The Approach, Diagnosis and Treatment of Chronic Inflammatory Response Syndrome

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INTRODUCTION:

The purpose of this written document is to provide a template of diagnosis and treatment of clients as well as training and policy for employees and physicians in training in the evaluation of CIRS (chronic inflammatory response syndrome) clients. As such, it is intended to be practical and useful while also being regularly updated.

CONTEXT and SCOPE of CIRS

Several significant revolutions in health care occurred in the twentieth century. Sterile technique, immunizations, antibiotics amongst others contributed to huge advances in human longevity. Taking its place in this context, the discovery and development of a mature method of diagnosing and treating CIRS will soon establish itself as one of the significant contributions of health care in the 21st Century. The scope of such a reach is beyond this simple missive but will be / should be in the back of many physicians' minds as they parse out the nuances and implications of CIRS. If we can all pay attention, accumulate data, and track treatment outcomes, we may collectively find that the cumulative impact of CIRS reaches deep into the etiology of autoimmune disease, adult respiratory disease, mental health, coronary artery disease, ADHD, autism, Alzheimer's (on and on). Certainly, the causation of chronic fatigue, fibromyalgia and other conditions entailing endless personal misery should now be looked at as CIRS conditions. The day should be gone when the clinician can say, "I only treat one complaint on each visit" lest one participate in the further misery of our clients. We are standing on the threshold of a new era in medicine in which well-being and robust health can be achieved for many who have previously hidden in mystery and unending distress.

Approximately 50% of buildings in modern society have evidence of water damage. (WHO) It is not the quantity of water but rather the time organic material stays wet that allows for the proliferation of ubiquitous spores and dormant forms of various bacteria. Some of these may be altered in recent years by the use of pesticides creating organisms with greater toxicity. The use of wood, wallpaper, air conditioning, basements, complex roof designs all combine to create environments in which complex colonies of toxin-producing molds, acintomycetes, mycobacteria and other organisms still to be determined are generated. The toxins produced are small (450 -1000 daltons) and prolific with trillions released per colony, hundreds of millions per square foot in the surrounding environment.

Most biotoxins that cause CIRS come from mold, but the scope of biotoxin source remains expanding. Lyme disease, reef fish, Pfiesteria, insect stings, blue-green algae, Black Widow spider are only some of the expanding list of biotoxin sources. Without simple diagnostic testing to identify these toxins, the diagnosis remains clinical. The ability of most biotoxins to move fluidly between cells and through membranes leaves them difficult to test for with typical standardized blood-based testing. A biological merry go round develops in which the mold

toxin sets off Toll receptor proteins and then are excreted by the canicular cells of the bile ducts, only to be reabsorbed in the gut to reignite the immune system once more. It's as though the victim has their 911 alarm system being activated with prank calls. Biological swatting ensues. Without the link to the adaptive immune system functioning as it should, the continual activation of the innate immune system drives continual, unregulated, innate cytokine response.

CIRS has fallen beneath the radar because the majority of people have immune systems with the ability to "see" the toxins of CIRS and excrete or metabolize them. When one takes the histocompatibility, complex HLA typing in humans, we find that about 24% of us cannot "see" biotoxins and thereby cannot dispose of them. These folks' immune system will react at the complement level of engagement with non-specific inflammatory responses, but no sophisticated secondary response of antibody or T-cell elimination of the toxin. And not all vulnerable folks get exposed to biotoxins, lowering the number who are ill. It's not 24% of the population that is ill, it's 24% of folks vulnerable to becoming ill, if exposed. Some of these patients may have mild symptoms as level of exposure is sufficiently modest to not invoke full-fledged symptoms. Two percent with the "dreaded" HLA subtypes will be particularly sensitive to exposure. They have been misdiagnosed and misunderstood. They respond with extreme dysfunction when exposed. Sicker, quicker is their fate.

The cytokine storm initiated in them sets of all sorts of diffuse symptoms that appear to lack cohesion or clearly differentiated illness when viewed from the paradigm of infectious disease, where one organism can be seen, cultured and treated with antibiotics. This mature construct has seduced modern medicine to thinking it represents the means by which all disease is mediated. The significance of biotoxin illness is that a new paradigm is forming that recognizes the diffuse nature of innate immune response. The mist of cytokines released by this biological mistake makes for a fog of symptoms that are at once not understood, and then attributed to a personality defect or character flaw.

Currently, many customers presenting to modern, protocol driven, acute care-oriented health care are expected to limit their concerns to one complaint at a time. When a client with CIRS is experiencing 15+ symptoms, it is not uncommon for that client to labelled as having personality issues, mental health issues or simply called a variety of mystery diagnoses such as fibromyalgia or chronic fatigue. Here is where this document hopes to bring clarity. Instead of fear and confusion on the part of the healthcare provider, the listing of many disparate complaints, should be met with sympathy, understanding and focus on the pathway to wholeness entailed herein.

What happens when one has a competent immune system, represented by the 76% majority of humans? These folks can handle biotoxins and either excrete them by stool or digest them in the liver. The exact means by which this occurs remains to be detailed and represents a rich source for future research.

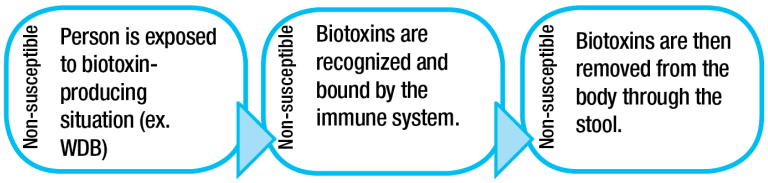


Figure 1. *Figure 1. Actions of biotoxins in the body of a non-genetically-susceptible person*

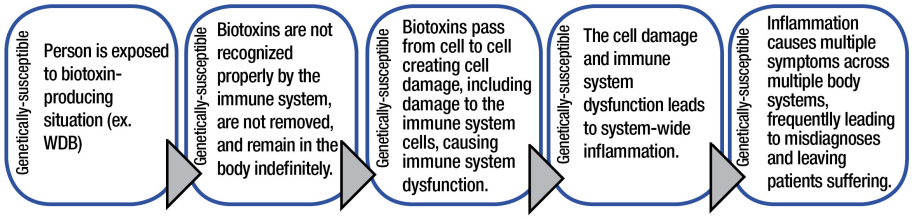


Figure 2. Actions of biotoxins in the body of a genetically-susceptible person

WHAT IS CIRS?

CIRS (Chronic Inflammatory Response Syndrome) is a multisystem, multisymptom illness caused by exposure to biotoxins. The GAO (Government Accountability Office) Report of 2008 on biotoxins lists[1] many elements involved in causation of symptoms. Using these elements, we can create 3 tiers in the definition of CIRS[2].

1. Tier I: Potential of **exposure** to biotoxins – from whatever source; Mold, Lyme, multiple insect stings, reef fish, Pfiesteria etc.

   Symptoms compatible with multisystem, multisymptom illness not explained by a differential diagnosis of similarly presenting diseases. (Usually means this person has seen many physicians and declared well.)

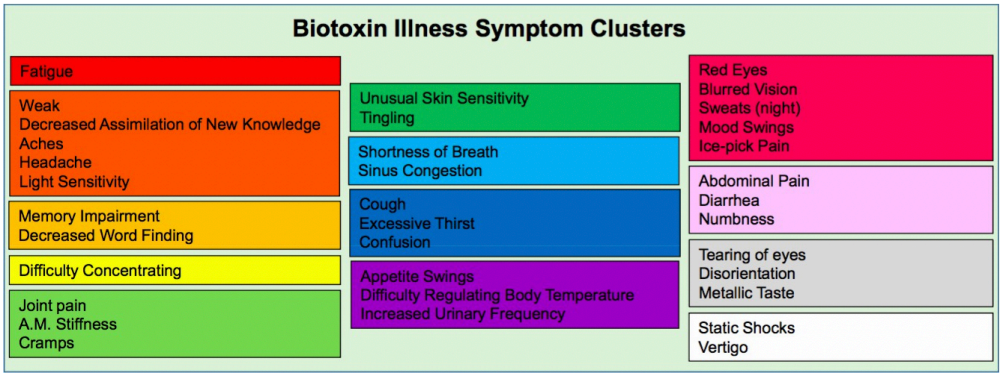
   a. Must have exposure of some sort, or multiple sources

   b. Must have differential diagnoses considered and ruled out. This could include diagnoses that are, in fact, CIRS but called asthma, CFS, fibromyalgia, ADHD, Alzheimer's, Depression etc.

