

Understanding Chronic Inflammatory Response Syndrome (CIRS)

Definition, Diagnosis, and Treatment

By Natasha Thomas, M.D.

What is CIRS? A Deeper Look at Biotoxins

Chronic Inflammatory Response Syndrome (CIRS), also known as biotoxin illness, describes a group of symptoms, lab findings, and targeted test results associated with biotoxin exposure, especially in genetically-susceptible people.

Most of what we know about biotoxin illness is the result of practice-based studies done by physician and researcher, Dr. Ritchie Shoemaker. His research dates back to 1997. When practicing family medicine in the rural coastal town of Pocomoke, Maryland, he linked a previously undefined illness to a toxin produced by a fish-killing dinoflagellate known as Pfiesteria. Since then, Dr. Shoemaker has linked this same kind of illness to toxins from water-damaged buildings, as well as toxins associated with tick-borne microbes. Over time, Dr. Shoemaker developed a thorough description of this illness and called it Chronic Inflammatory Response Syndrome (CIRS). Through his practice-based research, he also developed methods to diagnose and treat this illness, bringing back health to thousands of patients worldwide.

Exposure to Biotoxins

Routes of exposure may include:

- **Inhalation in WDB:** Occurs when a patient is exposed to biotoxins through breathing while inside a water-damaged building (WDB). WDB can harbor a dangerous mix of various chemicals, mold, bacteria, and inflammagens that together create a “biochemical stew,” which causes illness. CIRS is not caused by one particular element of this biochemical stew, but rather the combination of these things causing

Components of biochemical stew in WDB:

Fungi (mold and its fragments)

Bacteria (and its fragments)

Volatile Organic Compounds

Endotoxins

Actinomycetes

See Appendix 1 for additional details

multi-system inflammation. Shoemaker estimates that 80 percent of CIRS cases are caused by repeated exposure to water-damaged buildings. These cases are designated as CIRS-WDB.

- **Tick or Spider Bite:** Patients may not always realize they have been bitten by a tick, though the infections ticks carry can include Lyme disease (*Borrelia burgdorferi*) and Babesiosis (*Babesia microti*), among others. The bite of the recluse spider species may also cause biotoxin illness.
- **Ingestion:** Patients who have eaten reef fish contaminated with dinoflagellate algae (that produces Ciguatera toxin) may develop an illness. Exposure to the Ciguatera toxin occurs when eating reef fish that have eaten smaller fish that consumed the toxin producing dinoflagellate.
- **Direct Contact with Contaminated Water:** Patients may be exposed through direct contact with water contaminated by toxins in areas of fish kills such as *Pfiesteria* and Cyanobacteria, including inhalation of airborne or aerosolized toxins from this source.

Most biotoxins have the structural form of ionophore or amphipath. These are extremely small molecules capable of moving from cell to cell through cell membranes without being carried in the bloodstream. This ability of biotoxins to pass through cell membranes with ease means they are difficult or impossible to find in standard blood tests.

How do biotoxins get into the body and why doesn't the immune system take care of them? As mentioned, biotoxins can enter the human body through inhalation, ingestion, tick or spider bites, and direct contact with contaminated water sources. The biotoxins can cause acute illness, but for people who are genetically susceptible, they can cause lasting chronic illness. For many people, biotoxins are recognized by the immune system correctly, broken down, and removed from the body. However, genetically-susceptible people have immune systems that do not recognize the biotoxins and fail to remove them, leaving the biotoxins circulating in the body indefinitely, and causing inflammation throughout the body.

Diagnosing CIRIS

Diagnosing CIRIS and biotoxin-related illness can be difficult, if not impossible without understanding biotoxins and how they cause damage in the body.

