits>

For accuracy, the following conditions need to be met:

- 1) Visual acuity must be better than 20:50.
- 2) Patients must wear their corrective eyewear
- 3) Lighting must be sufficient
- 4) Patients must sit 14 inches away from the screen for visual acuity, 18 inches for contrast sensitivity.<sup>19</sup>

If a patient either passes or fails the VCS test and there is still a high index of suspicion for biotoxin illness based on a history of exposure, symptom cluster analysis and/or signs on physical examination, it is still advisable to proceed with HLA and inflammatory biomarker testing.

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<sup>16</sup> Shoemaker R. State of the Art answers to 500 Mold Questions Question 212.

<sup>17</sup> Shoemaker R, Hudnell K. Possible Estuary-Associated Syndrome: Symptoms, Vision and Treatment Environmental Health Perspectives Vol 109. No5 May 2001.

<sup>18</sup> Shoemaker, 2011, June 27, DVD.

<sup>19</sup> Shoemaker R., Letter to St Barnard Parish, 2/22/2006. pg. 8

## VCS Left Eye

	A	B	C	D	E
9	✗	✗	✗	✗	✗
8	✗	✗	✗	✗	✗
7	✗	✗	✗	✗	✗
6	✗	✗	✗	✗	✗
5	✗	✗	✗	✗	✗
4	✓	✗	✗	✗	✗
3	✓	✗	✗	✓	✗
2	✓	✗	✗	✓	✓
1	✓	✗	✗	✓	✓

## VCS Right Eye

	A	B	C	D	E
9	✗	✗	✗	✗	✗
8	✗	✗	✗	✗	✗
7	✗	✗	✗	✗	✗
6	✓	✓	✓	✗	✗
5	✓	✓	✓	✗	✗
4	✓	✓	✓	✗	✗
3	✓	✓	✓	✓	✗
2	✓	✓	✓	✓	✗
1	✓	✓	✓	✓	✓

**Result: Fail**

## 2. Human Leukocyte Antigen (HLA) Genetic Testing

- Approximately 24 % of the USA population have HLA gene types that make them susceptible to biotoxin illness i.e.- they do not have the genetic capability to clear biotoxins. The susceptible population makes up 95 % of the CIRS patients. The remaining 5% of CIRS patients do not have this genetic susceptibility. Approximately 76 % of the population is not susceptible to CIRS.
- HLA refers to the Human Leukocyte Antigen genes on chromosome 6. HLA's are found on the surface of nearly every cell in the human body. They provide instructions for making a group of related proteins known as the HLA complex which helps the immune system distinguish between the body's own proteins and proteins made by foreign invaders such as bacteria,

viruses, and fungi. This gene encodes for proteins that present foreign antigens to immune cells for removal. The HLA DR test determines ones susceptibility to CIRS plus many other diseases. <sup>20</sup>

- These HLA DR/DQ encoded proteins are found on antigen presenting cells such as macrophages, B cells and dendritic cells and they present foreign cells from outside the cell to naive T lymphocytes. The T lymphocytes eliminate the antigen and transfer to B lymphocytes the ability to identify the antigen for removal. The structures of the HLA DR molecules are critical to the initial peptide/antigen recognition. The alleles most important for chronic illness expression include DRB1, DQ, DRB3, DRB4, and DRB5.
- Just as we inherit one red blood cell type from our parent, we also inherit white cell types from our parents. However, the proteins inherited are not just one or two as in red cell proteins; they are many more combinations of proteins into groups resulting in over 50 different HLA types. The chart below will demonstrate which haplotypes are associated with which biotoxin illness susceptibility
- The following haplotypes are associated with these different biotoxin illnesses.
  1. Multi-susceptible: 4/3/53; 11/3/52B; 12/3/52B; 14/5/52B
  2. Mold specific: 7/2/53; 7/3/53; 13/6/52A, B or C; 17/2/52A; 18/4/52A
  3. Borrelia specific: 15/6/51; 16/5/51
  4. Dinoflagellate specific: 4/7/53; 4/8/53
  5. MARCoNS susceptible: 11/7/52B
  6. MSH low: 1/5
  7. Mold- low risk: 7/9/53; 12/7/52B; 9/9/53

## HLA-DR Patterns

Susceptibility	DRB1	DQ	DRB3	DRB4	DRB5
<b>Multi-susceptible</b>	4	3		53	
<i>Unable to clear an/all toxins from system</i>	11 or 12	3	52B		
	14	5	52B		
<b>Mold</b>	7	2 or 3		53	
<i>Unable to recognize or clear mold toxins</i>	13	6	52 A, B, C		
	17	2	52A		
	18*	4	52A		
<b>Chronic Lyme-post Lyme syndrome</b>	15	6			51
<i>Unable to clear Lyme toxins</i>	16	5			51

<sup>20</sup> Shoemaker RC. Johanning E. Sick Building Syndrome in Water-damaged Buildings: Bioaerosols, Fungi, Bacteria, Mycotoxins and Human Health, pp 66-77, 2005

<b>Dinoflagellates</b>	4	7 or 8		53	
<b>MARCoNS</b> – immune system lacks ability to recognize and attack methicillin resistant staph infections	11	7	52B		
<b>Low MSH</b>	1	5			

### Clinical Observation

- 4-3-53 - has 12 subtypes DRB1- 0401, -0402 and -0404 are the worst, 3% incidence, the worst RA, malaria, autoimmune hepatitis. Have the highest C4a and TGF beta-1. 0401 is the worst.
- 11/12-3-52B – 1% incidence, tall, hypermobile, long arm span, good athletes. With free/unbound TGF  $\beta$ -1, they get “sicker quicker” upon exposure.
- 17-2-52 A,B,C and 7-2-53 haplotypes associated with celiac disease
- If a Lyme patient does not have the Lyme or multi-susceptible haplotypes there is a higher chance that he will respond to antibiotics alone.
- If the patient is not better with antibiotics and he has one of these haplotypes, he will need a biotoxin pathway approach. Taking antibiotics for prolonged periods alone will not fix these patients.
- Low risk mold HLA types are: 7-9-53; 12-7-52B; 9-9-53;
- No recognized significance types are: 8-3,4,6.  
1-5,6,8

## 3. Matrix Metalloproteinase 9 (MMP-9)

### Lab Results

Normal range: 85-332 ng/ml; 28.14-109.89 nmol/l

A prechilled SST tube is essential to use. Following the lab draw, the specimen should be immediately centrifuged and frozen. This step will prevent the release of MMP9 from the white blood cells into the blood specimen which can double or triple at room temperature in as little as 30 minutes. Use LabCorp.

- MMP-9 is an enzyme activated by macrophages inducing inflammatory cytokines of the innate immune system that destroys the basement membrane of endothelial cells. This provides a barrier between the blood and tissue
- With high MMP-9, as when the immune system is chronically stimulated, the basement membrane is porous, allowing inflammatory compounds/chemokines to penetrate tissues such as muscles, joints, brain, lungs, peripheral and autonomic nervous system.<sup>21</sup>
- High MMP-9 will increase blood-brain barrier permeability.<sup>22</sup>

<sup>21</sup> Shoemaker RC. Defining Sick Building Syndrome in adults and children in a case-control series as a biotoxin-associated illness: American Journal of Tropical Hygiene and Health; 2005;73 (6):228

<sup>22</sup> Candelario-Jalil E, Thompson J, Taheri S, Grossetete M, et al. Matrix metalloproteinases are associated with increased blood-brain barrier opening in vascular cognitive impairment. Stroke. 2011 Mar 31.

- MMP-9 can contribute to the destruction of connective tissue as seen in arthritis, atherosclerosis and cardiomyopathy.
- MMP-9 increases lipoprotein a and oxidized LDL
- MMP-9 correlates with high toxic load, total cytokine load, reflect disease progression, exposure, Herxheimer reaction (with TNF). It is a great marker for hidden cytokine production.
- Increased in head injury
- Patient may feel worse with CSM if they have high MMP9.

## 4. ACTH/Cortisol

### Lab Results:

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Normal Range:

ACTH: 8-37 pg./ml; 1.76-8.14 pmol/l

Cortisol: A.M. 4.3-22.4 ug/dl; 3.07-15.99 umol/l

P.M. 3.1-16.7 ug/dl; 2.21-11.92 umol/l

Absolute or relative ACTH dysregulations may be seen:

- 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- two-tiered test
- 4) Relative: ACTH was > 15 when cortisol was > 16 - two-tiered test

- ACTH and cortisol are hypothalamic-pituitary-end organ dysregulation markers. ACTH and cortisol measure hypothalamic regulation of the adrenal glands. ACTH is released with the breakdown of POMC. It stimulates the adrenals to release cortisol, a stress hormone.
- Cortisol release raises blood sugar. Levels are higher in the morning and lower at night. Cortisol levels begin to increase at approx. 6 am in an individual with normal circadian rhythms (i.e. not a shift worker).
- Cortisol is said to “boot us up - mentally and physically” in the morning. If higher during the night, this may result in insomnia.
- When stressed either physiologically or mentally, both cortisol and DHEA rise in tandem. We may adjust to long term stress with higher than average levels of both DHEA and cortisol. However, over time, levels of DHEA may start to decline, followed by cortisol levels. We may also have dysregulated day and night levels of cortisol with low daytime and high night time levels. Daytime fatigue and nighttime insomnia with awakening issues can result.
- The normal response of ACTH to cortisol is that if cortisol levels fall, ACTH levels should rise.
- Both of these may be elevated in the beginning stages of CIRS but later both may be decreased.
- Having low ACTH in relationship to cortisol is often a common pattern seen in CIRS.
- Cortisol regulation is lost in 50 % of people with low MSH
- Early in the CIRS diagnosis, as MSH falls, high ACTH is not associated with many symptoms
- As ACTH falls, there is a marked rise in symptoms
- People who are quite ill can have low ACTH and low cortisol levels.
- Treating CIRS through the different stages may correct these abnormalities.

- Adrenal support through lifestyle and/or supplementation may also be needed. This approach, however, is not part of the Shoemaker protocol.

## 5. Antidiuretic Hormone (ADH) and Osmolality

### Lab Results

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Normal range: ADH: 1- 13.3 pg./ml; 0.9 – 12.28pmol/l;  
Osmolality: 280-300 mOsm/kg.

High serum osmolality - High ADH = normal

Low serum osmolality - Low ADH = normal

High serum osmolality with low ADH = abnormal. Consider treatment with Desmopressin

Absolute or relative ADH dysregulations may be seen:

- 1) Absolute high: ADH > 13 or osmolality > 300
- 2) Absolute low: ADH <5 or osmolality <275
- 3) Relative: ADH was < 2.2 when osmolality was 292-300 - two-tiered test
- 4) Relative: ADH was > 4 when osmolality was 275-278 - two-tiered test

- ADH and osmolality are hypothalamic-pituitary-end organ dysregulation markers
- Dr. Shoemaker published data showing that up to 80 % of patients with CIRS have dysregulated ADH/osmolality levels.
- If mold is remediated, biotoxins are bound with CSM, the VCS improves and MARCoNS is eradicated, low ADH will normalize in many cases on its own. Some patients will still require treatment.
- ADH is a marker of disrupted MSH function. Reduced hypothalamic output of ADH in response to increased osmolarity is associated with reduced VEGF production in response to low microcirculatory oxygen levels. Low ADH is also associated with autistic behaviour and social avoidance behaviour in CIRS patients.<sup>23 24</sup>
- The hypothalamus contains cells called osmoreceptors that respond to serum osmolality.
- When the serum osmolality is high (body fluids/blood concentrated due to dehydration), the osmoreceptors shrink and release antidiuretic hormone from the posterior pituitary where it is stored. ADH is a 9-amino acid peptide. ADH binds to receptors on cells in the collecting ducts in the kidneys and reabsorbs water. Thus, cells become rehydrated and ADH levels fall.
- When serum osmolality falls (overhydrated, more water in the blood), the osmoreceptors swell and block ADH release from the posterior pituitary. ADH levels drop and free water is lost in the kidneys.
- In CIRS patients there is a dysregulation of this mechanism. Most commonly ADH levels are low (they may however be high) and osmolality levels are high (dehydrated); however, they may be low). What is apparent is that the ADH levels and the osmolality levels do not appear to be synchronous with each other as they should be in a healthy non-CIRS patient.

<sup>23</sup> Berndston K. Chronic Inflammatory Response Syndrome pg. 15

<sup>24</sup> Tansey KE, Hill MJ, Cochrane LE, Gill M, et al. Functionality of promotor microsatellites of arginine vasopressor 1A (AVPR1A): implications for autism. Molecular Autism. 2011 Mar 31;2(1):3

- Patients with CIRS often have increased thirst and increased urination. They are also susceptible to electric shocks from touching door handles. This happening is due to the fact that as salt levels rise in blood due to the dehydration, salt is released onto the skin, through the sweat glands and creates a battery-like effect that increases the electrostatic shock potential. Chloride levels may be higher than cystic fibrosis patients in some cases.
- Dehydration may also produce migraine like headaches.<sup>25</sup>
- ADH also affects VIP and MSH levels in the suprachiasmatic nucleus of the hypothalamus. Without these three hormones, the hypothalamic regulation is significantly affected. Patients with low MSH will most often have low levels of ADH.
- Treatment is to use DDAVP.