[1] United States Government Accountability Office. Indoor Mold: Better Coordination of Research on Health Effects and More Consistent Guidance Would Improve Federal Efforts. September 2008

[2] Shoemaker R, Rash J, Simon E. Sick Building syndrome in water damaged buildings: generalization of the chronic biotoxin associated illness paradigm to indoor toxigenic fungi. Bioaerosols, fungi, bacteria, mycotoxins and human health. Dr. Eckardt Johanning MD editor 2006.

c. Symptoms compatible with CIRS. Typically, at least 8 of 13 clusters must be met. 10 symptoms highly correlate with mold illness.



2. Tier 2: Positive **Lab Tests** looking at those markers relevant to CIRS
   Here: THREE of SIX must be positive

   1. Positive VCS (Visual Contrast Sensitivity) test. Biotoxins damage nerve cells directly. The retina is an extension of the brain and demonstrates that damage by the inability to see the fine details of black dots as they fade in successive patterns.
   2. HLA Blood Test. Testing to see if a "pattern" of sensitivity is met in one of the clearly known HLA types. 11-3-52B, 12-3-52B, 4-3-53, 14-5-52B are the dreaded types.
   3. MMP-9 is the protein that permits / facilitates biotoxin penetration beyond basement membranes and into the intracellular matrix. It correlates highly with symptoms. It should be below 332 with LabCorp.
   4. MSH. Melanocyte stimulating hormone. It is the first of the hypothalamic products of Pro-opiomelanocortin to take a hit when the leptin receptor is damaged. MSH should be above 35. It has myriad effects.
   5. ADH. Anti-diuretic hormone. This neuro-regulatory hormone helps maintain the incredibly important concentration of blood: the osmolality. Every membrane in the body depends on this careful balance. (More to follow)
   6. ACTH/Cortisol. Another hormone derived from the pro-opiomelanocortin complex, this is the foundation and nexus of circadian rhythms, energy flow and mental alertness.

      Remaining labs do not make the grade for diagnostic criteria, though helpful for management. These include TGF-Beta 1 (transforming growth factor beta one), VEGF (vascular endothelial growth factor), C4a, AGA (antigliadin antibody) and MARCoNS (multiple antibiotic resistance coagulase negative staphylococcus). These participate in driving the 11 steps of management that follow.

3. Tier 3: **Response to treatment.**

   a. Symptoms should improve. The symptom list being reviewed from presentation to treatment should show progressive improvement. A lowering from 10-15+ symptoms to 3-5+ is the goal.
   b. VCS should improve. The VCS test is the most efficient and cost-effective form of repeat testing. This should guide treatment by indicating when the effective threshold has been reached.
   c. Lab tests should improve commensurate with symptoms. Improvement in MSH, TGF-beta 1, MMP-9, C4a will all improve when the proper SEQUENCE is followed.

      (Key: The need to honor the sequence provided herein is key. Each stage allows the next to be successful, or to fail if skipped. As though a row of dominoes were lined up to clear up CIRS, the first domino must be repaired before the second, and so on.)

MEANS OF EXPOSURE TO BIOTOXINS

Biotoxins can invade by any of several means by which chemicals can get into the body. The most common is inhalational. This is the means by which mold causes damage, and mold likely represents the majority of known biotoxins. (Some experts claim Actinomycetes are equal villains.)

1. **Inhalational**: Not the spores of mold, but the DNA and proteins (99% smaller than spores) of various mold species (of which 5-6 are the most toxic but several hundred are known), actinomycetes, various mycobacteria as well as inflammagens such as endotoxins, beta glucans, hemolysins, proteinases, mannans and possibly spirocyclic drimanes; as well as volatile organic compounds all collaborate to set off the CIRS response. (Typical particle counts in clean households per cubic foot run 250,000-3,000,000 particles – we breathe 500 mls tidal volume 12 times a minute.)

2. Insect Bite: Tick or spider bites. Ticks can carry *Borrelia burgdorferi* (Lyme disease), *Babesia microti* (Babesiosis) and other infections (*Bartonella, Anaplasma, Ehrlichia*) . The Brown Recluse spider and the Mediterranean Recluse can cause biotoxin illness.

3. Direct contact with contaminated water. Pfiesteria releases its toxin when challenged by chemicals in the water like excess copper. Blue-green algae, cyanobacteria (*Cylindrospermopsis* and *Microcytsis*)**,**

4. Oral. Eating reef fish like barracuda can lead to ciguatera poisoning, caused by larger fish eating smaller fish that have eaten toxic dinoflagellates. The antibiotic CIPRO may have somewhat a similar action.

MECHANISM of DAMAGE

Biotoxins are share some common traits. They are small molecules that have a hole in them. The chemical name is amphipathic ionophore which essentially means it creates a disruptive channel in a cell membrane through which critically important ions leak out. Cells depend on ion gradients across membranes. When these are disrupted, the cell loses energy and function. Because they are so small and fat-soluble, they can pass through membranes and damage internal elements of the cell as well, notably the mitochondria. They appear to have a predilection for hearts, brains, joints, fat tissue and intestines.

WHO GETS SICK?

76% of people have immune systems that allow them to recognize, tag and excrete biotoxins. They don't get sick on exposure, at least as reliably as the 24% with HLA types that indicate vulnerability. This opens a rich source for research. Whether the immune system can tag and the liver subsequently digest and the kidney excrete – the normal route of digestion and excretion, or some yet to be determined intracellular dismantling of toxins, most folks can be exposed to the low levels found in water damaged buildings and not show disabling effects. Rather than a dose-related response there is an exponential reaction making re-exposure very problematic.

However, 24% of folks have HLA genotypes that fit the pattern of vulnerability. Dr. Shoemaker's database of over 8,000 cases is large enough to have statistical significance and give a meaningful lens by which to examine risk. This makes HLA typing an important diagnostic criteria. It is likely the nexus between the innate system and the adaptive system that is defective.

> The INNATE system is very primitive and essentially non-specific. It simply reacts to patterns that are designed into the system: Pattern Recognition Receptors or PRRs are on fat cells, white cells and blood vessel lining cells. They react to and identify invading toxins with so-called pathogen-associated molecular patterns or PAMPS. If invading cells or organisms cause cellular injury they get called DAMPS for damage associated molecular patterns. The innate system sets off non-specific reactions by what is called the "complement" system that essentially results in holes being punched in the wall of the invader. Along the way a whole host of activating chemicals are released like falling dominoes that

magnify the reaction quickly and forcefully. The innate system then communicates to the adaptive system by way of macrophages that present the new invading antigen (PAMP or DAMP) along with HLA markers to T cells and dendritic cells that start the process of making antibodies to the PAMP or DAMP, but not to the HLA antigen. This way the immune system knows to tag the invader, not the self.

The ADAPTIVE system responds after being presented with the antigen to make specific responses via either antibodies or activated T cells. These learned or ADAPTED responses are specific and long-term. This leads to more sophisticated, localized and lethal responses to invasion. It also takes more time. T cells get grouped into different families and decisions are made whether an up-close response by a killer T cell is the way to go, or long-distance antibodies made by B cells is the proper response. Unbalanced and dysfunctional T cell response then plays a role in autoimmunity when not done right.

HOW DOES CIRS EXPRESS ITSELF?

The 24% of folks with vulnerable HLA typing cannot recognize the antigen to mount an effective clearing response. The biotoxin is secreted by bile secreting cells in the liver, and then promptly reabsorbed by the gut. This leads to an endless cycle of re-exposure to the toxin and reigniting of the innate immune system. Like an endless Ground-Hog day, there is no way to get out of the cycle.

With activation of the innate system happening recurrently, the internal messaging system of the innate complex keeps being set into play. MMP-9, TGF-beta 1, VEGF, C3a and C4a are all cytokines that keep being affected endlessly. The role that they are meant to play in a healthy system gets subverted by the recurrent activation and diffuse, nonspecific symptoms that can't be easily attributed to a specific organ system or local patterns of disease. Hence, Dr. Shoemaker's list of 37 symptoms that appear to have no coherent pattern comes into play and is not recognized by modern "disease-based" pattern recognition.