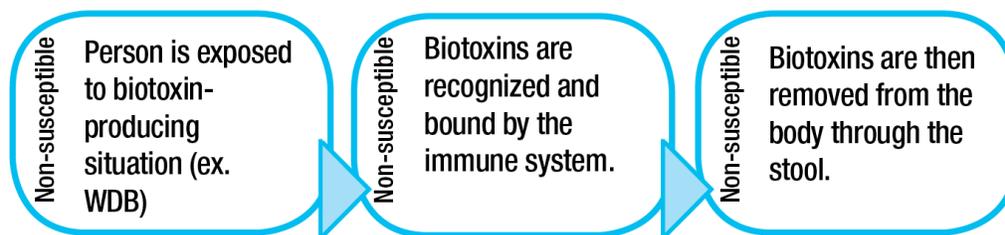


Figure 1. Actions of biotoxins in the body of a non-genetically-susceptible person

Figure 1 (above) shows the way biotoxins impact a person who is not genetically susceptible to developing biotoxin illness. In this situation, the immune system correctly recognizes the biotoxin, leading to antibody production and removal from the body. Figure 2 shows the way biotoxins impact a person who does have genetic susceptibility. The immune system is unable to correctly identify the biotoxin, bind it, and remove it. This allows the biotoxin to recirculate throughout multiple body systems repeatedly, causing damage along the way. In this case, the biotoxin can remain in the body indefinitely.

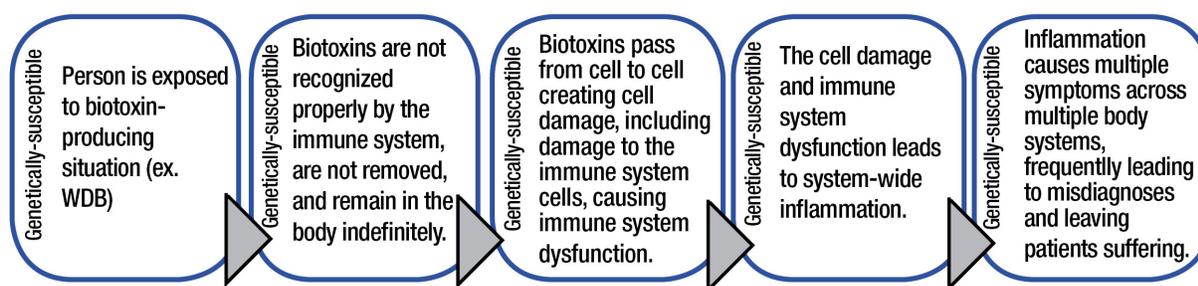


Figure 2. Actions of biotoxins in the body of a genetically-susceptible person

Due to the way biotoxins cause illness and the way they move throughout the body and its various systems, more common testing methods like basic blood tests are rarely helpful. What's more, the microbes or irritants that released the biotoxins into the body could already be eliminated from one's system. This is where evidence-based medicine and testing comes in. To look for biotoxins and

make a diagnosis in cases of CIRS and biotoxin-related illness, we have to look for the evidence of the damage the biotoxins cause in various body systems, particularly the immune system.

In many other types of illness, doctors can test for the pathogen or disease-causing organism itself. In suspected cases of CIRS, the biotoxins transfer from cell to cell through cell membranes so they aren't present in the serum of the blood (that's why standard blood tests are rarely helpful in these cases), and makes finding the damage biotoxins cause the key to the diagnosis. There is a comprehensive set of tests we use to find the evidence we need to determine that biotoxins are involved. However, first we must start with a complete medical history and physical exam. It is essential to document all of the symptoms the patient is experiencing, and medical history along with any history of known exposure to common sources of biotoxin-producing elements. After collecting all of this information, we move onto a comprehensive list of tests.

Symptom Cluster Analysis: Understanding CIRS Symptoms

While CIRS symptoms may appear random at first, Dr. Shoemaker's statistical analysis revealed that symptoms do have commonalities that allow them to be broken into 13 distinct clusters as shown below. Each block below in Figure 3 lists a unique cluster of symptoms.