## 6. Melanocyte Stimulating Hormone (MSH)

### Lab Results

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Normal Range: 35-81 pg/ml; 206-478.7 pmol/. Run through LabCorp:

- MSH is one of the most critically suppressed neuroregulatory peptide hormones in the dysregulation seen in CIRS patients.
- MSH is decreased in more than 95 % of patients with CIRS.
- One of most potent anti-inflammatory compounds in the body; it regulates the innate immune system.
- Inflammatory cytokines bind to leptin receptors, usually activating MSH and beta endorphins. MSH would then control leptin. In biotoxin illness, cytokines block leptin receptors, MSH is not made, disrupting nerves, hormones and immune function.
- MSH is controlled by leptin in the pituitary gland; pro-opiomelanocortin (POMC) is split into three components- alpha-MSH, or adrenocorticotrophin (ACTH) and beta-endorphin.
- MSH functions include: melatonin production, immune surveillance of mucous membranes intestinal permeability, nasal pathogen protection), regulates ADH and VIP, reduces inflammation, controls cytokine release in skin and gut, prevents Candida infections, controls pain through endorphin release
- When abnormal, the result is problems with sleep, pain, gut symptoms, fluid dysregulation due to ADH with increased thirst and increased urination, cortisol dysregulation, fatigue, nasal colonization with MARCoNS, stress management problems, reduced sex hormones.
- Due to leptin issues, weight gain which does not respond to more exercise and less eating, can be a problem.
- Low MSH causes dysregulation of T reg cells leading to inflammation and autoimmune disorders
- MSH has been shown to regulate the inflammatory cytokines (TNF and nitric oxide) found in inflammatory bowel disease.<sup>26</sup>
- Low MSH associated with anti-gliadin positivity.

Important: Markers of hypothalamic illness include high leptin and osmolality, low MSH, low ADH, ACTH and/or VIP.

<sup>25</sup> Shoemaker R. Biotoxin Illness Treatment Protocol pg. 6

<sup>26</sup> Rajora N, alpha MSH Modulates Inflammatory Bowel Disease Peptides Vol 18 Issue 3 pg. 381-385.

## TIER THREE CRITERIA

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These criteria were based on the 2010 Consensus Report as written by Dr Shoemaker and his research committee.<sup>27</sup> These criteria are evaluated after treatment has begun and are the final validation of the diagnosis of CIRS.

Improvement in the following areas is required to validate the CIRS diagnosis.

- 1) Symptoms and VCS improve with treatment; and
- 2) Lab markers (leptin, MMP 9) return to normal levels.

## SUMMARY OF THE THREE TIERS CRITERIA FOR DIAGNOSIS OF CIRS:

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- Thus, in summary, with these Shoemaker criteria in mind, three of the Tier-Two criteria in addition to all of the Tier- One criteria must be met to make the preliminary diagnosis of CIRS.
- Once the diagnosis is made, there are other proteomic, genomic and imaging studies which can be done in order to establish the diagnosis and assist in the treatment protocol.
- One of the most striking features of the CIRS diagnosis is the absence of the anti-inflammatory neuropeptides vasoactive intestinal peptide (VIP) and melanocyte stimulating hormone (MSH), with the concurrent master immune regulator TGF beta-1 being abnormally increased.<sup>28</sup>
- Patients should present with at least four out of the eight objective serum markers found in CIRS – TGFB1, VIP, MSH, MMP9, C4a, VEGF, ACTH/cortisol and ADH/osmolality.

## Government Accountability Office (GAO) 2008 Case Definition

The GAO issued its case definition in 2008 which became the standard for case definition. The GAO definition focuses exclusively on CIRS from water-damaged buildings and not from other initiating triggers.

1. Patient exposed to WDB -verified by presence of musty smells, visible mold or mycological testing.
2. Multiple symptoms from multiple systems similar to Dr Shoemakers published research.
3. Lab abnormalities similar to Dr Shoemaker's lab abnormalities.
4. Improvement with therapy similar to those found in peer-reviewed published research.

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<sup>27</sup> Shoemaker RC, Mark L and McMahon S, Research Committee Report on Diagnosis and Treatment of Chronic Inflammatory Response Syndrome Caused by Exposure to the Interior Environment of Water-Damaged Buildings. Mold Research Committee, Pocomoke 2010

<sup>28</sup> Shoemaker R.C. Ryan JC Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. Health 5 (3), 396-401

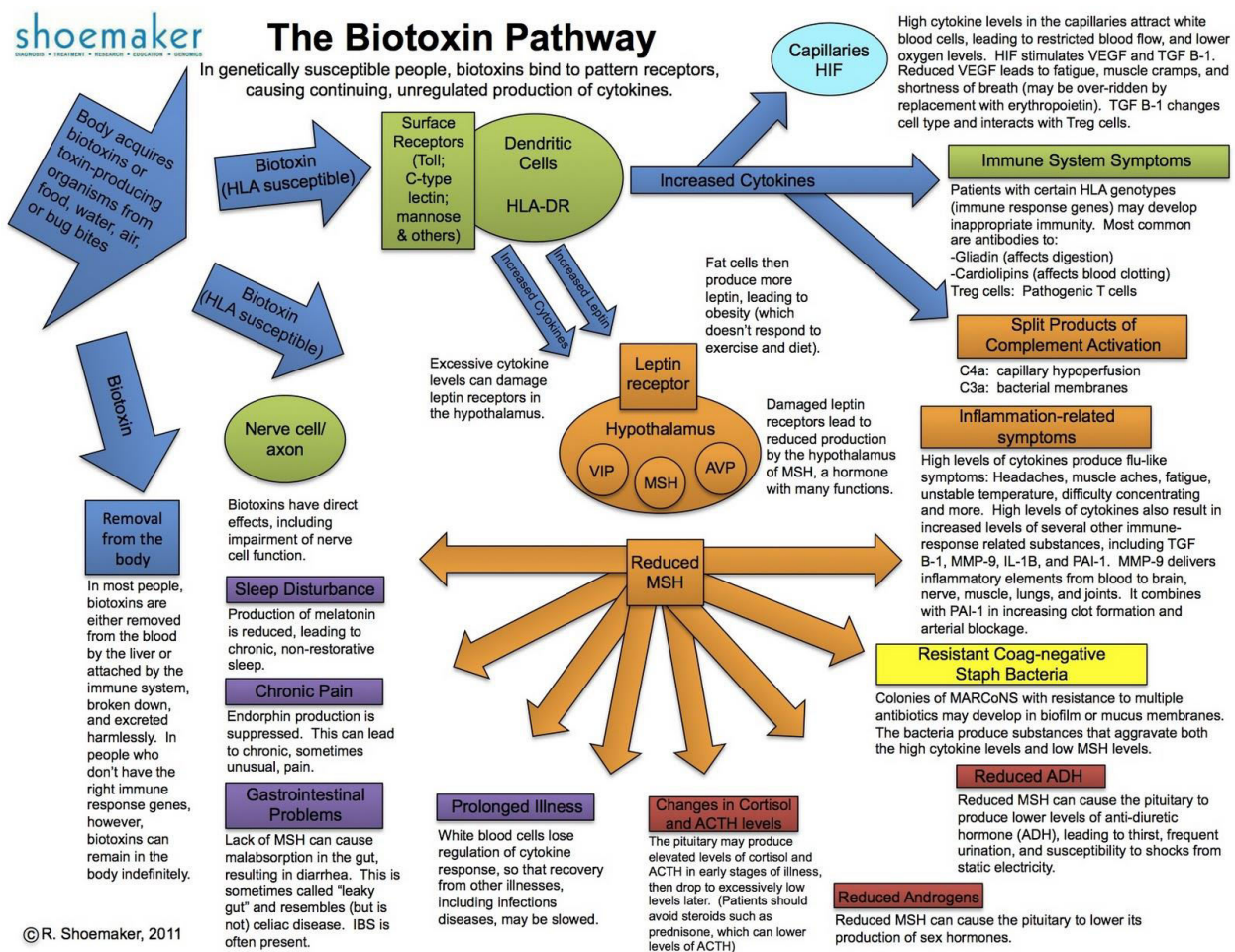
# Challenges with CIRS Case Definition

One of the challenges of the CIRS case definition is that it takes more than one visit to confirm the diagnosis, patients need to have labs, need to take their medications, and thus the diagnosis cannot be made on the first visit.

## Further Diagnostic Tests

If a patient has a positive exposure history, more than 6 symptom clusters, a positive VCS test, and fulfills the diagnostic criteria of the first 2 tiers, then further confirmatory lab testing must be done to confirm or disprove the CIRS diagnosis.

The following chart gives a visual representation of the biotoxin pathway with some of the lab markers being represented.



## FURTHER BIOMARKERS/IMAGING/TESTS ASSESSED IN CIRS:

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- ERMI
- MARCoNS
- Antigliadin antibodies
- Androgens
- Leptin
- C3a
- C4a- run through Quest
- VEGF
- TGFbeta-1
- VIP
- Von Willebrands
- CD4+CD25+
- Anti-cardiolipin antibodies
- PAI-1
- Pulmonary Function Tests
- VO2 Max
- Stress Echocardiogram
- Neuroquant
- Genomics

# PHYSICIAN ORDER SHEET

Please Draw	Test	Lab to Use		Code #	DX Codes	CPT codes
	HLA DR by PCR	LabCorp	Spec	167120	D84.1 D83.1 D89.89	81375
	VIP	Quest	Lavender, room temp	920	D84.1 D89.89	84586
	MSH	Lab Corp only	Lav - freeze-trasylol	010421	E23.0 R65.10	83519
	Leptin	LabCorp	Lav - freeze-trasylol	146712	E23.0 R65.10	82397
		Quest	Lav - freeze-trasylol	90367	E23.0 R65.10 995.93	83520
	ADH	LabCorp	SST - freeze	10447	E23.0 R65.10 995.93	84588
		Quest	SST - freeze	252	995.93 R65.10	83930 84588
	Osmo	Labcorp	LAV freeze	2071	E23.2	83930
		Quest	LAV freeze	677	R65.10 995.93	83930
	ACTH	Labcorp	SST - freeze	004440	E27.4	82924
		Quest	SST - freeze	211	E27.40 255.41	82024
	Cortisol	LabCorp	Lav - freeze	004051	E27.40 255.41	82533
		Quest	Lav - freeze	4212	E27.40 255.41	82533
	DHEAS	LabCorp	SST freeze	004020	E27.40 255.41	82627
		Quest	SST freeze	402	E27.40 255.41	82627
	Testosterone	LabCorp	SST - freeze	140103	E29.1	84402 84403
		Quest	SST - freeze	873	E29.1	84402 84403
	Androstenedione	LabCorp	red top - room temp	500171	E27.40 255.41	82157
		Quest	red top - room temp	17182x	E27.40 255.41	82157
	CRP	LabCorp	SST - freeze	120766	R79.82	86141
		Quest	SST - freeze	17182x	R79.82	86141
	ESR	LabCorp	SST - room temp	5215	D89.89 279.49	85652
		Quest	SST - room temp	809	D89.89 279.49	85652
	TGF-B1	LabCorp	Lav	905036	D84.1 D83.1	83520
		Quest	Lav	91238	D84.1 D83.1	83520
	MMP-9	LabCorp	Lav freeze (platelet poor plasma)	500124	D89.89 R53.81	83520
	PAI-1	LabCorp	SST - freeze	146787	I67.6	85415
		Quest	SST - freeze	36555	D68.9 286-9 I67.6	85415
	CBC	Quest	Lav - room temp	17182x	E27.40 255.41	85025
		LabCorp	Lav - room temp	5009	E27.40 255.41	85025
	CMP	LabCorp	SST - room temp	322000	E27.40 255.41	80053
		Quest	SST - room temp	10231x	E27.40 255.41	80053
	GGT	LabCorp	SST - room temp	001958	E27.40 255.41	82977
		Quest	SST - room temp	10231x	E27.40 255.41	82977
	VEGF (not serum)	LabCorp	Rm temp	117006	E23.0 R65.10	83520
		Quest	Rm temp	14512	995.93 R65.10	83520
	Erythropoietin	LabCorp	Red - freeze	140277		82668
		Quest	Red - freeze	427x		82668
	Anticardiolipins	LabCorp	Red - freeze	161950	M32.1	86147
		Quest	Red - freeze	7352	286.9 D68.9	86147
	Antigliadin, IgA, IgG	LabCorp	SST - freeze	161646/161687	K90.0	83516
		Quest	SST - freeze	8889x	279.8/D89.89	83516
	C3a RIA (not Futhan)	Quest only	SST - freeze	17689	279.8/D89.89	86160
	C4a RIA (not Futhan)	Quest only	Lav - freeze	19956	279.8 / D89.89	86160
	IgE	Quest	Lav - freeze	542x	279.03 D80.3	82785
		LabCorp	Lav - freeze	002295	279.03 D80.3	82784
	Lyme WB	Quest	SST - freeze	8593	088.81/A69.20	86617
	TSH	LabCorp	SST - freeze	004259	244.8	84443
		Quest	SST - freeze	899x	244.8	84443
	von Willebrand's profile	Quest	SST - freeze	15540x	286.9 D68.9	85240
	Fe /TIBC	Quest	Blue freeze - 3 aliquots	7573x	R53.81	83540
		LabCorp	Blue freeze - 3 aliquots	001321	R53.81	83540