Circulating cytokines create problems with the leptin receptor in the hypothalamus. The net result is a higher leptin levels than expected. Without a properly functioning leptin receptor, downstream effects include down-regulation of the pro-opiomelanocortin complex [3] with subsequent depletion of MSH, VIP and ADH production. MSH is possibly the most immediate and far-reaching, but VIP remains the last hope for repair if all else fails.

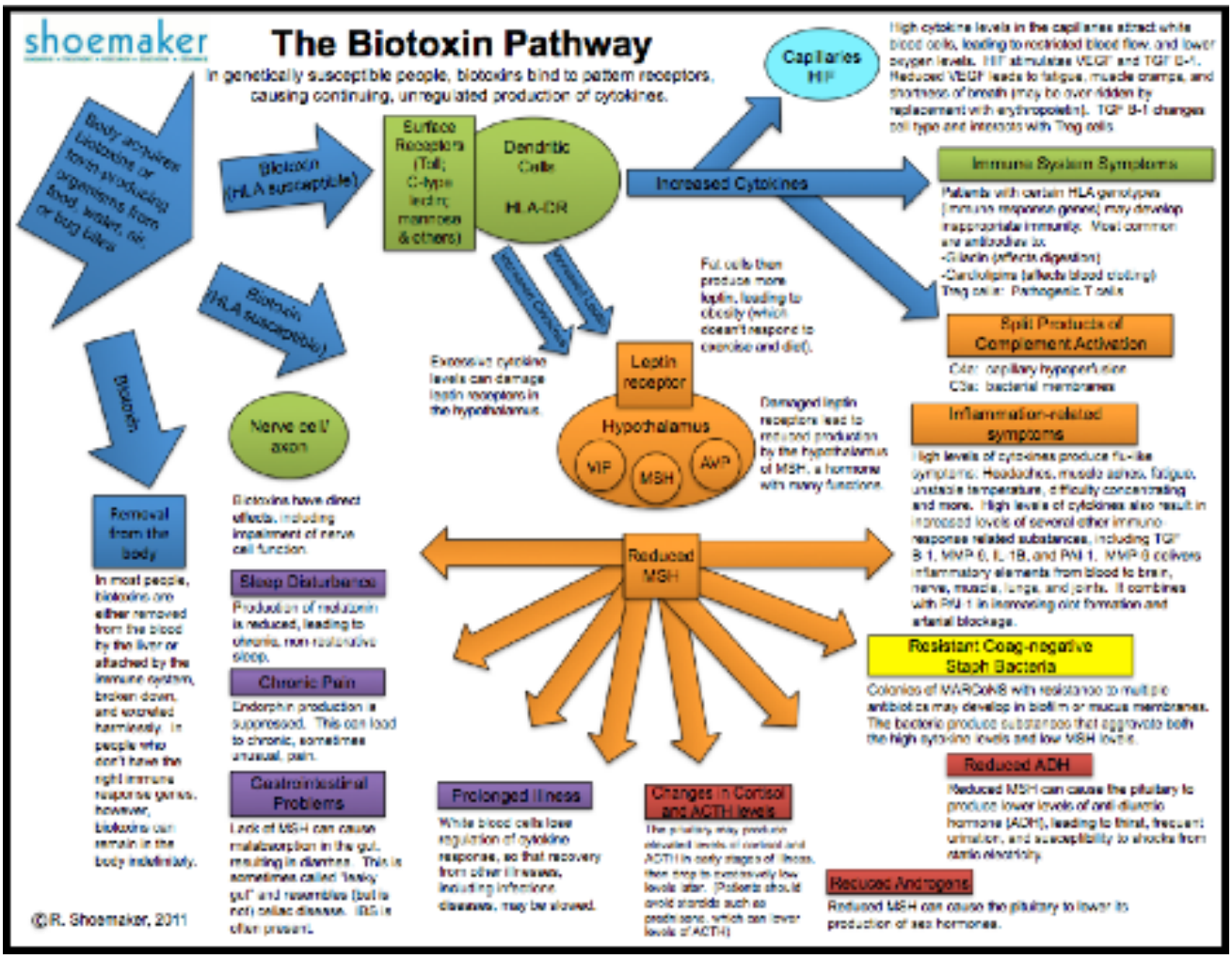
[3] Zhou and Rui Front Med. 2013 Jun; 7(2): 207–222.

With low MSH, most membranes become poorly defended including gut, nose, skin, blood vessel, lungs etc. A seemingly innocuous skin bacteria, Staph epidermidis, becomes commensal in the nasopharynx where it does two problematic behaviors. One, it forms a biofilm in which bacteria swap genes for antibiotic resistance and protect themselves from antibiotic penetration. Two, they create two lytic proteins that continue to lyse MSH, inactivating it and maintaining incompetent membrane immune protection. It's a perfect storm for continued low MSH, resulting in ongoing sleep disorders, pain control, sexual dysfunction, energy level issues, leaky gut, weight gain and more. Recent research even shows low MSH and MARCONs associated with root canals and dental infections.

Understanding the dynamics of MARCONs and its suppression of MSH, and the subsequent control of MSH over many physiological functions, one can begin to clarify the need to have a rigid, sequential treatment algorithm to treat CIRS. Each step has to be completed prior to the next step.

Understanding the dynamics of TGF-beta 1 opens up another physiological control problem. TGF-beta 1 is deeply involved in T cells sorting out their function. Too much TGF-beta 1 lowers T-rag cells, leading to inflammation and autoimmunity taking root.

A summary of the Biotoxin Pathway by Shoemaker is helpful to conceptualize all this complexity.



Note how the leptin receptor and MSH are parked in the middle of the whole system. And herein you can see how to put together a treatment program. Start at the very beginning in the upper left-hand corner with the invasion of biotoxins. That has to be stopped, first.

EVALUATION

The history is the key. A tuned clinician will hear the pattern of unexplained illness with multiple, odd symptoms having seen multiple physicians without satisfaction. Careful exploration may uncover symptoms worsening in certain buildings, strange effects like frequent urination (15 times a day may not feel abnormal to someone who got used to it slowly) or electric shocks from light switches. Fatigue for hours, if not days after exercise needs to be enquired about. Metallic taste won't be mentioned, unless asked for. Dr. Shoemaker's 37 symptom list is useful, but a gently persistent and curious clinician will uncover a lot more. Red

eyes on going to the basement? Wheezing after being in church? Get a cold every time you go to Grandma's? Vomited for two days after swimming in the farm pond? Diarrhea for three weeks after having red snapper at the dock in Key West, or just from your local Seafood Place?

The 37 symptoms can be put into 13 clusters. 8 or more clusters has 98.4% accuracy at predicting CIRS. And in the absence of 8 clusters, 13 + of 37 is pretty close too.

-Fatigue
-Joint stiffness
-Cramps
-Weakness, [4]
-Decreased assimilation of new knowledge,
-Aches,
-Headaches,
-Light sensitivity
-Memory impairment,
- Decreased word finding
-Difficulty concentrating
-Joint pain,
-AM stiffness,
-Cramps
-Tingling,
Tremors,
-Unusual pain,
-Unusual skin sensations
-Shortness of breath,
-Sinus congestion
-Cough,
-Excessive thirst,
-Confusion
-Appetite swings,
-Difficulty regulating body temperature
-Increased urinary frequency
-Red eyes,
-Blurred vision
-Night sweats
-Mood swings
-Ice-pick pains
-Abdominal pain,
-Diarrhea,
-Numbness
☒earing of eyes,
-Disorientation,
-Metallic taste
-Static shocks,
-Vertigo

The physical exam is not as rewarding.

a. Red eyes
b. Hyper-flexibility,
c. Wingspan exceeding height,
d. Resting tremor
e. Cool Hands and Feet
f. Pallor
g. Discolored Hands and Feet
h. Decreased muscle strength in hand and feet
i. Decreased muscle strength in shoulder flexion
j. Decreased tidal volume
k. Dermatographias
l. Nasal polyps
m. Asymmetric peripheral neuropathy

[4] McMahon, Scott. Alternate Diagnosis CIRS PowerPoint presentation 2016 October CIRS Conference

n. Cranial nerve palsies (III, IV, VI, VII)

…….are a few clues but may be absent. The absence of much positive is in itself a clue, as this has what has tripped up other physicians. A complete exam should be ruled out with negative findings. The negative findings are notable.