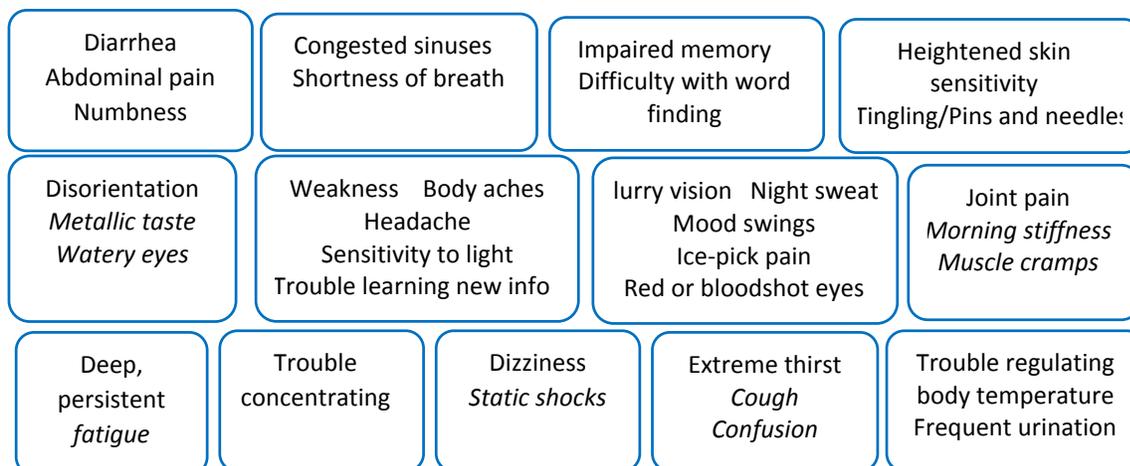


Figure 3. The 13 unique symptom clusters used in symptom cluster analysis

Patients experiencing CIRS are frequently misdiagnosed with other debilitating illnesses, often leaving a patient suffering for years, going from doctor to doctor in search of a correct diagnosis and treatment. Common misdiagnoses include:

- Chronic Fatigue Syndrome (CFS)
- Fibromyalgia
- Depression and Anxiety
- Allergies
- Somatization (ex. Hypochondria)
- Attention Deficit Hyperactivity Disorder (ADD/ADHD)
- Irritable Bowel Syndrome (IBS)
- Post-traumatic Stress Disorder (PTSD)

Testing for CIRS: Visual, Genetic, MRI, and Biomarker Testing

Visual Contrast Sensitivity (VCS) Testing

Biotoxins and the inflammatory response they produce have been shown to cause nerve dysfunction, leading to a variety of neurological symptoms, including diminished Visual Contrast Sensitivity (ability to detect visual

patterns). According to Dr. Shoemaker's research, this decrease in VCS is due to a

reduction in the velocity of flow of red blood cells reaching structures in the eye responsible for sending visual information through the optic nerve to the brain.

During a VCS test, the patient is shown a series of images specifically created to measure the person's ability to detect visual patterns. A person experiencing a biotoxin-related illness will perform poorly during this test. The VCS test is highly accurate and supports biotoxin-related illness diagnosis in 92 percent of affected people with only 8 percent presenting as false negative. The VCS test is performed at the initial visit and is repeated at each visit after to assess how well the patient is responding to the treatment.

Neurotoxin

Biotoxins that impact nerves and impair neurologic function are also called neurotoxins.

After making a clinical diagnosis of biotoxin illness and performing VCS testing, we move on to a set of specific lab tests to provide additional information that confirms diagnosis and helps gauge the severity of the illness.

Genetic Testing: Human Leukocyte Antigen (HLA) Test

To determine if a patient is genetically susceptible, we use HLA DR/DQ genetic testing. The Human Leukocyte Antigen (HLA) system is a set of genes on chromosome 6 that encode for proteins on the surface of cells that are responsible for regulation of the immune system in humans. These proteins help our immune system distinguish between our own cells and foreign cells.