Ferritin	LabCorp	SST - freeze		R53.81	82728
	Quest	SST - freeze	457x	R53.81	82728
HgB A1C	LabCorp	SST - freeze	001453	E08.00	83036
	Quest	SST - freeze	496x	E08.00	80306
Vitamin D3 (25-OH)	LabCorp	Lav - room temp	081950	R53.81	82306
	Quest	Lav - room temp	17306x	R53.81	82306
Estradiol	LabCorp	SST - freeze	004515	N95.8	82670
	Quest	SST - freeze	4021x	N95.8	82670
Lipase	LabCorp	SST - freeze	001404	789.00/R10.9/K85.9	83690

Reference: [www.survingmold.com](http://www.survingmold.com)

## ENVIRONMENTAL RELATIVE MOLDINESS INDEX (ERMI)

- If water damaged buildings/mold is suspected, an ERMI is essential.
- Mold illness and CIRTS arise from any indoor environment that is damaged by water intrusion. Until recently, there had been no standardized objective methods available to quantify the indoor air mold burden.<sup>29</sup> Air sampling has come under much criticism due to the fact that it samples air for just a few minutes in time, does not separate all the toxigenic molds into the correct genera, and does not take into account *Wallemia*. *Stachybotrys* can often be missed as it is not an airborne mold, being heavy in nature and existing mostly on the ground. Not all molds are toxic to humans and not all “mold is mold.”
- Dr. Stephen Vesper and his team at the Microbial Exposure Laboratories of the EPA in Cincinnati pioneered the use of Mold Specific Quantitative Polymerase Chain Reaction (MSQPCR), and its application called the Environmental Relative Mold Index (ERMI).<sup>30</sup> ERMI is an objective, standardized DNA-based method that will identify and quantify molds. ERMI does not measure the DNA of all fungi, but those that carry the highest implications for the relative mold burden in water damaged buildings.
- There are currently three labs that offer the ERMI test: EMSL Analytical [www.emsl.com](http://www.emsl.com), Mycometrics [www.mycometrics.com](http://www.mycometrics.com) and EMLab P&K [www.emlab.com](http://www.emlab.com). Mycometrics is the most accurate according to Dr Shoemaker and provides both a Swiffer cloth method of detection and offers the HERTSMI-2 score.
- The ERMI classifies 36 species of mold into 26 species or clusters associated with WDB (Group 1) and 10 common species/clusters not associated with WDB (Group 2) and commonly found outside.<sup>31</sup> The number calculated as the ERMI is the sum of the logs of the concentrations of the DNA of the different species. The mold index (ERMI) is the difference between Group 1 and Group 2. The ERMI was calibrated to the specific measurements (3 feet by 6 feet) in the living room and bedroom for 5 minutes and all the national standards reflect measurements from these areas only. Measuring mold in the basement only is not recommended as a first line measurement for these reasons.
- Computerized ERMI values are graphed from the lowest to the highest (see figure below). The ERMI value is typically between -10 (lowest mold levels) and 20 (highest relative mold levels). An

<sup>29</sup> Lin K-T, Shoemaker R.C. Inside Air Quality Filtration News Vol 26, No 3, pg. 32, 2007.

<sup>30</sup> Ibid

<sup>31</sup> Ibid

ERMI above 5 is in the top 75 % of homes for relative mold burden. An ERMI of -4 and below is on the lowest 25 % of homes in the US.

## MYCOMETRICS, LLC.

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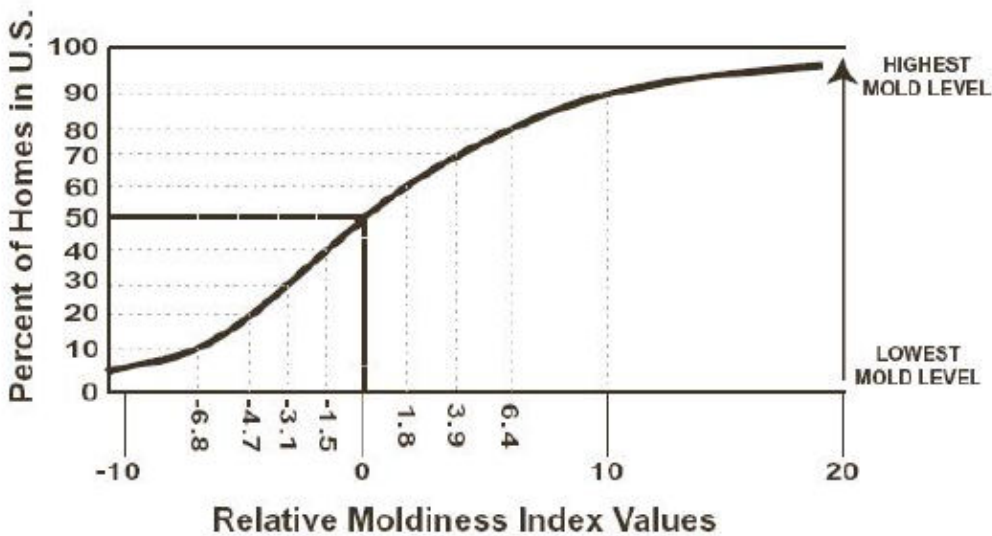
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Address:  
Project ID:  
Date Sampled:  
Date Received:  
Samples Submitted By:  
Date Analysis Completed:  
Mycometrics Report No.:  
Mycometrics Report Date:



### ERMI Report



As Dr. Shoemaker and Dr. Lin point out, the ERMI is a mold index, not a health index.

- If the ERMI is low and there are people living in the home with positive symptoms for CIRS, that is, exceeding the cut-off criteria, and/or failing the VCS test, the ERMI should be repeated in different areas of the house. An ERMI does not exclude the value of a thorough top to toe visual inspection by a mold indoor specialist.
- If you are not ill, an ERMI will help determine if your home is safe for visitors who have the mold susceptible gene and who are known to have health effects from moldy buildings
- If the ERMI is low and no one is ill, one's sense of security increases. Doing an ERMI is very helpful before one considers buying a new home.
- Elevated ERMI test result have been shown to have a positive correlation with lab abnormalities associated with CIRS, symptoms of CIRS, neurotoxicological studies, measurements of abnormal

brain metabolites and symptoms of cognitive decline including brain fog, memory deficits and poor executive cognitive functioning.<sup>32</sup> Dr. Shoemaker writes that the high levels of mold translate in genetically susceptible patients into inflammation that reduces blood flow in particular parts of the brain so that it does not work efficiently. Furthermore, if a person is adequately treated but returns to a home with an ERMI above 2, he relapses.

- In general, an ERMI value greater than 2 is considered unsafe for CIRS patients if the MSH is less than 35 and the C4a is less than 20,000. If the MSH is less than 35 and C4a is greater than 20,000, the ERMI score needs to be less than -1.

## HEALTH EFFECTS ROSTER OF TYPE SPECIFIC FORMERS OF MYCOTOXINS AND INFLAMMAGENS - HERTSMI-2

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- A secondary result can be calculated called a HERTSMI-2. This scoring system is application of the DNA testing shown on ERMI test results. The new roster is designed to help patients previously sickened by water-damaged buildings and genetically predisposed understand if a given building is safe for occupancy. The roster is based on the results of 738 ERMI consecutive test results with 592 that were over 2 and 146 under 2.
- This uses values of five specific molds- *Aspergillus penicilloides*, *Aspergillus versicolor*, *Chaetomium globosum*, *Stachybotrys chartarum* and *Wallemia sebi* - from group 1 on ERMI based on 2 criteria:
  - 1) Representative of varied water saturations (60-80%; 80-90%; 90-100%); and
  - 2) Relative risk for enrichment is WDB compared to non-WDB is at least 10.

A specific scale is used to grade the counts of each of the five species as and added up.

10 points are awarded for:

- *Aspergillus penicilloides* >500 spore E/mg
- *Aspergillus versicolor* >500 spore E/mg
- *Chaetomium globosum* >125 spore E/mg
- *Stachybotrys chartarum* >125 spore E/mg
- *Wallemia sebi* >2500 spore E/mg

6 points are awarded for

- *A. penicilloides* or *A. versicolor* >100
- *Chaetomium* or *Stachybotrys* >25
- *Wallemia* >500

4 points awarded for

- *A. penicilloides* or *A. versicolor* >10
- *Chaetomium* or *Stachybotrys* >5
- *Wallemia sebi* >100

\*Any score over 15 is too dangerous for previously sickened patients to occupy.

\*Any score under 11 has been safe to date.

\* Some individuals may need a HERTSMI-2 score of <8 to not relapse

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<sup>32</sup> Ibid

\*Any score 11-15 is borderline. The building must be treated before safety can be assessed.

Fungal ID/Sample ID	Spore E./mg
<i>Aspergillus flavus/oryzae</i>	ND
<i>Aspergillus fumigatus</i>	ND
<i>Aspergillus niger</i>	ND
<i>Aspergillus ochraceus</i>	<1
<i>Aspergillus penicillioides</i>	13
<i>Aspergillus restrictus*</i>	<1
<i>Aspergillus sclerotiorum</i>	ND
<i>Aspergillus sydowii</i>	ND
<i>Aspergillus unguis</i>	<1
<i>Aspergillus versicolor</i>	190
<i>Aureobasidium pullulans</i>	140
<i>Chaetomium globosum</i>	ND
<i>Cladosporium sphaerospermum</i>	<1
<i>Eurotium (Asp.) amstelodami</i>	9
<i>Paecilomyces variotii</i>	<1
<i>Penicillium brevicompactum</i>	45
<i>Penicillium corylophilum</i>	1
<i>Penicillium crustosum*</i>	10
<i>Penicillium purpurogenum</i>	<1
<i>Penicillium spinulosum*</i>	ND
<i>Penicillium variable</i>	<1
<i>Scopulariopsis brevicaulis/fusca</i>	ND
<i>Scopulariopsis chartarum</i>	13
<i>Stachybotrys chartarum</i>	<1
<i>Trichoderma viride*</i>	<1
<i>Wallemia sebi</i>	230
<b>Sum of the Logs (Group I):</b>	<b>12.61</b>
<i>Acremonium strictum</i>	1
<i>Alternaria alternata</i>	19
<i>Aspergillus ustus</i>	ND
<i>Cladosporium cladosporioides 1</i>	130
<i>Cladosporium cladosporioides 2</i>	6
<i>Cladosporium herbarum 63</i>	510
<i>Epicoccum nigrum</i>	93
<i>Mucor amphibiorum*</i>	1
<i>Penicillium chrysogenum</i>	26
<i>Rhizopus stolonifer</i>	<1
<b>Sum of the Logs (Group II):</b>	<b>10.26</b>
<b>ERMI (Group I - Group II):</b>	<b>2.35</b>

## MULTIPLE ANTIBIOTIC RESISTANCE COAGULASE-NEGATIVE STAPH (MARCoNS)

### Lab Test: API-Staph culture

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Resistance to two or more distinct classes of antibiotics plus the presence of a biofilm.

- MARCoNS plus biofilms is identified by a nasopharyngeal culture. Thrives in deep aerobic spaces of nasal cavity.
- Must use API Staph Isolate to get biofilm forming coagulase negative Staph. This is not a routine nasal culture technique that is only cultured for two days at Quest or LabCorp.
- Biofilms are slimy polysaccharide matrixes that surround the bacteria, acting as a protective barrier protecting bacteria from the immune system.
- Dr Shoemaker observed in 1998 that in MSH deficient patients, over 80 % had MARCoNS in the nasopharynx and in MSH normal patients, less than 1 % were positive for MARCoNS.
- MARCoNS will result in MSH deficiency.
- MARCoNS release endotoxin A and B which cleave MSH, rendering it ineffective and thus leading to immune dysregulation.
- MARCoNS release hemolysins, which disrupt red blood cells and endothelial cell membranes increasing inflammation, coagulation risk, and anti-phospholipid abnormalities.
- Low MSH impairs its ability to coordinate dendritic cell responses within gut and respiratory mucous membrane compartments.<sup>33</sup>
- With low MSH, multiple neuro-immune pathways are impacted leading to dysregulation in ACTH, cortisol, androgens, ADH and osmolality, melatonin (sleep disturbances), endorphins (pain issues.) In addition, cytokines are stimulated.
- MSH acts as a guard immune modulator on the skin and mucous membranes and kills fungi and coagulase negative staphylococci. With normal MSH, MARCoNS will not survive.<sup>34</sup>
- Inadequate treatment of MARCoNS will reduce the efficiency of CSM therapy possibly because of MARCoNS continued effect on MSH.
- Low MSH patients rarely get better until MARCoNS is treated. Hard to raise MSH with MARCoNS present.
- With MARCoNS, thick biofilms are made which prevent antibiotics and natural immune function from dealing with the offending organisms.
- MARCoNS colonization produces no symptoms but dysregulates MSH.
- MARCoNS can also be isolated from dental cavitations.
- MARCoNS with low MSH patients have a differential genomic profile than negative MARCoNS patients and low MSH.<sup>35</sup>
- MARCoNS not to be confused with other coagulase -negative staphylococci that are not antibiotic resistant.