CAN A REASONABLE DIAGNOSES BE CONSIDERED ON THE FIRST VISIT?

Before someone has the benefit of retrospective proof, the clinician may want to make a reasonable prediction from initial lab, history, and physical findings. Scott McMahon, MD has provided us with that analysis

- **Review of Systems Symptoms Clusters** – 8 or more out of 13 symptom clusters for is diagnostic in adults, with a sensitivity 98.4%

- **Screens** – Three of the Following Screens:

  1) Visual Contrast Sensitivity (VCS),

  2) 13 Symptoms from the list of 37 symptoms

  3) measure of shoulder anti-gravity muscles/ grip /shrug

  Adults, having these 3 out of 3 screens has a specificity 86.7%, positive predictive value 97.4%

- **Labs** – 5+ abnormal tests of the following 10 tests:

HLA,	MARCoNS,	ACTH/cortisol,
MSH,	VIP,	ACLA/AGA
TGF-β1,	C4a,	
MMP-9,	ADH/osmolality,	

  (In adults, having 5 positives results in a specificity is 73.3%, positive predictive value is 97.7%, the likelihood by chance alone is less than 1 in 10,000,000,000)

Thanks to this analysis, clinicians can take a practical and actually quite precise "guestimate" on the first visit and follow-up:

We can use few or absent symptom clusters to *help rule out CIRS.* This can help the clinician who is taking CIRS into account on the differential.

- **We can use 3 screens or 5+abnormal laboratory tests to *help rule in CIRS.*** If the 3 screens are positive the CIRS provider can start the first steps of treatment after the first visit while other labs may still be pending.
- Shoemaker R. Biotoxin Illness Treatment Protocol pg. 6

CASE DEFINITION

(Tier I – ALL THREE MUST BE MET)

1. Exposure

a. Mold.
b. Lyme
c. Ciguatera
d. Pfiesteria
e. Reef Fish
f. Brown Recluse Spiders
g. Cyanobacteria
h. Probably more to be revealed

2. **Differential of other diseases ruled out**. Many other diagnoses have often been considered and treatment venues tried, without success. Anxiety, hypothyroidism, adrenal fatigue, PTSD, Chronic fatigue, fibromyalgia, migraine, depression, Alzheimer's, ADHD, somatization are all part of the diagnoses applied to CIRS people by a medical system that is as unable to "see" the diagnosis as the immune system can see the biotoxin. Many of these illnesses have had diagnostic procedures performed and treatment modalities tried. Their lack of efficacy is part of the diagnostic criteria. There is real hypothyroidism, real Alzheimer's, so the alternatives must be mature carefully considered.

3. Mutli-symptom, multisystem disease

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, icepick 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, diarrhea
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 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						
Subtotal						
Weakness						
Decreased Assimilation of New Knowledge						
Aches						
Headache						
Light Sensitivity						
Subtotal						
Memory Impairment						
Decreased Word Finding						
Subtotal						
Difficulty Concentrating						
Subtotal						
Joint Pain						
A.M. Stiffness						
Cramps						
Subtotal						
Tingling						
Tremors						
Unusual Pain						
Unusual Skin Sensitivity						
Subtotal						
Shortness of breath						
Sinus Congestion						
Subtotal						
Cough						
Excessive thirst						
Confusion						
Subtotal						
Appetite swings						
Difficulty Regulating Body Temperature						
Increased Urinary Function						
Subtotal						
Red Eyes						
Blurred Vision						
Sweats (night)						
Mood Swings						
Ice-pick Pain						
Subtotal						
Abdominal Pain						
Diarrhea						
Numbness						
Subtotal						
Tearing of Eyes						
Disorientation						
Metallic Taste						
Subtotal						
Static Shocks						
Vertigo						
Subtotal						
TOTAL						
Reference: Ritchie Shoemaker - April 2012						

LABORATORY TESTING

(Tier II – 3 of the 6 must be met to meet criteria of diagnosis)

1. Visual Contrast Sensitivity

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

   Dr. Shoemaker and Ken Hudnell published a study in 1997 that showed that patients with exposure to biotoxins have abnormal VCS results when they have biotoxin illness. The visual contrast test measures the ability of the optic nerve to transmit data from the retina to the cortex by measuring the least amount (threshold) of contrast difference between adjacent areas (contrast) necessary for an observer to detect a visual pattern. Biotoxins directly damage nerve tissue and decrease the ability to generate energy.

- The test measures contrast sensitivity for five sizes (spatial frequencies) of light, gray and dark bar patterns (sinusoidal gratings) in circles with lines slanting at different angle.
- There are pattern differences that healthy individuals will see which is the curve formed by the most subtle form of contrast they can detect, versus the CIRS patients who will have lower contrast sensitivities and their curves will fall below the healthy control line. Higher contrast sensitivity is revealed by seeing more detail, requiring better nerve function.

- 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 biotoxins removed and nerve function improving. With an intensification reaction to cholestyramine, there will be a fall in column E followed by a fall in Column D[5]. 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[6]. 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. This is key

- 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. 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

  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.

[5] Shoemaker R. State of the Art answers to 500 Mold Questions Question 212

[6] Shoemaker R, Hudnell K. Possible Estuary-Associated Syndrome: Symptoms, Vision and Treatment Environmental Health Perspectives Vol 109. No5 May 2001.

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	✓	✓	✓	✓	✓

2. **HLA GENOTYPE TESTING**.

This test measures the genetic vulnerability to developing CIRS. The vulnerable patterns herein revealed give confidence to the clinical course. This is where the 24% of the population that is vulnerable reveal themselves to be different than the 76% who have a much more robust ability to identify and remove biotoxins. Every cell in any individual has these markers as indicator of "self" for the immune system to see and "accept." They are also used to participate in presenting non-self, foreign antigen to be identified as "non-self" and thereby worthy of being attacked or excreted.

There are five categories in which the HLA types are listed: DRB1, DQ, DRB3, DRB4, and DRB5

Then numbers provided by LABCORP need to be translated to the recognizable formats as follows[7].

1) Under the DRB1, there will be two numbers for each person which will be the first numbers in the listed triads that each person possesses. If a person as a DRB1 – 13 and a DRB1 17, their two numbers will be 13 and 17 for their two triads or "alleles." If the first numbers are 1 , 8 or 10, there will only be two numbers, not three. And, as an odd exception to the rule, if there is a DRB1 of 3, it is written as a 17.
2) Under DQ there may be two different numbers, or just one. If just one, it is used as the second number twice.
3) Finally, there are the DRB 3,4 and 5.
    a. The DRB 3s are either a 1,2 or 3 and are listed as 52-A, 52-B, and 52-C respectively
    b. DRB4 is listed as a 53
    c. DRB5 is listed as a 51.
    d. IF you have two of the 3/4/5 you can mix and match with the DRB1 and DQ so if you have a 52A and a 51; you effectively have two options for identifying a vulnerable haplotype

The following table presents the known risk types by their combination of haplotypes as indicated above.