The HLA type and related immune response are a key part to whether or not a person goes on to develop the inflammation that leads to CIRS. The immune system is comprised of the innate immune system (the immunity we're born with) and the adaptive immune system (immunity we develop after birth).

The innate immune system is non-specific and acts as the first line of defense by identifying antigens (foreign proteins) to signal the adaptive immune system by releasing high levels of inflammatory molecules (such as cytokines), split products of complement, and TGF beta-1. Unlike antibodies, the inflammatory molecules do not have a specific target and cannot remove biotoxins. The adaptive immune system provides long-term immunity by creating immunological memory after the initial exposure to specific pathogen (such as a biotoxin).

In susceptible people, the innate immune system "sees" the biotoxins and keeps signaling to the adaptive immune system. However, the adaptive immune system cannot "see" the biotoxins and does not make proper antibodies against them. The persistent carriage of biotoxins continues to trigger the innate immune system. In turn, the overactive innate immune system creates high levels of inflammation which leads to dysregulation of multiple systems in the body and development of CIRS.

Dr. Shoemaker's review of international gene registries, matched by case-controlled studies, revealed that 24 percent of the population is "mold susceptible" due to their HLA haplotype, putting them at risk of developing a chronic biotoxin-related illness from exposure to water-damaged buildings. Dr. Shoemaker also noted that 21 percent of the population is "Lyme susceptible,"

making these patients less likely to respond to antibiotics for Lyme disease and more likely to develop chronic illness in response to the biotoxins present after contracting Lyme disease (“Post-Lyme Syndrome”). Depending on their individual HLA gene combinations, a person may be susceptible to one or more biotoxin-related illness. For instance, one person could be “mold susceptible,” while another person is “Lyme susceptible,” and another is “multi-susceptible.”

Biomarker Testing: Transforming Growth Factor beta-1 (TGF beta-1)

TGF beta-1 is a molecule that plays an important role in controlling the immune system by producing or suppressing inflammation. Elevated levels of TGF beta-1 indicate the occurrence of a current overactive immune response. For instance, people with asthma, multiple sclerosis, and various autoimmune diseases often have elevated levels of TGF beta-1. These elevated levels of TGF beta-1 damage normal T-regulatory cell functions that control or prevent autoimmunity, leaving the person at risk for autoimmune-related illness. Lab Values: Transforming Growth Factor beta-1, normal range < 2382 pg/ml.

Biomarker Testing: C4a

C4a is a biomarker involved in activating a specific process of the innate immune system called a complement cascade and is useful in evaluating immune response in people with exposure to water-damaged buildings (WDB). By activating immune cells called mast cells and basophils, increasing smooth muscle contraction (smooth muscle is found in blood vessels and intestines), increasing vascular permeability, and causing mitochondrial dysfunction, elevated C4a levels can lead to

Common Terms and Definitions

Autoimmunity – An immune response where the body incorrectly classifies self cells as non-self, causing the immune system to attack the body’s own cells and tissues.

Biomarker – Measurable substance or characteristic that can show if various processes in the body are normal or dysfunctional.

Cytokines – Cell-signaling molecules that help direct immune system cells and processes.

Mast Cells and Basophils – Types of immune system cells that play a role in allergies and also in inflammation and autoimmunity.

Mitochondria(l) – A structure within a cell that manages cell metabolism and produces energy the cell needs to function properly.

Permeability – Degree to which body tissues like blood vessels and intestines allow substances or organisms to pass through the cell junctions of the tissue into or out of that body system.

T-Regulatory Cells – A type of immune cell that helps control autoimmune response in the body.

common CIRS symptoms like breathing difficulty, fatigue, and dysfunction in thinking and memory processes (cognitive ability). Dr. Shoemaker's research shows that patients with high C4a levels have decreased blood flow into the small vessels called capillaries, which impacts the brain causing decrease in the patient's cognitive ability. Lab Values: C4a normal range is 0-2830 ng/ml.