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<sup>33</sup> Catania A, Caterina L, Sordi A, et al., The melanocortin system in control of inflammation. The Scientific World Journal 2010; 10:1840-1853.

<sup>34</sup> Shoemaker R. Katz BEG DVD 2013

<sup>35</sup> Shoemaker R. Katz 2013 BEG DVD

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Tel: (781)276-4956 \* Fax: (781)275-6236Dr. J.D. MUSTO, DABB  
PRESIDENT & LAB DIRECTOR  
CLIA ID# 22D2089996

PATIENT:

CLIENT:

THE HOFFMAN CENTRE FOR INT MED  
1133 17TH AVE NW  
CALGARY, AB, CANADA T2M 0P7  
600010D.O.B. /SEX:  
DATE COLLECTED:  
TIME COLLECTED:  
DATE RECEIVED:  
LAB NUMBER:DOCTOR: B HOFFMAN  
DATE REPORTED: 02/20/2017  
DATE PRINTED: 02/28/2017  
PATIENT ID:

PAGE: 1

\*\* FINAL REPORT \*\*

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**RESULTS****NARES CULTURE**

SOURCE NARES

ORGANISM #1 STAPH COAG NEGATIVE-SMALL AMOUNT

**MARCoNS POSITIVE**

MARCoNS is a multiple antibiotic resistant coag neg staph that reside in the deep nasal passages, is common in biotoxin illness, is a marker of low MSH and produce biofilms which form a barrier to immune defenses and anti-infection therapy. Biofilm production in bacteria, mold or yeast may account for some cases of chronic nasal and sinus congestion and inflammation. MARCoNS releases exotoxins which lead to increased inflammation (decreased MSH) and hemolysins which disrupt RBCs and endothelial cells. It may be colonized or cause infection. If test results indicate coag neg staph is present with two or more antibiotics showing Resistant or Intermediate, these results are classified as MARCoNS whether Methicillin is resistant or not and whether there is a large amount or small amount. (Ref: Dr. Ritchie Shoemaker, 05/09/14)

SUSCEPTIBILITY #1	ANTIBIOTIC NAME	INTERPRETATION
=====	=====	=====
	CIPROFLOXACIN	S
	CLINDAMYCIN	R
	ERYTHROMYCIN	R
	GENTAMICIN	I
	LEVOFLOXACIN	I
	LINEZOLID(ZYVOX)	S
	MOXIFLOXACIN	S
	OXACILLIN(METHICILLIN)	R
	PENICILLIN G	R
	QUINUP/DALFO(SYNERCID)	S
	RIFAMPICIN	S
	TETRACYCLINE(DOXYCYCLINE)	R
	TIGECYCLINE	S
	TRIMETH/SULFA(BACTRIM)	S
	VANCOMYCIN	S

S=Sensitive I=Intermediate R=Resistant

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#### RESULTS

##### MISCELLANEOUS CULTURE-MARCONS

SOURCE DENTAL CAVITATION #18

ORGANISM #1 NO STAPH COAG NEGATIVE ISOLATED

NON-MARCONS

ORGANISM #2 ALPHA STREP-LARGE AMOUNT

ANTIBIOTICS SENSITIVITY NOT PERFORMED:  
ORGANISMS TYPICALLY SENSITIVE TO PENICILLIN, AMPICILLIN,  
AMOXICILLIN, AUGMENTIN, CEPHALOSPORINS AND RELATED DRUGS.

##### BIOFILM ANALYSIS

ORGANISM-MARCONS

NON-MARCONS

THEREFORE BIOFILM TEST WAS NOT PERFORMED AND NOT  
CHARGED.

STRONG, MODERATE, OR WEAK IS THE LEVEL OF BIOFILM  
PRODUCTION BY THE ORGANISM.

A bacterial biofilm is defined as a structural community  
of bacterial cells enclosed in a self-produced polymeric  
matrix adherent to an inert or living surface. Biofilm  
producing organisms are far more resistant to antimicrobial  
agents than organisms which do not produce biofilm.  
(Indian J. Crit. Care Med. 2013 Jul-Aug;17(4): (214-218)  
MARCoNS biofilm testing is a continuation of work started  
by Dr. R. Shoemaker in 2011.

\*\* FINAL REPORT \*\*

## ANTIGLIADIN- ANTIBODIES (AGA)

### Lab results

---

AGA normal range: 0-19 U

- Low MSH results in T reg dysregulation, leading to inflammation and possibly autoimmunity
- Serum IgA and IgG antigliadin antibodies (AGA) are antibodies against gliadin, the protein found in wheat, barley and rye. Some oats is cross-contaminated with gliadin but does not, in and of itself, contain gliadin.
- AGA is not specific for celiac disease, but it does indicate an inflammatory response to gluten
- I tend to do the HLA DQ2/DQ8 genes and serum tissue transglutaminase (TTG-IGA) levels to exclude celiac disease.
- Over 58 % of children with CIRS have elevated AGA levels according to Dr. Shoemaker.

## ANDROGEN DEFICIENCY

### Lab Results

---

Normal Range: DHEA and testosterone: Various ranges for age and gender

- Abnormal androgens are due to an upregulated aromatase enzyme.
- Testosterone is often dysregulated and DHEA may be low.
- Using testosterone is contraindicated in these patients.
- Due to low VIP and inflammation, testosterone is more rapidly converted into estrogen resulting in high estrogen and low testosterone.
- One may use DHEA.
- VIP nasal spray corrects aromatase activity.

## LEPTIN

### Lab results: LabCorp

---

Normal ranges: 0.5-13.8 ng/ml; in men  
1.1-27.7 ng/ml; in women

- Leptin is a hormone that controls how fat stores fatty acids. If the leptin receptors are disrupted, high levels of leptin will be seen.
- Leptin regulates the pro-opiomelanocortin (POMC) pathway, thus MSH pathways that also control ADH.
- Low leptin levels contribute to low MSH, ADH, VIP and ACTH.
- Leptin outside the brain binds to immune cells and increases inflammatory cytokines.<sup>36</sup>
- If leptin is high, fatty acids are stored in fat, resulting in weight gain.
- Leptin is not considered a major marker in the CIRS workup.

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<sup>36</sup> Bjorbaek C, Kahn BB. Leptin signaling in the central nervous system and periphery. Recent Progress in Hormone Research. 2004; 59: 305-31. PMID: 14749508

- Markers of hypothalamic illness include high leptin and osmolality, low MSH, low ADH, ACTH and/or VIP.

## C3a

### Lab results: Quest

---

Normal ranges: 55-486 ng/ml;

- C3a generated when C4a and C2a are made by activating MASP-2; splitting C4 and C2 creates C4b and C2a thereby activating C3
- C3a is only activated when the innate immune system is presented with a bacterial cell membrane.
- If elevated, tick -borne illness must be excluded or diagnosed.
- Increased C3a can cause anaphylaxis through an upregulated immune response resulting in vasoconstriction, capillary hypoperfusion, increased vascular permeability and WBC release of oxidants, leukotrienes and enzymes.<sup>37</sup>
- C3a will usually be low unless there is Lyme- usually more acute in nature.
- C3a elevates within 12 hours of a tick-bite
- If HLA is Lyme susceptible pattern – 15-6-51; 16-5-51, most likely will need longer than 3 weeks of antibiotics and CIRS can be a distinct possibility.
- Will need Cholestyramine to remove the biotoxins if inflammatory CIRS markers and positive VCS present.
- May need statin therapy if C3a persists after antibiotic therapy.

## C4a

### Lab Results: Quest

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Normal Range: 0-2830 ng/ml;

- If levels are very high, this could be due to delays in shipping, sample not frozen quickly enough or the specimen thawed in transit.
- C4a is an innate immune system biomarker. If high, it usually means that the innate immune system is in overdrive to PAMPS (pathogen -associated molecular patterns) and that a biotoxin burden is present.
- Usually results in capillary hypoperfusion of the CNS.
- C4a is a split product of the mannose binding lectin pathways of the complement system of the innate immune system and predicts the severity of CIRS.
- C4a has been associated with elevated levels of mannan-binding lectin serine protease 2 (MASP2) in patients with chronic fatigue syndrome.<sup>38</sup>
- C4a helps the antibodies and phagocytic cells remove infections and toxins from the body.

<sup>37</sup> Shoemaker R Biotoxin Illness Treatment Protocol pg. 8

<sup>38</sup> Sorensen B, Jones JF, Vernon SD, Rajeevan MS. Transcriptional control of complement activation in an exercise model of chronic fatigue syndrome. *Molecular Medicine* 2009 Jan-Feb; 15 (1-2): 34-42

- Complement proteins circulate as inactive precursors but when split into active components they amplify the immune response of the membrane attack complex (MAC).<sup>39</sup> MAC kills the outer layer of cells causing cell death.
- Both C3a and C4a are anaphylatoxins which cause smooth muscle release, can activate mast cells, increase histamine, increase basophils, increase vascular permeability, cause capillary hypoperfusion with resultant cellular hypoxia resulting in reduced mitochondrial function, increase lactate production from glycolysis, and can increase cognitive dysfunction (memory loss, concentration, word finding difficulties, disorientation, confusion, difficulty integrating new information.) as well as fatigue.<sup>40</sup>
- Brain fog caused by increased lactate and suppression of the glutamate/glutamine ratio. - increased inhibition versus excitation.
- When C4a with anaphylatoxin activity stimulates the degranulation of mast cells, vascular permeability ensues, dermatographia can exist on the skin and smooth muscle contractions occur.
- C4a can cause high lactate levels >1.29 and low glutamate/glutamine ratio <2.19 on MR spectroscopy.
- If C4a levels are above 20,000 with low MSH levels the individual cannot be in a home with an ERMI above -1.
- Cognitive functions improve when C4a drops.
- C4a can be elevated in Lyme disease and SLE.

## VEGF

### Lab results: LabCorp and Quest

Normal Ranges: 31-86 pg./ml

- VEGF is a marker of capillary hypoperfusion. A low level of skeletal muscle VEGF is associated with decreased muscle endurance.<sup>41</sup>
- Treat VEGF if less than 31. If high, say 105, it means the innate immune is activated, but does not give the cause.
- VEGF is high in renal failure and Bartonella infections.<sup>42</sup>
- Inflammatory cytokines bind to endothelial receptors, which release “glues”- adhesion and integrins. These hold the white cells together and narrow the capillaries creating hypoxia. This is sensed by regulatory cells which produce a gene controller hypoxia inducible factor (HIF), which produces VEGF.
- VEGF is a growth factor which stimulates blood vessel growth in response to HIF and dilates blood vessels in healthy people.

<sup>39</sup> Rapaport S. Evaluation and Treatment of CIRS pg. 7

<sup>40</sup> Ogata RT, Rosa PA, Zepf NE. Sequence of the gene for murine complement component C4a. The Journal of Biological Chemistry, 1989; 264(28): 16565-72.

<sup>41</sup> Olfert IM, Howlett RA, Tang K, Dalton ND et al. Muscle specific VEGF deficiency greatly reduces exercise endurance in mice. Journal of Physiology 2009 Apr 15; 587:1755-1767

<sup>42</sup> Kempf VA, Volkman 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 Microbiol. 2001 Sep;3(9):623-32.

- In biotoxin patients, inflammation and cytokines suppress VEGF, creating persistent capillary hypoperfusion.
- This results in fatigue, cognitive fallout, muscle aching, and poor recovery from exercise due to anaerobic mitochondrial metabolism.
- Usually glycolysis and protein are used for energy, taking several days to replenish glycogen.
- In lactic acid metabolism, due to low VEGF, one obtains only 2 ATP for every glucose molecule, instead of 36 ATP as is normally the case.
- Early in CIRS, VEGF can be increased, signifying that the body is trying to compensate for low oxygen delivery to tissues.

## TRANSFORMING GROWTH FACTOR BETA-1 (TGF beta-1)

### Lab results: LabCorp and Quest

Must be double spun plasma with Cambridge to make sure all plasma platelet contamination is gone. Not serum. If result is greater than 40,000, the specimen is likely mishandled.