A Summary Can Be listed as follows

1. Multiple Susceptibility (Worst ones) 11-3-52B, 12-3-52B, 4-3-53, 14-5-52B
2. Mold Vulnerable: 7-2-53, 7-3-53, 13-6-52A, 13-6-52B, 13-6-52C, 17-2-52A, 18-4-52A
3. Lyme Disease Vulnerable: 15-6-51, 16-5-51
4. Dinoflagellate (pfiesteria etc.) Vulnerable: 4-7-53, 4-8-53
5. Marcons 11-7-52B
6. Low MSH 1-5
7. Chronic Fatigue 4-3-53, 11-3-52B
8. MS: 15-6-51
9. Low Mold Risk: 7-9-83, 9-9-53, 12-7-52B

[7] Shoemaker R. Surviving Mold. Otter Bay Books 2010

	DRB1	DQ	DRB3	DRB4	DRB5	Clinical notes
Multi-susceptible *Unable to clear any / all toxins from system*	4	3		53		3%, highest C4a, TGFB1 DRB1- 0401, 0402, 0403 worst
	11/12	3	52B			1% Get sicker, quicker
	14	5	52B			
Mold *Unable to recognize or clear mold toxins*	7	2/3		53		7-2-53 associated with celiac
	13	6	52A ,B, C			
	17	2	52A			52 A, B, C associated with celiac
	18*	4	52A			
Borrelia , Post Lyme	15	6			51	
Unable to clear Lyme toxins	16	5			51	
Dinoflagellates	4	7/8		53		
MARCONS – *Inability to recognize / attack MARCONS*	11	7	52B			
Low MSH	1	5				
No recognized significance	8	3,4,5,6				
Low risk mold	7	9		53		
	12	7	52B			
	9	3,9		53		
Less common additional haplotypes	1	3,4,8				
	4	4		53		
	7	4,9		53		
	9	2,7,9		53		
	10	5				
	11	4,5,8	52B			
	12	5	52B			
	13	3,7	52A, B			
	14	3,7	52B			
	15	5			51	
	16	6			51	
	17	2	52B,C			
	17	3,4	52 A,B,C			
	103	5				

3. MMP-9, Matrix Metallopeptidase – 9

Normal Range: 85-332 ng/ml: 28.14-109.89 nmol/ml
It is essential to ask the lab to have PRECHILLED SST tubes and immediately centrifuge and freeze the specimen. These instructions should be on the lab requisition sheet. Otherwise the white cells in the specimen will release MMP-9 in as little as 30 minutes to double or even triple the baseline.

- MMP-9 is the enzyme activated by the innate immune system in the face of biotoxin presence to dissolve and open up access beyond the basement membrane. It, in effect, dissolves the last barrier protecting cells from whatever is in the blood. When white cells need to enter the intracellular space to fight bacteria, this is useful. When biotoxins can enter, unimpeded, it's dysfunctional and results in localized damage to the exposed vulnerable cells. Higher MMP-9 in adult asthma in the lung is one example. Others include muscles, joints, brain, lungs, peripheral and autonomic nervous system[8].
- Similarly, high MMP-9 has been associated with increased blood-brain barrier permeability[9].
- 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 and symptom intensification.
- Increased in head injury
- Patient may feel worse with CSM if they have high MMP-9

4. Cortisol/ACTH

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. 1) Absolute high: ACTH > 45 or cortisol > 21
2. 2) Absolute low: ACTH <5 or cortisol <4
3. 3) Relative: ACTH was < 10 when cortisol was < 7- two-tiered test
4. 4) Relative: ACTH was > 15 when cortisol was > 16 - two-tiered test

[8] 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

[9] 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

- ACTH and cortisol normally maintain the energy flow and awake function of the human brain and body in a circadian fashion. ACTH is secreted by the pituitary in response to POMC activation, which in turn causes cortisol to be secreted by the adrenal glands. Cortisol naturally surges in a circadian fashion at the time of awakening, mobilizing glucose and brain alertness. Normal cortisol, at 4 am will be as much as one-tenth of normal at 8 am, so timing of specimens must insist of 7-9 am blood draw for accuracy. (Both should be performed at the same blood draw)
- ACTH and Cortisol are also released in response to intense stress or exercise. This is natural – and mobilizes energy and mental alertness to allow proper functioning in the light of higher activity. The POMC complex is activated and beta-endorphin is released-resulting in the "runner's high" of exercise.
- But, cortisol is also dysfunctionally released with stress, and in biotoxin illness, also dysfunctionally, resulting in sleep disorders and fatigue. "Wired and tired."
- 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 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.

5. Anti – Diuretic Hormone ADH

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

- ADH and osmolality are hypothalamic-pituitary regulators of blood "concentration" or osmolality – the measure of the number of particles in blood. ADH rises to instruct the kidney to hang on to water. It falls to allow the kidney to let water go.

- Dr. Shoemaker published data showing that up to 80 % of patients with CIRS have dysregulated ADH/osmolality levels. Many will not be aware of their frequent urination being attributed to abnormality, thinking it was a marker of aging.
- 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 osmolality is associated with reduced VEGF production in response to low microcirculatory oxygen levels. Low ADH is also associated with autistic behavior and social avoidance behavior in CIRS patients[10] [11].
- 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.
- 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[12].
- 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 (See Treatment Section)

6. **Melanocyte Stimulating Hormone MSH**

[10] Berndston K. Chronic Inflammatory Response Syndrome pg. 15

[12] Shoemaker R. Biotoxin Illness Treatment Protocol pg. 6

Normal Range: 35-81 pg/ml; 206-478.7 pmol/. Run through LabCorp: Note, some results report normal down to zero – a marker of how often people affected with CIRS are in the "normal" range. It is important to differentiate between what is observed in the population and what is healthy and functional. Zero is NEVER normal.

- MSH is one of the most critically suppressed neuro-regulatory 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 adrenocorticotropin (ACTH) and beta-endorphin. The conjecture here would be that intense exercise releases ACTH, beta-endorphin and MSH, making the link between exercise and beneficial health effects and longevity via MSH.
- 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[13].
- 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**.**

OTHER TESTS USEFUL IN ASSESSING CIRS

- ERMI
- MARCoNS
- Antigliadin antibodies
- Androgens
- Leptin

[13] Shoemaker R. Biotoxin Illness Treatment Protocol pg. 6

- C3a
- C4a- run through Quest
- VEGF
- TGF beta-1
- VIP
- Von Willebrands
- CD4+CD25+
- Anti-cardiolipin antibodies
- PAI-1
- Pulmonary Function Tests
- VO2 Max
- Stress Echocardiogram
- NeuroQuant
- Genomics

1. ERMI (ENVIRONMENTAL RELATIVE MOLD INDEX)

- If water damaged buildings/mold is suspected, an ERMI is essential. Because 50% of homes appear safe and have little evidence of water intrusion while still being positive, an ERMI test is almost a prerequisite for successful treatment before treatment starts.
- Mold illness and CIRS 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 mold burden[14]. Sampling for spores with the current methods widely sold now 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, nor does it take into account Wallemia. Furthermore, Stachybotrys (one of the more virulent molds) can be missed as it is often not an airborne molds, being heavy in nature and existing mostly on the floor level. 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)[15]. 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 one lab that offers the an accurate ERMI test: Mycometrics www.mycometrics.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[16]. The number calculated as the ERMI is the sum of the logs of the concentrations of the

[14] Lin K-T, Shoemaker R.C. Inside Air Quality Filtration News Vol 26, No 3, pg. 32, 2007

[15] ibid

[16] ibid

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 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 USA.
- 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 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 less than -1.

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

- 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 > 500 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

Add all the scores = Total of the above three scores added together

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

3. MARCoNS: MULTIPLE ANTIBIOTIC RESISTANCE COAGULASE-NEGATIVE STAPH

Lab Test: API-Staph culture

- MARCoNS does two problematic functions: It creates a biofilm in the nose and secretes two proteins that breakdown MSH.
- The biofilms can be identified by an API-Staph nasopharyngeal culture. The MARCoNs thrives in deep aerobic spaces of nasal cavity.
- Must use API Staph Isolate and cultured for 7 days – the usual 2-day culture will miss it.
- 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 being present will result in MSH deficiency.
- MARCoNS release endotoxin A and B which cleave MSH, rendering it ineffective and thus leading to immune dysregulation via further MSH 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[17].
- 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[18].
- 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 cavitation's.
- MARCoNS with low MSH patients have a differential genomic profile than negative MARCoNS patients and low MSH[19].

- MARCoNS not to be confused with other coagulase-negative staphylococci that are not antibiotic resistant.

4. ANTI-GLIADIN ANTIBODIES (AGA)

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

5. ANDROGEN DEFICIENCY

Normal

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

- Abnormal androgens can be due to an upregulated aromatase enzyme.
- Testosterone is often dysregulated and DHEA may be low.

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

[18] Shoemaker R. Katz BEG DVD 2013

[19] Shoemaker R. Katz 2013 BEG DVD

- 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.