Biomarker Testing: Matrix Metalloproteinase 9 (MMP-9)

Matrix Metalloproteinase 9 (MMP-9) is an enzyme involved in the breakdown of cell membranes in the blood vessel walls which allows inflammatory compounds to move out of the blood through vessel walls and into organs and tissues such as the lung, brain, muscles, joints, and peripheral nerves. In CIRS, cytokines trigger certain types of white blood cells to release MMP-9 into the bloodstream, increasing the amount of inflammatory compounds moving into tissues and causing widespread inflammation. Because cytokine activity increases MMP-9 production, MMP-9 is an excellent marker of "hidden" cytokine production. Lab Results: MMP-9 normal range is 85-332 ng/ml.

Biomarker Testing: Leptin

Leptin is known as a "satiety hormone" and is made by fat cells to help regulate energy balance by hindering hunger. High levels of leptin increase the amount of fat stored in the body, causing weight gain. In biotoxin-related illness, cytokines attach to leptin receptors in the hypothalamus, interfering with leptin signaling and creating leptin resistance. Weight gain due to leptin resistance is common in CIRS patients. Lab Results: Leptin normal range: men 0.5-13.8 ng/ml; women 1.1-27.5 ng/ml.

Biomarker Testing: Vascular Endothelial Growth Factor (VEGF)

Vascular Endothelial Growth Factor is a signal protein produced by cells that stimulates growth of new blood vessels in order to supply oxygen to the tissues when blood circulation is inadequate. In a healthy body, decreased blood flow in capillaries and resulting low oxygen supply will trigger the release of Hypoxia-Inducible Factor (HIF). HIF stimulates the production of VEGF and erythropoietin (EPO). VEGF increases blood flow by creating new blood vessels, while EPO increases production of red blood cells; both help to increase oxygen supply to the cells. In CIRS, VEGF is suppressed due to high cytokine levels which causes poor oxygen supply to the tissues, resulting in muscle cramping and post-

exertional fatigue (a period of extreme exhaustion after exercise or strenuous physical activity). Lab Results: VEGF normal range is 31-86 pg/ml.

Biomarker Testing: Anti-Gliadin Antibody (AGA)

Anti-Gliadin Antibodies (AGA) are produced in response to gliadin found in gluten. Gluten is a protein found in certain grains like wheat, barley, and rye. AGA is one of the antibodies that contribute to celiac disease. Gluten is made up of approximately 45 percent gliadin and 55 percent glutenins. The body breaks down gliadin into chains of amino acids called peptides. In order to use these peptides, our intestinal cells, tightly sealed like an interlocking gateway, have to pull apart to form openings to let the peptide go through. For healthy people, these gateway openings close immediately after allowing the peptides through. In certain CIRS patients and patients with celiac disease, the gliadin peptides cause an inflammatory and immune reaction that prevents the openings between the intestinal cells from closing properly. In this case, strictly following a gluten-free diet is crucial. Lab Results: AGA normal range is 0-19 units.

Celiac Disease

Celiac disease is an autoimmune illness in which the body launches an immune attack in the small intestine and other areas of the body when gluten is ingested, damaging the body's ability to absorb nutrients from food and contributing to overall inflammation in the body.

Biomarker Testing: Melanocyte Stimulating Hormone (MSH)

MSH is a hormone made in the pituitary gland that plays a crucial role in regulating many other hormones, inflammation responses, and defenses against foreign microbes. Leptin influences MSH production, however, during an inflammatory response where excess cytokines interfere with leptin receptors, MSH levels drop. Deficiency of MSH is very common in patients with CIRS and often does not return to normal levels despite treatment. Low MSH increases susceptibility to mold illness, chronic fatigue, chronic pain (from decreased endorphin production), insomnia (from decreased melatonin production), sexual dysfunction, and other hormonal abnormalities. In healthy people, a rise in leptin levels would trigger the brain to create more MSH. In a patient with biotoxin-related illness, this process fails when a rise in leptin levels doesn't result in the creation of more MSH due to cytokine interference with leptin receptors. When