Normal range: < 2380 pg/ml; =normal  
 > 5000 = symptoms appear  
 > 10,000 = restrictive lung disease, tremor, cognitive issues, joint problems may occur

- TGF beta-1 is a protein that causes cells to change and usually results in innate-adaptive immune system dysregulation. It can either produce or suppress inflammation.
- It must be addressed vigorously as it represents widespread tissue involvement, most common in people with highly susceptible 11-3-52B and 4-3-53 HLA haplotypes. Limiting mold exposure is crucial to down regulate this biomarker.
- Elevated levels usually indicate that the body is trying hard to down regulate an overactive T cell adaptive immune system as in allergy (asthma) and autoimmunity (multiple sclerosis) as well as an overactive innate system (CIRS)- both caused by biotoxins in the HLA susceptible host.
- TGF-beta-1 has a dual function in the innate immune system. If elevated it indicates an overactive immune system and it is a key marker of the CIRS severity.
- If stays high, it can indicate the person is having a difficult time recovering.
- It helps control the growth and differentiation of cells, cell motility and cell death. In utero, it helps form new blood vessels, regulates muscle and body fat development and wound healing.
- It is an inflammatory regulatory cytokine which affects autoimmunity through differential gene activation. It can damage T reg cells CD4+CD25+, which regulate TH1 (autoimmunity), TH2 (allergy), TH17 cells. It converts CD4+CD25+ T reg cells into pathologic T cells, thus activating TH17 (autoimmune system) driven inflammation. Together, TH-17 and T-regulatory cells are responsible for preventing autoimmunity. TGF beta-1 can thus activate or reduce autoimmunity.
- In the treatment, one must increase the low T reg cells (cellular immunity) and lower TGFB, thus improving humoral immunity.
- If T reg cells are low <4.66 %, TGF beta will be high > 2,380.
- VIP will raise T Reg cells (CD4, CD25).
- TGF beta-1 can cause tissue remodeling in the liver, heart, central nervous system and the kidney.
- If TGF beta-1 levels are >10,000, this may result in pulmonary remodeling and interstitial, restrictive lung disease (shortness of breath and asthma like symptoms), pulmonary

hypertension (where endothelial cells become thick fibroblasts and result in acquired pulmonary hypertension). Pulmonary stress testing can determine VO<sub>2</sub> max and pulmonary function testing can look for signs of restrictive lung disease. Stress echocardiogram to estimate pulmonary arterial pressure (the measurement of the tricuspid jet and right atrial pressure) can also be done and which will measure further pulmonary cell transformation

- High TGF beta-1 associated with joint inflammation
- High TGF-B-1 may result in neurological diseases (MS), seizures, tremor, Parkinson's, Autoimmune diseases (lupus, RA, dermatomyositis, ulcerative colitis, positive ANCA, ACLA, scleroderma), learning disabilities, vocal polyps and nasal polyps and cognitive symptoms.
- High TGF beta-1 can be seen in HIV, cancer and connective tissue disorders
- High TGF beta-1, along with low MSH can contribute to GI dysfunction which improves when immune markers are normalized.
- CD4+CD25++ blood levels = T reg cells. If low, the TGFbeta-1 would expect to be high.
- VIP will cause T reg cells to increase, but re-exposure to biotoxins will cause them to drop.
- TGF beta-2 will cause hair loss with increased catagen hair. Growing hair follicles are anagen, rest-phase hair is telogen but dying hair follicles are catagen due to TGF β-1.<sup>43</sup>

## VASOACTIVE INTESTINAL POLYPEPTIDE (VIP)

### Lab Results: Quest

---

Normal range: 23-63 pg/ml

- No accurate test for VIP at the moment.
- VIP is a 28-amino acid regulatory neuropeptide, neuro-immune modulator which downregulates cytokine levels with interactions with other peptides: MSH and Vasopressin.
- It has hypothalamic receptors; it regulates blood flow and distribution.
- Low levels are associated with capillary hypoperfusion and abnormal pulmonary artery pressure at rest or in response to exercise.<sup>44</sup>
- It is also made in the nerve endings, gut and pancreas.
- It can have a positive effect on the entire Biotoxin Pathway.
- Like MSH, it regulates peripheral cytokine responses and inflammation throughout the body.
- Low levels found in 98 % of CIRS patients and in less than 10 % of controls.
- VIP helps reduce pulmonary artery hypertension. If pulmonary artery pressure raised with tricuspid valve regurgitation, one can have shortness of breath, especially with exercise. VIP will help reduce post exertional fatigue and shortness of breath
- Helps with MCS, releases endorphins, reduces sicker-quicker phenomenon, downregulates MASP2- the enzyme that stimulates cleavage of C4-C4a; the key to reducing "quicker/sicker" phenomenon.
- VIP induces smooth muscle relaxation in the intestinal tract stimulating water secretion into bile and pancreatic fluid; it can reduce stomach acid and absorption of nutrients from the GI tract. Diarrhea can result.

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<sup>43</sup>Hibino T<sup>1</sup>, Nishiyama T. Role of TGF-beta2 in the human hair cycle J Dermatol Sci. 2004 Jun;35(1):9-18.

<sup>44</sup>Berndtson K. Chronic Inflammatory Response Syndrome. Overview, Diagnosis, and Treatment. Pg.7

- Restores hormone levels, Vit D 3 levels, decreases aromatase upregulation caused by cytokines thereby restoring estrogen and testosterone levels, corrects ADH/osmolality.
- Helps restore energy in chronically fatigued patients.
- Enhances IL-10 production
- Increases CD4+/CD25+ T reg cells, restoring their numbers and thereby regulated TH 17 autoimmune response. If used appropriately, it will suppress overly active inflammation and will regulate dendritic cells, the cells that mediate between the innate and adaptive immune systems. Inhibits TGF beta-1. Down regulates cytokines and thus is a down-regulator of inflammation
- Restores circadian rhythm.
- It helps treat genomic dysregulation caused by CIRS.
- VIP assists in treating the brain abnormalities found in NeuroQuant esp. caudate nuclei atrophy.
- Upregulates VEGF esp. if not responded to Actos or Fish oil 1 spray – alternating nostrils 4 times per day.
- Dr. Shoemaker published a study in 2013 on VIP used on CIRS-WDB patients which demonstrated the following:<sup>45</sup>
  - 1) refractory symptoms reduced to control levels
  - 2) corrected inflammatory biomarkers -C4a, TGF beta-1, VEGF and MMP 9 and reduced levels to controls
  - 3) raised VIP and MSH, corrected estradiol, testosterone and Vit D levels,
  - 4) corrected T-reg levels,
  - 5) retuned PASP during exercise to normal
  - 6) enhanced quality of life in 100% of patients in the study
- Dr. Shoemaker found that 100 % of over 500 patients with multiple chemical sensitivities were found to have low VIP.
- In order to use VIP, need to be out of a moldy building (ERMI less than 2), have a normal VCS and be MARCoNS free.

## CD4+ CD25+

- No commercial test is currently available although select centres may do the test under special circumstances.

## VON WILLEBRANDS PROFILE

### Lab results: Quest

- Factor VIII activity, von Willebrand Factor antigen, Ristocetin Cofactor, von Willebrand Factor Collagen Binding Assay, von Willebrand Antigen) –as well as coagulase study- PT, PTT, PT/INR - esp. if history of bleeding with exposure to WDB.
- Patients with levels of Factor VIII, von Willebrand' s antigen or Ristocetin associated cofactor either <50 or >150 IU are classified as abnormal for von Willebrand' s antigen.
- Blood will be thinner and bleeding will result.

<sup>45</sup> Shoemaker RC, House D, Ryan J. Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. Health, 2013; 5 (3) 396-401

- Acquired von Willebrand syndrome can be the result of increased C4a resulting in increased bleeding tendencies. Water damaged building avoidance is the first step in treatment as well as using DDAVP.

## ANTI-CARDIOLIPIN ANTIBODIES

- Marker of autoimmunity.

## PAI-1

- A marker of increased blood coagulation.

## PULMONARY FUNCTION TESTS

Unusual shortness of breath with post exertional fatigue warrants a workup for pulmonary function and possibly acquired pulmonary hypertension.

- In CIRS, pulmonary function tests may show a restrictive pattern rather than an obstructive pattern of respiratory difficulties. If restrictive test is shown, proceed to VO2 max.

## VO2 MAX

- VO2 max testing done on a treadmill may show abnormally low VO2 max, often lower than 20. This reflects capillary hypoperfusion and post exertional fatigue and malaise. High cytokine levels can first raise and then lower VEGF leading to chronic tissue hypoxia. CIRS patients have a lower threshold for hypoxia as a result.
- Exercise is very helpful for these patients but they must stay below their anaerobic threshold. If they stay below their anaerobic threshold, glycogen store depletion is prevented. This is determined by performing a cardiopulmonary stress treadmill test.
- VO2 max > 35 = normal
- VO2 max < 20 = CIRS patients
- VO2 max 12-15 = Stage IV Cardiac failure

## STRESS ECHOCARDIOGRAM

This is to be pursued in the patient with unusual shortness of breath, asthma like symptoms and excessive post-exertional fatigue/poor exercise tolerance.

- A stress echocardiogram will non-invasively measure the tricuspid jet and the right atrial pressure, thus estimating pulmonary arterial pressure (PA) response to exercise.
- Normally the pulmonary pressure drops with exercise, allowing for increased oxygenation.
- In CIRS patients, the PA pressure may increase, resulting in reduced oxygen absorbed into blood during exercise and thus poor exercise tolerance
- A high pressure at rest may be seen, esp. if TGF beta-1 is high and T-reg cells are low. Th-17, induced by high TGF beta-1 will convert T reg cells to pathogenic T cells.

- Avoid mold, use losartan and use VIP to correct this abnormality.

## NEUROQUANT

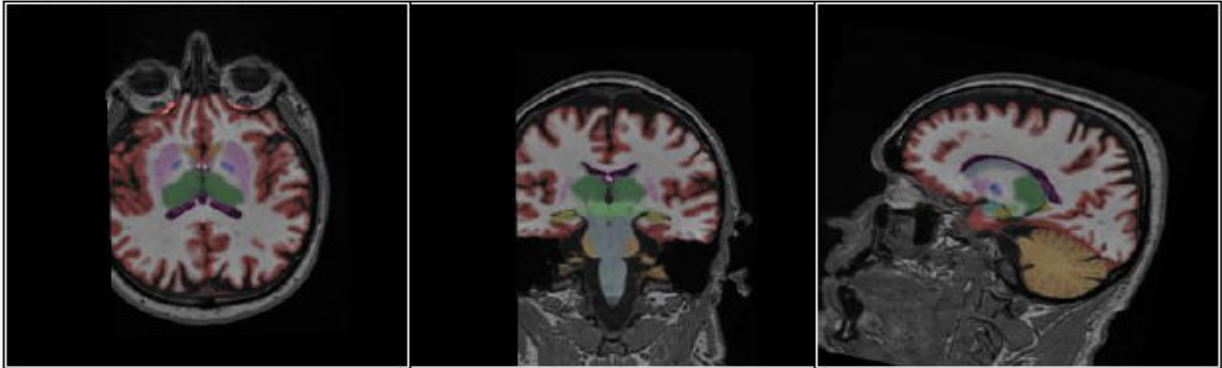
### NeuroQuant® General Morphometry Report

The Hoffman Centre for Integrative Medicine  
1133 - 17th Avenue NE  
Calgary, Alberta T2M0P7

#### PATIENT INFORMATION

<b>Patient ID:</b>	<b>Patient Name:</b>	<b>Sex:</b>	<b>Age:</b>
<b>Accession Number:</b>	<b>Referring Physician:</b> HOFFMAN, BRUCE	<b>Exam Date:</b>	

#### MORPHOMETRY RESULTS



<b>Intracranial Volume (ICV) (cm<sup>3</sup>)</b>	<b>1608.39</b>				
<b>Brain Structure</b>	<b>LH Volume (cm<sup>3</sup>)</b>	<b>LH Volume (% of ICV)</b>	<b>RH Volume (cm<sup>3</sup>)</b>	<b>RH Volume (% of ICV)</b>	<b>Asymmetry Index (%)<sup>‡</sup></b>
Forebrain Parenchyma	543.98	33.82	528.53	32.86	2.88
Cortical Gray Matter	214.91	13.36	207.52	12.90	3.50
Lateral Ventricle	9.16	0.57	9.19	0.57	-0.27
Inferior Lateral Ventricle	0.72	0.04	0.91	0.06	-23.78
Hippocampus	3.77	0.23	4.24	0.26	-11.59
Amygdala	1.61	0.10	1.38	0.09	15.20
Caudate	2.31	0.14	2.11	0.13	8.87
Putamen	6.38	0.40	6.05	0.38	5.42
Pallidum	0.65	0.04	0.43	0.03	39.93
Thalamus	8.29	0.52	7.97	0.50	3.84
Cerebellum	69.45	4.32	67.89	4.22	2.26

<sup>‡</sup>The Asymmetry Index is defined as the percentage difference between left and right volumes divided by their mean.

A Neuroquant MRI is a software addition to an MRI and assists in determining if there are any changes in brain volume and structure according to specific quantifiable determinants in 11 different brain regions.