6. LEPTIN

LabCorp Ranges: 0.5-13.8 ng/ml; for men
1.1-27.7 ng/ml; in women

- Leptin is a hormone that controls appetite and energy flow with fatty acids. If the leptin receptors are disrupted, high levels of leptin occur trying to compensate for the blockage.
- Leptin regulates the pro-opiomelanocortin (POMC) pathway, thus affecting MSH and ADH
- Disrupted leptin contribute to low MSH, ADH, VIP and ACTH.
- Leptin outside the brain binds to immune cells and increases inflammatory cytokines[20].
- 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.
- Markers of hypothalamic illness include high leptin and osmolality, low MSH, low ADH, ACTH and/or VIP

7. C3a

Preferred Lab: Quest

Normal Levels: 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[21]
- C3a will usually be low unless there is Lyme- usually more acute in nature.
- C3a elevates within 12 hours of a tick-bite

[20] Bjorbaek C, Kahn BB. Leptin signaling in the central nervous system and periphery. Recent Progress in Hormone Research. 2004; 59: 305-31. PMID: 14749508

[21] Shoemaker R Biotoxin Illness Treatment Protocol pg. 8

- 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.

8. C4a

Preferred Lab: Quest

Normal Range: 0-2830ng/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 due to PAMPS (pathogen -associated molecular patterns) activation because 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 mannin-binding lectin serine protease 2 (MASP2) in patients with chronic fatigue syndrome[22].
- C4a helps the antibodies and phagocytic cells remove infections and toxins from the body.
- 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[23].
- 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 causes 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.

[22] 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

[23] 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

- C4a can be elevated in all CIRS, Lyme disease and SLE.

9. VEGF

Preferred Lab: LabCorp or 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[24].
- 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
- 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.
- In biotoxin patients, inflammation and cytokines suppress VEGF, creating persistent capillary hypoperfusion.
- This result in fatigue, cognitive fallout, muscle aching, and poor recovery from exercise due to anaerobic mitochondrial metabolism.
- Intensely low perfusion results in glycolysis and protein catabolism for energy, requiring several days to replenish glycogen - and with symptoms of very prolonged fatigue.
- In lactic acid metabolism, due to low VEGF, one obtains only 2 ATP for every glucose molecule, instead of 38 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.

10. Transforming Growth Factor Beta -1 TGF beta1

Preferred Lab: Quest or LabCorp

1. 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

[24] Olfert IM, Howlett RA, Tang K, Dalton ND et al. Muscleespecific VEGF deficiency greatly reduces exercise endurance in mice. Journal of Physiology 2009 Apr 15; 587:1755-1767

- 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 downregulate this biomarker.
- Elevated levels usually indicate that the body is trying hard to downregulate 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 activated immune system and it is a vital marker of the CIRS severity.
- If it 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+CD27++, 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-1, thus improving humoral immunity.
- If T reg cells are low <4.66 %, TGF beta will often be high > 2,380.
- VIP will raise T Reg cells (CD4, CD25).
- TGF beta-1 can cause tissue remodeling in the liver, heart, lung, 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 VO2 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[25]

[25] Hibino T, Nishiyama T. Role of TGF-beta2 in the human hair cycle J Dermatol Sci. 2004 Jun;35(1):9-18

11. Vasoactive Intestinal Peptide (VIP)

Preferred Lab: Quest

Normal Range: 23-63

- 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 and systemic 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.
- 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[26].
- 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.
- Restores hormone levels, Vitamin 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.
- Dr. Shoemaker published a study in 2013 on VIP used on CIRS-WDB patients which demonstrated the following[27]:

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[26] Berndtson K. Chronic Inflammatory Response Syndrome. Overview, Diagnosis, and Treatment. Pg.7

[27] 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

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 Vitamin 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.

12. CD4+ CD25+

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

13. von Willebrand's Profile

Preferred Lab: Quest

- Factor VIII activity, von Willebrand Factor antigen, Ristocetin Cofactor, von Willebrand's Factor Collagen Binding Assay, von Willebrand Antigen) –as well as coagulase study- PT, PTT, PT/INR - esp. if a 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 less viscous and bleeding will result. 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.

14. Anti-Cardiolipin Antibodies

Preferred lab: Local or any

- Marker of autoimmunity.

15. PAI-1

Preferred lab: Local or any

- A marker of increased blood coagulation.

16. Pulmonary Function Testing

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 a restrictive test is shown, proceed to VO2 max.

17. VO2 Max

- VO2 max testing done on a treadmill may show abnormally low VO2 max, often lower than 20 (age-related). 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

18. 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.

19. NeuroQuant

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:[28]

- Forebrain parenchyma increased
- Cortical gray increased
- Hippocampus increased – although not included in the criteria
- Caudate decreased – reversible through use of VIP according to Dr. Shoemaker's clinical experienced
- Pallidum increased

Patients with CIRS due to Lyme neuroborreliosis have the following pattern: [29]

- 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 4 points and no controls had 4 or more points. One needs to take the average of the two sides to determine the points awarded.

20. Genomics

[28] 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 Biotoxin Associated Illness, Pocomoke

[29] Ibid

- 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.[30]
- 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 chronic inflammation[31]. 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)[32]. These were down-regulated 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 up-regulated immune response.[33]
- 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. MMP-9 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.
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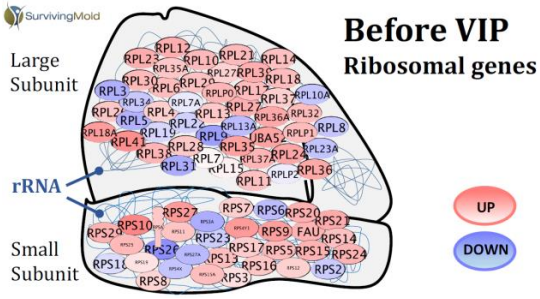
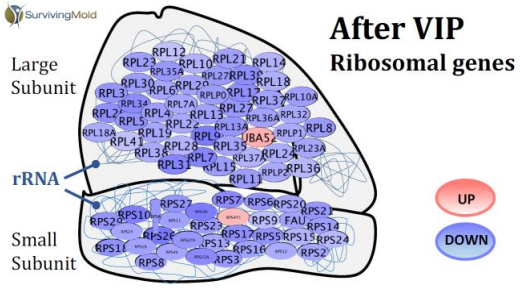
30 Berndston K.

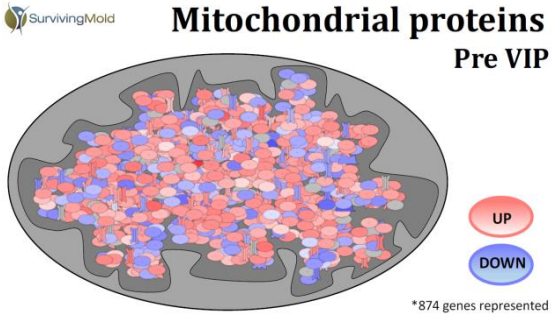
31 Ryan J, Shoemaker RC, RNA-Seq on patients with chronic inflammatory response syndrome (CIRS) treated with vasoactive intestinal polypeptide (VIP)shows a shift in metabolic state and innate immune fluctuations that coincide with healing. Medical Research Archives Vol 4 Issue 7 2016.