MSH levels don't rise, the body produces more leptin, leading to leptin resistance and causing weight gain and protein wasting. In addition, MSH plays a key role in closing the intestinal gateway openings created in the processing of gliadin peptides discussed in the previous section and preventing inflammation. Low MSH levels allow inflammation to rise out of control and cause those intestinal gateways to remain open, leading to a condition commonly known as leaky gut (gut permeability). Additionally, 80 percent of patients with low MSH have MARCoNS (Multiple Antibiotic Resistant Coagulase Negative Staph). MARCoNS is detected through an API-Staph culture of nasal bacteria. MARCoNS secrete toxins that decrease MSH, making it critical to treat MARCoNS to bring MSH levels back to normal. Lab Results: MSH normal range is 35-81 pg/ml.

Biomarker Testing: Anti-Diuretic Hormone (ADH) and Osmolality

Anti-Diuretic Hormone (ADH), also known as vasopressin, is a hormone made in the hypothalamus that controls the body's ability to hold on to free water. Osmolality is the concentration of all chemical particles (such as sodium, potassium, and calcium) that are in the fluid part of blood (serum). In Biotoxin illness patients, a lack of regulation of salt and water balance is apparent when ADH is low (or too high) but osmolality is relatively high (or too low). Affected patients will experience frequent urination, dehydration, excessive thirst, and dehydration-related migraine headaches. As the sodium (salt) level in the blood rises because of a lack of free water, the patient's sweat will also contain more salt. The electrical properties of the increased salt create a battery-like effect that increases static electrical shocks. Lab Results: For ADH normal range is 1.0-13.3 pg/ml; For Osmolality normal range is 278-305 mOsm/kg.

Biomarker Testing: Adrenocorticotrophic Hormone (ACTH) and Cortisol

Adrenocorticotrophic Hormone (ACTH) is a very important regulatory hormone released by the pituitary gland to signal the adrenal glands to produce cortisol. Cortisol is a steroid hormone produced by adrenal glands and is involved in several processes in the body, including creation of new glucose (blood sugar), regulating glycogen storage in the liver, immune regulation, and the physical response to stress commonly known as "fight or flight." Normally, cortisol is released in a regular pattern – levels rise in the early morning (peaking around 8

am) and drop in the evening. Chronic stress caused by inflammation or prolonged illness causes cortisol production to become irregular and disrupts the body's ability to deal with normal daily stressors such as sleep disturbance, blood sugar imbalances, or emotional stress. Usually, when cortisol levels rise or drop, a signal is sent to the hypothalamus and then to the pituitary gland to adjust the production of ACTH. In CIRS patients, this feedback mechanism is disrupted due to hormone dysregulation, resulting in symptoms such as daytime fatigue, nighttime insomnia, dizziness, and low blood sugar. Lab Results: For ACTH normal range is 8-37 pg/ml; for Cortisol normal ranges are - a.m. 4.3-22.4 and p.m. 3.1-16.7 mcg/dl.

Biomarker Testing: Plasminogen Activator Inhibitor-1 (PAI-1), Anti-cardiolipin Antibodies (ACA), and Von Willebrand Factor

Plasminogen Activator Inhibitor-1 (PAI-1), Anti-cardiolipin Antibodies (ACA), and Von Willebrand Factor are biomarkers for abnormal bleeding conditions. All three of these biomarkers play a role in blood clotting. Inflammatory conditions such as CIRS can cause elevated PAI-1, which can increase the formation of blood clots as well as fibrosis (abnormal formation of connective tissue). ACA are antibodies that target our own tissues by interfering with the phospholipid proteins in cell membranes. ACA are elevated in connective tissue disorders such as scleroderma and lupus, and are associated with first trimester miscarriages. Together, the combination of PAI-1 and ACA strongly increases the risk of stroke, heart attack, and deep vein thrombosis (DVT). CIRS patients can also develop a type of acquired Von Willebrand Syndrome, which prevents blood from clotting properly, leading to symptoms of frequent or heavy nosebleeds and heavy periods in women.