Patients with CIRS due to mold exposure have a specific pattern of abnormalities as compared to controls:<sup>46</sup>

- Forebrain parenchyma increased
- Cortical gray increased

<sup>46</sup> Shoemaker R, D House R, Ryan J, Structural brain abnormalities in patients with inflammatory illness acquired following exposure to water-damaged buildings," Center for Research on Biotxin Associated Illness, Pocomoke

- Hippocampus increased – although not included in the criteria
- Caudate decreased – reversible through use of VIP according to Dr. Shoemaker’s clinical experience
- **Pallidum increased**

Patients with CIRS due to Lyme neuroborreliosis have the following pattern:<sup>47</sup>

- Small forebrain parenchyma
- **Small putamen**
- **Large thalamus** – (isolated post gray matter change)
- Large cerebellum

Neuroquant also assists in the detection of other nuclei that can be atrophied and is helpful when looking at brain atrophy in dementia Alzheimer’s disease.

In Dr. Shoemaker’s research, no confirmed case of CIRS had less than 5 points and no controls had 3 or more points. One needs to take the average of the two sides to determine the points awarded.

<b>Black = Mold Red = Lyme</b>	1 point	2 points
<b>Forebrain</b>	$\geq 31.9$	$\geq 32.5$
<b>Cortical Gray</b>	$\geq 16.3$	$\geq 17.0$
<b>Caudate</b>	$\leq 0.255$	$\leq 0.235$
<b>Pallidum</b>	$\geq 0.07$	$\geq 0.08$
<b>Putamen</b>	$\leq 0.345$	$\leq 0.335$
<b>Right thalamus</b>	$\geq 0.58$	$\geq 0.60$
	Atrophy	Hypertrophy
Forebrain	$\leq 29.00$	$\geq 31.9$
Cortical Gray	$\leq 13.50$	$\geq 16.3$
Hippocampus	$\leq 0.255$	$\geq 0.31$
Amygdala	$\leq 0.10$	$\geq 0.14$
Caudate	$\leq 0.255$	$\geq 0.30$
Putamen	$\leq 0.345$	$\geq 0.375$
Pallidum	$\leq 0.055$	$\geq 0.07$
Thalamus	$\leq 0.495$	$\geq 0.58$
Cerebellum	$\leq 3.50$	$\geq 4.55$

## GENOMICS

[www.survivingmold.com/store1/progene-dx](http://www.survivingmold.com/store1/progene-dx)

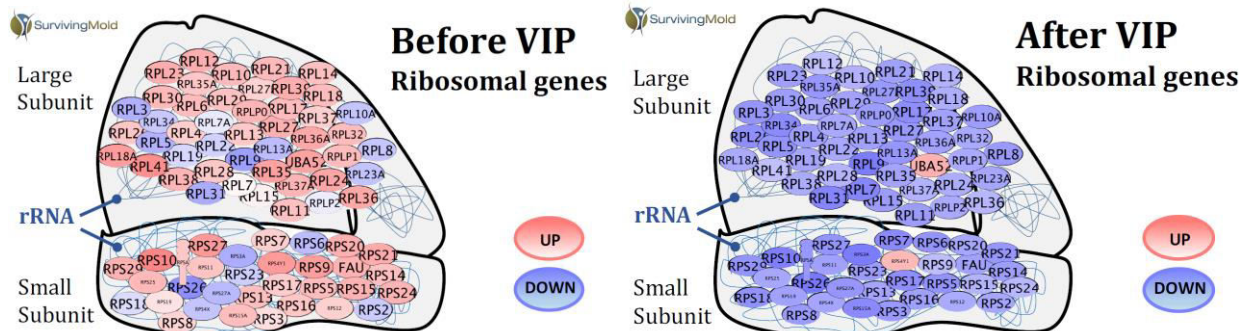
- PAX genomics allows for measurement of mRNA and miRNA in serum samples so as to assess metabolic patterns of cellular function based on RNA transcription patterns.<sup>48</sup>
- A 2016 paper by Dr Shoemaker and James Ryan set out the underlying genomic abnormalities found in white blood cells that can result in someone suffering from a CIRS diagnosis leading to

<sup>47</sup> Ibid

<sup>48</sup> Berndston K.

chronic inflammation.<sup>49</sup> 14 patients who had failed the normal CIRS protocol were investigated genomically while using VIP.

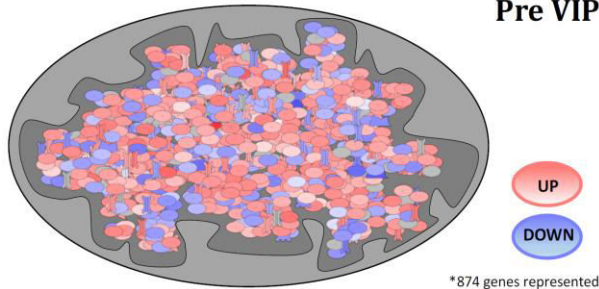
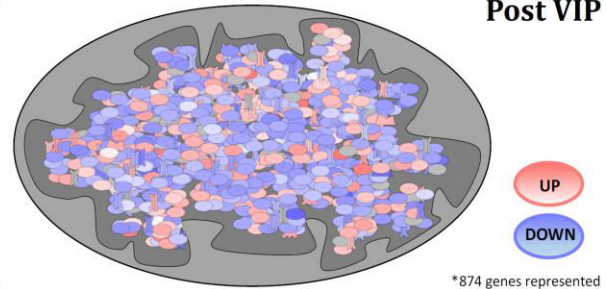
- This new RNA sequencing focuses on the abnormal gene expression found in the white blood cells of CIRS patients. Several key immune regulators were found to be differentially expressed over the course of the investigation including CD244, CD3D, CD48, CD 52, granzymes, defensins, and the Ikaros family of lymphoid transcription factors.
- Two families of genes upregulated in CIRS are alpha defensins (these are antimicrobial peptides which keep bacteria in bodies from spreading by using mucosal layer coating inside the gut, airways or nasal passages) and granzymes (these are cytotoxic proteases found elevated in patients with autoimmune disease and infections).<sup>50</sup> These were downregulated with VIP.
- The Ikaros family of five different zinc finger transcription factors may indicate a decline in lymphocyte proliferation after treatment with VIP.
- In addition to these down regulated innate immune functions, there was a significant metabolic shift with a downregulation of ribosomal and mitochondrial gene expression possibly indicating a quietening of the overall upregulated immune response.<sup>51</sup>
- Patient reporting of CIRS symptoms decreased from a mean of 12.9 to a 3.3 over the duration of the therapy. TGF beta-1 and C4a were significantly lower after VIP therapy. MMP9 was lower post VIP but not significantly and VEGF was unchanged.
- In addition, ribosomal genes as well as nuclear encoded mitochondria genes were shown to be down regulated after treatment with VIP and this coincided with the abatement of symptoms. This argues the return to normal function of ribosomal and mitochondrial gene expression.
- It is a great advance in the treatment of CIRS that both pre- and post-genomic expression patterns can be measured. Added to the measurement of proteomic expression and Neuroquant evaluation pre- and post treatment, the genomic insights add much additional value to quantifying the patients return to normal functioning.
- Diagrams per Jimmy Ryan presentation at 2016 Surviving Mold conference Irvine, California.



<sup>49</sup> Ryan J, Shoemaker RC, 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 fluctuations that coincide with healing. Medical Research Archives Vol 4 Issue 7 2016.

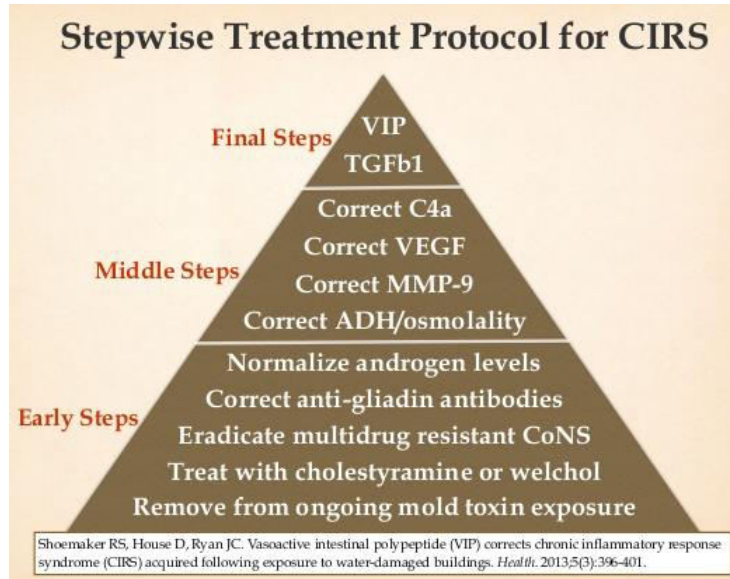
<sup>50</sup> [www.survivingmold.com](http://www.survivingmold.com)

<sup>51</sup> Ibid.

**Mitochondrial proteins****Pre VIP****Mitochondrial proteins****Post VIP****OTHER LAB TESTS DONE IN CIRS**

- These lab tests are done to rule out other possible illnesses.
- CBC, Metabolic panel, Lipid panel, C-reactive protein, ESR, ANA, ENA, Thyroid studies with thyroid antibodies, sex hormones (estradiol, progesterone), pregnenolone, cardiolipin antibodies, PTT, Prothrombin time, Thrombin time, d-Dimer, IgE, Immunoglobulin panel, protein electrophoresis.
- If autoimmunity is suspected, check anti-gliadin antibodies, (due to low MSH and dysregulation of T reg cells) anticardiolipin antibodies, lupus anticoagulant, phospholipid.
- If mast cell activation syndrome is suspected, consider doing serum histamine, serum tryptase, urinary prostaglandin D2, enolase.

**Treatment Steps**



### Dr. Shoemaker's Surviving Mold Protocol involves a number of specific steps:

It must be kept in mind that CIRS is an inflammatory upregulation of the innate immune system and is thus an immune disorder occurring in genetically susceptible individuals. It will not therefore just respond to removal of the initial triggers. The particular triggers do need to be taken into account, but so does the immune dysregulation, the inflammatory markers, the neurohormonal abnormalities, potential autoimmune dysregulation as well as possible coagulation disorders.

- 1) Removal from exposure – monitor home or WDB with ERMI or HERTS-MI-2 testing
- 2) Removal of biotoxins with either cholestyramine or Welchol – monitor with VCS
- 3) Treat MARCoNS with BEG spray or EDTA- Check API-Staph nasal culture
- 4) Begin a gluten free diet if anti-gliadin antibodies present
- 5) Correct abnormal androgens – use DHEA-S if indicated
- 6) Correction of elevated MMP-9
- 7) Correction of low VEGF
- 8) Correction of elevated C3a
- 9) Correction of elevated C4a
- 10) Reduce elevated TGF-beta-1
- 11) Treat low VIP
- 12) Recheck labs and VCS

### STEP 1: REMOVAL FROM EXPOSURE

- This is the most important step in the treatment process if a diagnosis of CIRS has been established. Attempt to determine the source of the biotoxin exposure; was it from *Borrelia* spirochete, dinoflagellate food poisoning or ciguatera. A person may be exposed to one or more of these toxins. If the source is identified, every effort must be made to remove the individual from the source of exposure.

- If water damaged building is the issue and as up to 50 % of all USA homes have some form of water damage, mold exposure and all the corresponding inflammagens are the most frequent source of biotoxin illness. An ERMI test must be done and a visual inspection must be undertaken by a qualified mold/indoor air specialist. The article *Inside Indoor Air Quality* by Dr. Ritchie Shoemaker and Dr. King-Teh Lin is a helpful resource.
- If an ERMI test is positive with a reading >2, the building or home is considered unsafe for occupation with the CIRS diagnosis.
- Once a building has been declared unfit for occupation due to the visual inspection and the patient fulfilling the CIRS diagnosis, a sick patient should most often have to be removed from the building and a mold remediation team is called in.
- One of the challenges for CIRS patients is what to do with belongings as they often have to be removed (clothing, furniture that cannot be adequately wiped down, contents esp. paper and cloth products and personal effects). All porous material should be removed and taken out of the house and discarded. Non-porous items need to be thoroughly and professionally cleaned.