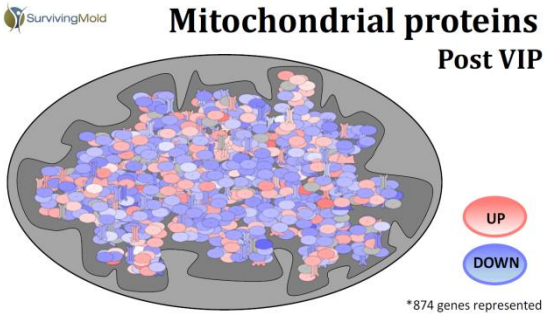
32 www.survivingmold.com

33 Ibid.





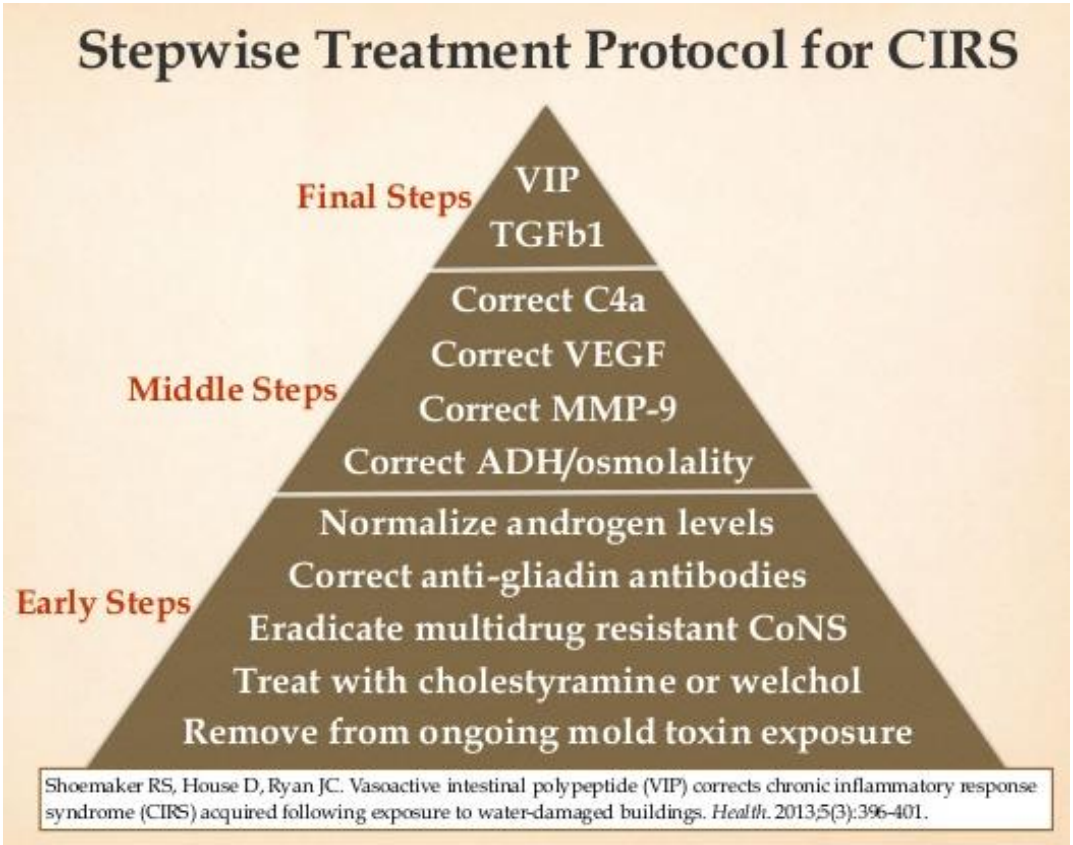




Other Lab Tests In CIRS

- These lab tests are done to rule out other possible illnesses.
- CBC, Metabolic panel, Lipid panel, C-reactive protein, ESR, ANA, Thyroid studies with thyroid antibodies, sex hormones (estradiol, progesterone), pregnenolone, cardiolipin antibodies, PTT, , d-Dimer, IgE, Immunoglobin panel.
- 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.

THE STEPS AND SEQUENCE OF TREATMENT FOR CIRS



CIRS is more than just an inflammatory upregulation of the innate immune system. Set in motion is an immune disorder occurring in genetically susceptible individuals. It therefore requires stopping the initiating process but then a sequential resolution of the immune dysregulation, the inflammatory processes that sustain the dysregulation, the neurohormonal abnormalities, and finally the potential autoimmune dysregulation as well as possible coagulation disorders. Of note, this broad range of dysfunction requires a carefully crafted sequential order of intervention to guarantee success.

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: REMOVE 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, or food poisoning with ciguatera? The vast majority is mold, but alternatives should be considered. 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-The 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 cleaned.
- 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 larger 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

Biotoxins must be removed from the body, particularly in a patient with the genetic predisposition to biotoxin illness. These patient's antigen presentation system cannot recognize the biotoxins and needs 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 must be taken on an empty stomach away from meals and medications and/or supplements.
- Many people start with 1⁄4 teaspoon a day. Take the CSM 1⁄2 hour before meals with, drugs or supplements an hour after the meals.
- Drink 6 - 8 oz. of water with each 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 passes the VCS test.
- 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 patients have problems with toxin release or treatment reactions on starting CSM, start with Actos 15-45mg a day, or EPA 2.4 gms DHA 1.8gms for 5 days, then restart the cholestyramine again.
- If Leptin <7 use omega 3 fatty acids instead of the Actos/pioglitizone
- Be aware that fat-soluble vitamins A, D, E, K are bound by CSM.
- If CSM causes too many side effects, switch to Welchol 625 mg capsules and gradually - 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.
- Pediatric Doses or for folks. <120 lbs. or less than 18 years old.: Use 60 mg/kg/dose TID with 6 oz. water 30 mins before food.
- If re-exposed- use Welchol or CSM for 3 days at full dose
- CSM should works within a week.- and does provided the patient is not being reexposed
- Be proactive with constipation is this is a common reason for treatment failure: Be proactive and treat constipation with magnesium oxide or citrate powders. One half a cap of 70 % sorbitol (MiraLAX) daily will often work.
- Recheck VCS one month after starting treatment and then with each subsequent step
- If the VCS normalizes, 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, false negative ERMI, non-compliance or MARCoNS still needing to be treated.

STEP 3. TREAT MARCONS

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

RX: Bactroban (Mupirocin) 0.2%, Edetate Disodium (EDTA) 1%, Gentamicin 0.5%

- Start one month after starting CSM
- 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 after one month
- If symptoms worse after starting, it may imply re-exposure; VCS row D and E will fall and MMP-9 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. 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.
- Eradication of MARCONs is essential if subsequent steps are to succeed
- If symptoms worsen after 1 month, check for re-exposure, recheck VCS and MMP-9 levels.
- If patient better, stop BEG spray, recheck API- Staph nasal culture and VCS.

STEP 4: ELIMINATE GLUTEN IN AGA POSITIVE SUBJECTS

- 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 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[34]

STEP 5: CORRECT ANDROGENS, ACTH, DHEA, CORTISOL

Treatment:

- DHEA-25-75mgaday-men.5-25mgaday-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

[34] Shoemaker RC. Surviving Mold: Life in the Era of Dangerous Buildings. Otter Bay Books. Baltimore 2010.

- Do not use aromatase inhibitors with a low-MSH patient<35, this will cause significant deterioration.

STEP 6: CORRECT ADH/ABBERANT OSMOLALITY

Goal: Correct ADH/osmolality Normal Range:
ADH - 1.0-13.3 pg/ml; Osmolality [280-300 mOsm Quest] [275−295 mOsm LabCorp]

Objective: correct blood osmolality

Symptoms addressed: include polyuria, polydipsia, orthostatic hypotension, recurrent headaches and static shocking

Neurotoxicity in CIRS and Lyme-complex illness patients often have low to below detection threshold AVP/ADH levels with resultant increased serum osmolality [too concentrated and "thick"]. Patients typically complain of increased thirst, dry mouth and frequent urination of typically clear urine. They may only state "They drink a lot of water". Salt levels in blood rises as you loses free water due to inadequate ADH and subsequent free water loss by the kidneys. Sweat will have increased sodium/chloride [exceeding cystic fibrosis] with resultant generation of static electricity and static shocks.

- Use DDAVP when osmolality is high>295 or Osmolality > 292 and ADH < 2 (relatively low ADH for the height of osmolality – you will see an ADH of 4.5-6 with normal folks)
- Use 0.2 mg every other night to verify tolerance and absence of side effects especially if weight gain.
- ADH can lead to edema and rapid weight gain due over correction of deficit with resultant fluid retention.
- After 5 doses - check serum osmolality, ADH and electrolytes verifying normal sodium.
- If symptoms persist, especially on "off days", switch to 0.2 mg daily and check electrolyes weekly. .
- Some people (especially those with POTS) may need to be on drug indeterminate period.
- Some may need it twice daily.
- ADH abnormalities usually normalizes over time – sometimes as early at 10 days.
- Curiously, this treatment may also correct acquired von Willebrands syndrome by mobilizing the monomers from vessel wall reservoirs - AND help reduce MMP-9 (and C4a) levels. Acquired Von Willebrand's patients should be instructed to carry DDAVP to stop episodic nose bleeds.
- 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.
- Medical trivia: Taurine can cause polyuria and Lithium can cause ADH resistance.)

STEP 7: CORRECT ELEVATED MMP-9

Treatment: Actos (Pioglitazone) and/or EPA/DHA Fish oil

MMP-9 is produced by cleaving MMP-14. This is a marker for spread of inflammation through soft tissues; MMP-9 allows inflammatory mediators to migrate through tissues, spreading inflammation through the extracellular matrix that it has broken down. This level will be elevated in uncontrolled CIRS. It is high in lungs with adult asthma. It correlates with symptoms.