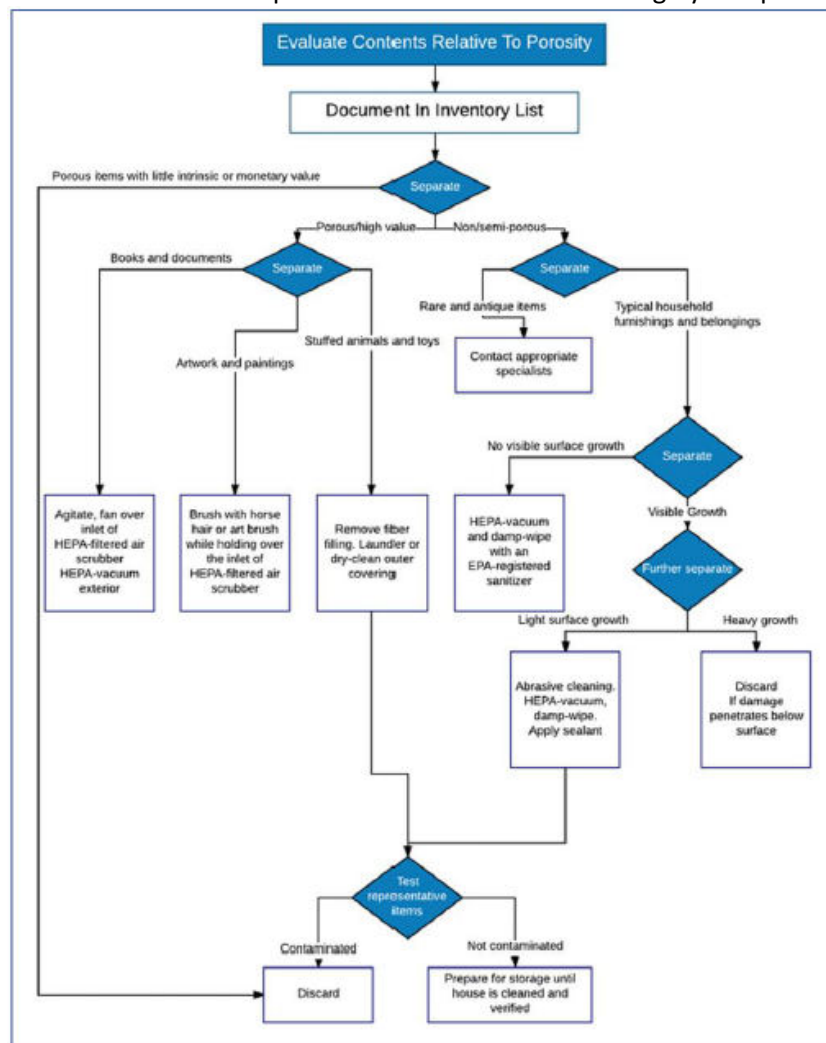


Diagram: Written permission granted by Dr Lynese Lawson

- Finding someone who can adequately undertake the remediation is often a major problem. An organized approach to the problem is vital but often is not able to be initiated due to the cognitive difficulties many people face with the CIRS diagnosis.

- Small brief exposures must be avoided due to “sicker, quicker” phenomenon.
- Patients that I see are given a list of companies that can assist them in their assessment and remediation process. HEPA filters (IQ air and Blue Sense Air filters) are used which can remove particles smaller than 0.3 microns in size. Air purifiers such as the Air Oasis are also used.
- It is important that remediation efforts are continued until ERMI levels are down to safe levels - ERMI less than 2 or = 2 in patients with MSH <35; ERMI to < or = to – 1 if MSH <35 and C4a >20,000 with HERTSMI-2 < 11.
- Post remediation testing should occur 3-5 weeks after remediation. One can place black or green garbage bags and collect new dust.

## STEP 2: REMOVE TOXINS AND INFLAMMAGENS

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Biotoxins must be removed from the body, particularly in a patient with the genetic predisposition to biotoxin illness. These patients cannot recognize the biotoxins and need help in doing so.

Cholestyramine (CSM), a bile acid sequestrant, has a quaternary cation structure that binds negatively charged ionophore biotoxins which possess an anion dipole. The biotoxins are excreted in bile and removed from the body while bound to the CSM, through the GI tract. This excretion prevents enterohepatic recirculation of the biotoxins. A handout should be given and consent obtained.

CSM can also bind industrial chemicals

- CSM must be taken on an empty stomach away from meals and medications and/or supplements.
- Many people start with ¼ teaspoon a day. Take ½ hour before meals and 1 hour after meals, drugs or supplements.
- Drink 6 - 8 oz. of water with the dose.
- Juice is often a better mix for this very chalky tasting medication.
- Side effects include heartburn, GERD, belching, bloating, nausea, bad tastes and/or constipation.
- Welchol is a second option, although not as effective. There is said to be a 4:1 differential in terms of efficiency for biotoxin removal. CSM has 4 times as many electrically active sites. However, Welchol may be better tolerated but longer to change lab tests in the right direction.
- These two binding agents are to be taken until the patient either passes the VCS test and/or eradicate MARCoNS.
- Some patients combine the two meds: CSM twice per day – morning and bedtime and Welchol – lunch and dinner. Avoid the CSM with aspartame additives.
- Chemically sensitive patients and patients with GI issues and/or food allergies, do better on Welchol.
- If problems with toxin release or treatment reactions, start with Actos 15-45mg a day, or EPA 2.4 gms DHA 1.8gms for 5 days, then add cholestyramine again.
- If Leptin <7 use omega 3s.
- Watch fat-soluble vitamins A, D, E, K as CSM can bind these.
- Welchol 625- work up to 2 caps three times per day.
- CSM dosing: 4 -9 grams four times a day. Mix with 6 oz. water or juice. 30 mins before food. Followed by 4-6 oz. water.

- Paed. <120 lbs. or less than 18 years old. Use 60 mg/kg/dose TID with 6 oz. water 30 mins before food.
- Use Welchol 625 bid (1 tab) if out and about and exposed to mold.
- If re-exposed- use Welchol or CSM for 3 days.
- Works within a week.
- Treat constipation with magnesium oxide or citrate powders. Can use 70 % sorbitol (Miralax).
- Recheck VCS one month after starting treatment and then with each step.
- When VCS normalized, switch to Welchol 625 mg twice daily if person is out a lot.
- If at home mostly, no meds used.
- If treatment fails, consider continued exposure, non-compliance or MARCoNS not adequately treated.

### STEP 3: ERADICATE MARCoNS

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If positive for MARCoNS on API-Staph culture and if associated with a biofilm, eradication is important. BEG spray:

- Start one month after using CSM
- Comprised of Bactroban, EDTA, and Gentamycin.
- Blow nose first.
- Use for 30 days 2 sprays each nostril 3 times per day in adults, 1 spray alternative nostril in children- seldom need to use
- The patient may feel worse after starting treatment due to “die-off” .
- Use low amylose diet, high dose fish oil and Actos if this occurs.
- Repeat nasal culture to see if eradicated.
- If symptoms worse after starting, it may imply re-exposure; VCS row D and E will fall and MMP9 will go up
- If still positive after treatment, consider pet dog as source of reservoir, re-exposure to mold, or a partner with low MSH and MARCoNS
- Rifampin has been used in the past at 600 mg per day with adults or 10-20 mg/kg/day in children. Start the rifampin the same day as the BEG spray to discourage resistance
- Rifampin is known to induce multiple enzymes responsible for drug metabolism including cytochrome P450 (CYP)1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and some glucuronidation pathways. In addition, it has been reported to induce the activity of several drug transporters, such as the organic anion transporter and P-glycoprotein.<sup>52</sup> Need to quite careful with anticoagulants and pain medications (may reduce their efficiency).
- Recent MARCoNS resistance to multiple antibiotics has emerged due to what Dr Shoemaker believes to be the overuse of -azole antifungals.
- This step is essential if VIP is going to be successful.
- If symptoms worsen after 1 month, check for re-exposure, recheck VCS and MMP9 levels.
- If patient better, stop BEG spray, recheck API- Staph nasal culture and VCS.

### STEP 4: ELIMINATE GLUTEN IN AGA POSITIVE PATIENTS

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<sup>52</sup> <http://www.pharmacytimes.com/publications/issue/2011/april2011/druginteractions-0411>

- If positive for AGA, it is imperative they are completely gluten free for at least 3 months.
- This will reduce GI sources of inflammation
- The no-amylose diet prescribed during CSM treatment is already gluten free, thus no gluten continues for an additional 3 months assuming that the VCS corrected.
- No amylose diet involves eliminating:
  - Grains- wheat, rice, barley, oats, rye – corn appears to be okay as has a natural inhibitor of amylase- no sugar added.
  - Fruits-all fruit allowed except bananas. Can use fresh fruit juice.
  - Vegetables - all okay except root vegetables grown below the ground (potatoes, yams, radishes, carrots, beets). Garlic and onions are okay.
  - Other foods - glucose, dextrose, sucrose, maltodextrin, low-fat corn syrup, cereal, chocolate, fast food, soft drinks, commercial fruit juices. Lactose (milk), artificial sweeteners, spices and condiments, diet soft drinks and caffeine drinks are allowed
  - Many patients will have many other possible food issues including but not limited to IgE allergies, IgG sensitivities, oxalate issues, salicylate issues, FODMAPS issues, SIBO issues, high histamine issues etc. These issues are not part of the Shoemaker protocol but need to be taken into account when addressing and treating chronic GI issues.
- If AGA is negative after 3 months, reintroduce gluten and keep monitoring for GI symptoms.
- If patient feels better off gluten, and/or AGA returns as positive, stay off gluten for life.
- If a patient is known to have celiac disease, it is imperative he follows a strict gluten free diet for life.<sup>53</sup>

## STEP 5: CORRECT ANDROGENS: DHEA/Testosterone/Androgens and Cortisol

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### Treatment:

- DHEA - 25 -75 mg a day- men. 5-25 mg a day -women
- HCG injections 125 250 mg twice weekly. This raises LH. Not part of Shoemaker protocol
- VIP nasal spray 4 times per day for 30 days- can stabilize aromatase and rebalance androgens
- Measure DHEA before treatment and monitor estradiol levels- at least every 3 months
- Resist using testosterone replacement
- Do not use aromatase inhibitors with a low-MSH patient<35, this will cause significant deterioration.

## STEP 6: CORRECT ADH/OSMOLALITY

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### Treatment: Desmopressin Acetate (DDAVP)

- Use DDAVP when osmolality is high>295
- Use 0.2 mg every other night to verify tolerance and absence of side effects especially if weight gain. Initial correction of ADH can lead to edema and rapid weight gain due to fluid retention.
- After 5 doses - check serum osmolality, ADH and electrolytes verifying normal sodium and not too low.
- If symptoms persist, especially on “off days”, use 0.2 mg daily.
- Check electrolytes and osmolality after 10 days.
- Some people (especially those with POTS) may need to be on drug daily for indeterminate basis.

<sup>53</sup> Shoemaker RC. Surviving Mold: Life in the Era of Dangerous Buildings. Otter Bay Books. Baltimore 2010.

- Some may need it twice daily.
- ADH abnormalities usually normalizes over time.
- This treatment may also correct von Willebrand syndrome and help reduce MMP9 (and C4a) levels. Von Willebrands patients need to carry DDAVP to stop nasal hemorrhage.
- One needs to taper DDAVP when endpoint of normal ADH for a given osmolality is reached.
- Children need to use 1-4 sprays based on weight and age.
- If odd symptoms occur while on treatment, stop treatment and check electrolytes and serum osmolality.
- Taurine can cause polyuria and Lithium can cause ADH resistance.
- Symptoms addressed include polyuria, polydipsia, orthostatic hypotension, recurrent headaches and static shocking.

## STEP 7: CORRECT ELEVATED MMP-9

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### Treatment: Actos and/or EPA/DHA Fish oil

- The goal of therapy is to upregulate PPAR-gamma production and reduce MMP-9 expression.
- Lowers TNF, leptin, MMP9, PAI-1, and raises low VEGF.
- If low leptin-less than 7 or less than 18 years, can't use Actos.
- If leptin less than 7, use high dose fish oil: EPA 2.4 mg, DHA 1.8 mg daily.
- If high or normal leptin, use Actos- low carb/amylose, high protein diet.
- Actos 45 mg once daily for 30 days.
- If get swollen and hypoglycemic have to stop.
- Watch kidney function and blood sugar.
- Actos is also implicated in bladder cancer with long term use.
- Takes longer to work but is effective.
- Recheck labs after 30 days.
- High MMP-9 patients may get worse when starting CSM with Herxheimer reactions.
- Herxheimer reaction defined as- symptoms gotten worse, new symptoms arise, reactivation of old symptoms.
- With an increase in MMP-9 there is worsening in row E of the VCS test.
- Trental, progesterone, curcumin, glutamine, glutathione and phosphatidyl choline have been anecdotally shown to lower MMP-9- not part of Shoemaker protocol.

## Step 8: CORRECT VEGF – Correction of Hypoperfusion

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- The previous steps may have improved VEGF.
- If not improved, exercise is added to the protocol to increase low VEGF.
- Graded exercise below anaerobic threshold 7 days per week is recommended.
- Patients are asked to start very slowly but may end up exercising to a maximum of 45 minutes
- Suitable routine eventually may include 15 minutes of cardio, 15 minutes of weights, 15 minutes of abdominal exercises.
- Corrects low VEGF.
- Procrit and VIP can increase VO2 max.