Goal of therapy: upregulate PPAR-gamma production and reduce MMP-9 expression.

- Pioglitazone Actos 45 mg with NO-Amylose diet
- Lowers TNF, leptin, MMP-9, PAI-1, and raises low VEGF.
- If low leptin- (less than 7) or less than 18 years, don'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/or hypoglycemic have to stop.
- Watch kidney function and blood sugar.
- Actos is also implicated in bladder cancer with long term use.
- Omega fats take longer to work but are also effective.
- Recheck labs after 30 days.
- High MMP-9 patients may get worse when starting CSM with intensification reactions.
- With an increase in MMP-9 there is worsening in row E of the VCS test.
- Glutathione, Trental, progesterone, curcumin, glutamine, and phosphatidyl-choline have been anecdotally shown to lower MMP-9- not part of Shoemaker protocol.

STEP 8: CORRECT VEGF – CORRECTION OF HYPOPERFUSION

Normal Range: 31-86 pg/mL

Objective: improve oxygen delivery to cells

Low VEGF can occur despite the lack of appropriate delivery of oxygen and nutrients at the capillary/cellular level. Typically VGEF increases when cellular starvation is occurring. Blocking VEGF is being used as a therapy against cancer. CIRS patients can develop this issue as a result of their disorder.

- 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.
- No-amylose diet with pioglitazone may correct this as well.
- Procrit can increase VO2 max but comes with black box warnings, cost and politics.
- VIP works well too and might be the better option.

Step 9: CORRECT ELEVATED C3a

Normal Range 55-486 ng/mL

Objective: improve oxygen delivery to cells and decrease inflammation, Identify Lyme

C3a is a product of split complement present in only some biotoxin illness patients such as acute Lyme disease or SLE. C3a is one of the more potent factors of the complement system. C3a attracts and activates neutrophils to release their granules, which causes capillary under perfusion, vasoconstriction, increased vascular permeability. C3a promotes pathological inflammation and must be corrected. There is significant symptom overlap between Lyme-complex illness and CIRS from water damaged buildings.

- 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 prior to starting the statin
- Then start statins - Zocor 80 mg day, Pravastatin, Atorvastin, Fluvastatin, 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 should be taken with great caution or not at all. Also, notice that one should avoid large amounts 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 C4a

This split product of the MBL (mannose-binding lectin) pathway of the complement system is a key marker of how severe a patient's CIRS is.

Goal: Correct elevated C4a

Normal Range 0-2830 ng/mL

Objective: improve oxygen delivery to cells and decrease inflammation

- 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 which increases the 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.
- Most Practitioners now use VIP 4 sprays a day instead of 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[35].
- Recheck MRI spectroscopy after Procrit = normal G:G, normal lactate and improvement in 6 areas of cognitive functions.

Step 11: REDUCE ELEVATED TGF beta -1

Goal: Correct abnormal TGF-beta1

Normal range: <2380 pg/ml)
Quest Test: Quest 60336

- Most folks with TGF beta-1 less than 5,000 do not tend to be symptomatic
- TGF beta 1 will rise upon VIP therapy when there is an ongoing mold exposure, Lyme disease, or an imbalance in T-regulatory CD4+CD25++ cells and TH-17 cells exists

[35] Shoemaker R. Biotoxin Illness Treatment Protocol pg. 10

- Every effort must be made to reduce this biomarker – there is body wide damage happening
- 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 beta-1.

- 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

- 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 is in order and may be the most effective treatment
- 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.
- 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

- **VIP Administration Protocol: First Dose**:
    - 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++,

Vitamin 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.
    - CIRS patients will often have over 8 mm Hg elevation of PASP- this can result in palpitations and dyspnea not responsive to asthma medication[36].
- 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.

- **<u>VIP Dosing and Follow-up Care</u>**
- 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.

[36] Shoemaker R. Biotoxin Illness Treatment Protocol pg. 12.

HOW CAN WE PROVE WHAT WE ARE DOING IS THE RIGHT THING

RE-EXPOSURE TRIAL – Be a MOLD WARRIOR

Treating CIRS is new and conceptually complex. Considering that the cost of STEP 1, removal from toxin exposure, is expensive both at home and in the workplace, it leads to controversy, and sometimes disputes. One can calmly and rationally prove the effectiveness of this program by reproducing the same conceptual proof of the time-honored Koch's Hypothesis, the foundation of infectious disease. Koch maintained that a bacteria had to be found in folks with a disease, and only in those folks. And it's absence results in cure, and re-introduction results in disease. This is the foundational basis for Infectious Disease, and much of modern medicine as it is practiced.
With Biotoxin Disease (CIRS-WDB), the same process can be followed by: Measurement of blood markers of biotoxin illness at baseline, after two weeks of Cholestyramine therapy, after 2 more weeks of biotoxin avoidance and no cholestyramine, for three days in a row after re-exposure, and then again after retreatment with cholestyramine. This demonstrates initial inflammation that resolves with treatment, stays resolved without exposure, recurs with exposure over 3 days, and is cured again with retreatment. So-called ABB'AB design is the biotoxin equivalent of Koch's procedure, and is easily explained to the non-scientific mind- Add in symptom resolution and recurrence and VCS testing, and the proof is robust and tight.

More rigorous proof can also be obtained with MRI technology. The use of MRI to quantify the volume of various regions of the brain shows that the brain shrinks with CIRS in some regions, and they then recover with treatment. This is called NeuroQuant and can be performed in just a few minutes. Once Genomics become widely available and part of consensual medicine, the field of biotoxin illness will be mature.

SEQUENTIAL activation of innate immune elements (SAIIE)

- After CSM use has ended, draw the following labs: C4a, TGF beta-1, MMP-9, 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 and obtain labs.
- Restart medications. Record symptom scores, and VCS. Labs get scored by office.

VIII Sequential Activation of Innate Immune Elements (SAIIE) [37]

	BASELINE	DAY 1	DAY 2	DAY 3
VCS	-	Deceasing	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 MMP-9 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

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 β-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 β-1

[37] http://www.tequestafamilypractice.com/articles/CIRS_Overview.htm#SAIIE

B) Gene activation following receptor resistance (leptin)
C) Bottom line; this is absolute proof of causation. Koch's Hypothesis for Biotoxin Illness
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

The saying goes: progress in medicine follows three stages: First you are ridiculed, then resisted violently, then taken for granted. Be prepared.

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: new therapies will emerge. New diagnostic methods will be refined. The implications of Genomics are just starting to be decisive. It is an exciting time to be a scientist/physician.

Adequate standards of remediation are another problem many patients frequently encounter. The real estate market will adjust and drive stricter controls. The current method of most so-called mold experts is to sample for spores and do a cursory walk through. Anyone with more than 6 months of CIRS experience will find dismayed clients who have engaged such experts and now are confronted with abnormal lab tests, continued illness and an ERMI score of 12. A home with such a score will soon be

unsellable, once the SAIIE program has been implemented a few times in the courts and shown to be repeatedly valid.

Thanks to the recent Consensus Statement on the investigation and remediation of water-damaged buildings in case of CIRS-WDB[38] guidelines now exist for patients, practitioners, and indoor air practitioners to follow in cases of those patients with a known CIRS diagnosis. It is up to the community of CIRS practitioners to carry forward the rigor of this intellectual pursuit.

It will take some time before critical mass is reached and this diagnosis and treatment protocol makes its way into everyday clinical practice. My goal is to live long enough to see this protocol be a major proportion of primary care practice as physicians learn the true art of medicine. The paradigm shift of thinking involved with biotoxin illness will be as meaningful to medicine as the introduction of antibiotics – as we learn to resolve the risks for diseases to which biotoxin vulnerability plays a meaningful role: Alzheimer's, asthma, ADHA, CFS, Fibromyalgia, Autoimmune, Pulmonary Hypertension, chronic pain, uncontrolled obesity,……. This list will be added to in the years following.

And then we will have the satisfaction of being taken for granted. And our clients will be well.

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[38] Schwartz L, Weatherman G, Schrantz M, Spates W, Charlton J, Berndtson K, Shoemaker R. Indoor Environmental Professional Panel of Surviving Mold – Consensus Statement