## Step 9: CORRECT ELEVATED C<sub>3a</sub>

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- Statins show reduction in T cell activation, macrophage infiltration and vascular wall infiltration.
- Statins inhibit an enzyme HMG-COA reductase that controls the rate of cholesterol production.
- Must be used with Coenzyme Q10 (CoQ10) - needed by mitochondria to make ATP.
- Coenzyme Q10 levels can be measured in the serum.
- Start Coenzyme Q10 150-300 mg for 10 days.
- Then start statins - Zocor 80 mg day, Pravastatin, Atorvastin, Fluvastin, Rosuvastatin and Lovastatin may all be used.
- Statins metabolized by Cytochrome P450 3A4.
- Drugs that inhibit CYT 3A4= Sporonox, Ketoconazole, Erythromycin, Clarithromycin, HIV protease inhibitors, Nefazodone, gemfibrozil, Biaxin, Ketek and Posaconazole.
- No large quantities of grapefruit juice.
- With Lovastatin, do not exceed 20 mg dose if on danazol, diltiazem or verapamil.
- Monitor liver function, renal function and creatine.
- May increase cognitive symptoms and raise blood sugars.

## Step 10: CORRECT ELEVATED C<sub>4a</sub>

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- Reduce C4a with erythropoietin (Procrit) 8,000 units twice weekly (Mon and Thurs) for 5-8 doses with baby aspirin. 40,000 units per vial.
- Higher doses once per week not effective due to short half-life of 1.5 days.
- Erythropoietin causes tissue remodeling and repair.
- Informed consent must be signed as there is a black box warning.
- Most practitioners now use VIP instead of Procrit.
- Monitor CBC, iron studies, blood pressure, D-dimer.
- Use baby aspirin when using Procrit.
- Check levels of C4a, TGF beta-1, T reg cells and VEGF before each dose to ensure efficiency of treatment.
- Ensure no polycythemia occurs thus increase risk for thrombus formation.
- Keep track of symptoms to see if improvement- breathing easier, increased mental clarity.
- High C4a can cause decreased cognitive function due to hypoperfusion.
- Treating C4a can improve cognitive deficits- memory, concentration, word finding, assimilation of new knowledge, confusion, disorientation.
- Can use VIP 4 sprays a day if cannot use Procrit.
- High C4a can cause hypoperfusion and increased brain swelling as seen on Neuroquant. Will see high lactate (>1.29) in frontal lobes and hippocampus and low glutamate/glutamine ratio (<2.19). These findings result in cognitive dysfunction and brain fog.
- Assess cognitive function: if abnormal, do MRI spectroscopy.
- If MRI abnormal showing low glutamate/glutamine ratio (capillary hypoperfusion) – then use Procrit.<sup>54</sup>
- Recheck MRI spectroscopy after Procrit = normal G:G, normal lactate and improvement in 6 areas of cognitive functions.

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<sup>54</sup> Shoemaker R. Biotoxin Illness Treatment Protocol pg. 10.

## Step 11: REDUCE ELEVATED TGF beta -1

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- Every effort must be made to reduce this biomarker as it represents widespread tissue involvement.<sup>55</sup>
- Losartan can prevent TH17 conversion of T reg cells and thus correct TGF beta-1 levels.
- Losartan/Cozaar 12.5 mg bid, up to 25-50mg a day.
- Child dosage is 0.6-0.7 mg/kg/day bid.
- VIP also lowers TGF-b1.
- Use 4 sprays VIP a day if can't use Cozaar due to low b.p. Patient must meet VIP criteria.
- If CD4+CD25++ T reg cells <4.66% and TGF beta -1 >2,380 and blood pressure normal.
  - Treat with Cozaar 25 mg daily- start with 12.5 mg.
  - Increase to 25 mg bid if necessary.
  - Monitor TGFB monthly and blood pressure daily.
- Transfer Factor may also reduce TGF beta-1. This is not part of the Shoemaker protocol.

## STEP 12: REPLACE LOW VIP

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- If patients have cleared a number of the Dr. Shoemaker biomarkers (see below) but still have signs of capillary hypoperfusion with fatigue, unusual shortness of breath with exertion and post-exertion malaise, a trial of VIP may be the most effective treatment so far in the treatment protocol.
- Neuroquant findings will also determine suitability of use
- Patients must be given a VIP handout before treatment.
- VIP is dispensed in a brown bottle, must be refrigerated in upright position. It can last for 90 days if stored properly.
- If deficient in VIP, the final step can provide significant relief.
- Most people will have at least 75% of their symptoms relieved before starting VIP providing all the preceding steps have been done successfully.
- All prior steps need to be fulfilled prior to use of VIP:
  - MARCoNS must be eradicated
  - VCS must be normal
  - Lipase must be normal
  - No significant exposure can be tolerated- home must have an ERMI of less or equal to 2 or Health Effects Roster Type Species Mycotoxin and Inflammagen test (HERTSMI-2) must be less than or equal to 10
- Once decision made to use VIP the following steps need to be taken:
  - Patients must be in the office
  - Pre -VIP administration labs: VIP, MSH (this may be one of the last hormones to correct and may need VIP), TGF-beta-1, C4A, VEGF, MMP-9, CD4+/CD25++, Vit D-25-OH, estradiol, total testosterone and lipase should also be measured
  - Baseline stress echo to measure tricuspid regurgitation/ pulmonary artery systolic pressure (PASP) - verify it does not rise over 8 mm during exercise.

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<sup>55</sup> Berndston K. pg. 14

- CIRS patients will often have over 8 mm Hg elevation of PASP- this can result in palpitations and dyspnea not responsive to asthma medication.<sup>56</sup>
- After bloods are drawn, test spray one dose 50 mcg in one nostril.
- Patient observed for any symptom improvement.
- Vital signs (b. p. pulse) followed every 5 minutes for 3 separate occasions. Look for rash.
- Watch for improvements in shortness of breath, reduced joint pain and improved cognition.
- Post-VIP 15 minutes, redraw TF beta-1 and C4a levels. If there is a twofold increase, hidden mold may be present.
- Patient leaves office if they tolerate the second dose.
- Dosing thereafter is 1 spray 50 mcg 4 times per day for 30 days.
- Redo stress echo and blood pressure after 30 days. Redo lipase, C4a, TGF beta-1, VCS.
- Dosage can be increased to 8 sprays or reduced to less than 4 sprays per day.
- One needs to watch for pancreatitis and increased lipase levels. Lipase needs to be checked monthly and any signs of abdominal pain need to be noted.
- If lipase rises, VIP needs to be stopped.
- One must check for gallbladder issues if lipase remains elevated.
- If TGF-beta-1 and VCS are stable, lipase is normal and symptoms are improving, VIP can continue for 30 days tapering to twice daily and then discontinued.
- Check at 6 months when off VIP: lipase, VCS and stress echo for any changes to PASP.
- Can use VIP for up to 4 years without adverse effects.
- Patients with MCS and chronic fatigue syndrome may improve over time. CFS patients will have low VIP.
- Can use Cialis 20 mg 3 times per week if VIP low and poor response to exercise.
- VIP will increase CD4 + CD25 + FoxP3 and reduce shortness of breath and cognitive problems.
- However, reduced joint stiffness may be seen in as little as 10 minutes as it causes immediate endorphin release.
- Improved exercise tolerance will occur as well as overall all symptoms will improve.
- Tight clenched hands can open and patients able to take a deeper breath on VIP.
- Immediate pain relief is a huge relief for most patients.
- Cognitive issues respond more slowly.

## Re-exposure Protocol

The phrase used by Dr Shoemaker is that patients previously exposed who are re-exposed will become “sicker-quicker” due to the immediate upregulation of immunological markers.

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<sup>56</sup> Shoemaker R. Biotoxin Illness Treatment Protocol pg. 12.

The following steps to be used if re-exposed:

- 1) Treat with CSM or Welchol immediately. A VCS is an excellent idea to monitor biotoxin exposure. Measure key labs: C4a, leptin, MMP-9, TGF beta-1, VEGF, von Willebrands (if bleeding).
- 2) Patient to move to safe environment immediately the issue is discovered.
- 3) Stay off binders and other meds if patient's labs and VCS stable

## Re-exposure Trial

If it is needed to prove that a certain building is unsafe for occupation, the following protocol can be followed: SEQUENTIAL activation of innate immune elements (SAIIE)

- After CSM use has ended, draw the following labs: C4a, TGF beta-1, MMP9, leptin, VEGF and CD4+CD25+
- Stop all treatment meds- CSM and Welchol.
- Stay away from building for 3 days
- Document symptoms having been away from the building for 3 days. Do VCS and do same labs as above.
- Return to the suspicious building for 8 hours on no meds. Record symptoms and redo above labs
- Return to building for a second 8 hours on the second day. Record symptoms and redraw same labs
- Return for the 3<sup>rd</sup> day, document symptoms and obtain labs.
- Restart medications. Record symptom scores, and VCS. Labs get scored by office.

### VIII Sequential Activation of Innate Immune Elements (SAIIE)<sup>57</sup>

	BASELINE	DAY 1	DAY 2	DAY 3
VCS	-	Decreasing	Decreasing	Decreasing
C4a	-	Increasing	Increasing	Increasing
VEGF	-	Increasing	Decreasing (2 to TGF β-1)	Decreasing
Leptin	-	Stable	Increasing	Increasing
MMP9	-	Stable	Spikes	Increasing
vWF Factor VIII	-	Decreasing	Increasing	Normalizes
vWF Ristocetin	-	Normal	Decreasing	Decreasing/may bleed on day 3
CD4+CD25+	-	Decreasing	Decreasing	Decreasing
Compare to baseline		C4a, VEGF	Leptin, MMP9	MMP9, CD's, VEGF, & symptoms

Scoring the SAIIE;

- Compare the C4a on day 1 to baseline
- Compare Leptin on day 2 to baseline
- Compare MMP9 as average of day 2 and 3 to baseline
- Compare VEGF to baseline; rise on day 1, fall by day 3
- Compare symptoms day 3 to baseline.
- Add the values

<sup>57</sup> [http://www.tequestafamilypractice.com/articles/CIRS\\_Overview.htm#SAIIE](http://www.tequestafamilypractice.com/articles/CIRS_Overview.htm#SAIIE)

SAIIE Scores;

- 5 for 100%; 4 for 80%, 3 for 70%, 2 for 60%, and 1 for 50%
- Controls mean is 6.3
- Cases mean is 17.9
- TGF  $\beta$ -1 rapidly changes
- CD4+CD25+; it drops rapidly.

What is SAIIE really showing?

- A) Looking at the progression of innate immune responses- extremely sensitive C4a and TGF  $\beta$ -1
- B) Gene activation following receptor resistance (leptin)
- C) Bottom line; this is absolute proof of causation.
- D) A/B/B'/A/B research design.
  - A Person at baseline
  - B Intervention fixes them
  - B' Stop medicine
  - A Re-expose
  - B Intervention fixes them again

This is demonstrative of:

- A) Pattern recognition; antigen presentation gone awry
- B) Inflammatory responses not controlled, neuropeptides are depleted
- C) Innate immune abnormalities become chronic as a host-response syndrome

## Summary

Patients who present with a CIRS diagnosis, at present, have an enormous amount of information to ingest and, on occasion, significant skepticism to overcome. Skepticism usually rises when the patient returns to the primary care provider or specialist, to discuss the diagnostic and therapeutic path that may have been outlined. There is a common saying in life, "what you are not up on, you are usually down on." Nowhere is this more evident than in the world of medicine. It is not uncommon for medical

doctors to dismiss outright any information that is not part of their consensual reality. Even if one is not trained in this area of emerging medicine, it still requires a deep commitment to study the literature, learn the diagnostic and therapeutic criteria for CIRS and apply them to complex multi-symptom, multi system patients who fit the CIRS diagnosis.

At present, the CIRS diagnosis may be dismissed, diminished, misdiagnosed or misunderstood. It may take some time before the full scope and implications of this diagnosis make its way into clinical practice and hence consensual reality. In the meantime, it is incumbent upon practitioners of the CIRS protocol to continue learning the emerging science, particularly the role of genomics in the diagnosis and treatment protocol.

Adequate standards of remediation are another problem many patients frequently encounter. Too often I have heard of patients phoning a mold specialist who does not perform an adequate attic to basement visual inspection of the house but instead does an air sample and proclaims that the home is “mold free.”

Thanks to the recent Consensus Statement on the investigation and remediation of water-damaged buildings in case of CIRS-WD,<sup>58</sup> specific guidelines now exist for patients, practitioners, and indoor air practitioners to follow in cases of those patients with a known CIRS diagnosis.

It will take some time before critical mass is reached and this diagnosis and treatment protocol makes its way into everyday clinical practice. Having worked with the Dr. Shoemaker protocol for over five years, it has been my experience that if a patient is correctly diagnosed and follows the protocol exactly as it has been set out, the possibilities in their returning to good, if not excellent health, are directly proportional to the effort he applies to strictly following the diagnostic and treatment criteria. It is certainly a rewarding moment to witness patient’s symptom scores fall away as he makes progress with the protocol. The protocol does not produce overnight miracles, but at each step of the way, gains are made as the patient’s lives slowly return to normal. It is a wonderful experience to be a part of this transformation.

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<sup>58</sup> Schwartz L, Weatherman G, Schrantz M, Spates W, Charlton J, Berndtson K, Shoemaker R. Indoor Environmental Professional Panel of Surviving Mold – Consensus Statement