Biomarker Testing: Vasoactive Intestinal Peptide (VIP)

Vasoactive Intestinal Peptide (VIP) is a very important neuropeptide produced in many places in the body including the gut, pancreas, and the hypothalamus in the brain. Like MSH, VIP helps regulate inflammation throughout the body. VIP also helps regulate blood flow and exercise response of the pulmonary artery (the artery that moves blood from the heart to the lungs to pick up oxygen). In patients with low VIP levels, pressure in the pulmonary artery builds during exercise causing shortness of breath and difficulty with exercise. VIP replacement

is the important last step of Dr. Shoemaker's protocol, restoring health for chronically ill patients. Lab Results: VIP normal range is 23-63 pg/ml.

MRI Testing with NeuroQuant® Analysis

A newer tool in the diagnostic toolbox is an FDA-cleared software program called NeuroQuant that analyzes standard MRI brain scans for structural damage and shrinking of brain volume (atrophy). The software uses information gathered from thousands of brain scans to find these areas of damage with greater accuracy than what is often possible to find with analysis done by a radiologist. Damage to specific structures in the brain can be linked to specific biotoxins. For example, biotoxins from mold have been found to impact different structures in the brain than biotoxins from Lyme disease. NeuroQuant is a promising new avenue in the diagnosis of biotoxin-related illnesses.

The Shoemaker Protocol: Treatment for Biotoxin Illness

Step 1: Removal from Exposure

The first and most important step is for the patient to be removed from the source of exposure! The other steps in the protocol will not be effective if the patient is experiencing repeated exposure. Water-damaged buildings and the biochemical stew found inside are the most common source of exposure for CIRS patients. (For additional information on the biochemical stew found in water-damaged buildings, see Appendix 1).

NIOSH (National Institute for Occupational Safety and Health) estimates that up to 50 percent of all American buildings have water damage. Sources of water damage can come from slow leaking pipes, poor fitting drains, poorly ventilated crawl spaces, water intrusion in the basement and roof leaks, to name just a few.

To determine whether your home or workplace has been water damaged, testing by an accredited lab like Mycometrics is required. Mycometrics uses MSQPCR (Mold-Specific Quantitative Polymerase Chain Reaction) analysis, also known as Environmental Relative Moldiness Index (ERMI) or its derivative HERTSMI-2 (Health Effects Roster of Type Specific [Formers] of Mycotoxins and

Inflamagens, second version). ERMI tests for more than thirty types of mold while HERTSMI-2 tests for the five types of mold most commonly involved in CIRS.

If ERMI or HERTSMI-2 tests indicate water damage has occurred, an indoor air quality specialist (IAQ) should be consulted in order to diagnose the cause of water damage and help ensure proper remediation.

Step 2: Removal of Biotoxins

CSM (cholestyramine) is a non-absorbable polymer resin that has been FDA-approved for use in lowering cholesterol. Due to its chemical structure, CSM has a net positive electrical charge that attracts and binds negatively charged biotoxins.

In CIRS patients, when the liver secretes bile during digestion, the bile contains some of the biotoxins. Before starting CSM, the biotoxins in the bile are reabsorbed in the intestine and cycled back to the liver during the normal bile circulation process. Once the patient has started taking CSM, it binds the biotoxins as described above and then carries them out through the stool, stopping them from being reabsorbed and cycled back to the liver. Over time, CSM removes more and more biotoxins from the body. CSM must be taken on an empty stomach or between meals. The typical dose of CSM is 4 mg four times daily. CSM can cause constipation, bloating, acid reflux, and heartburn. Supplementation with magnesium can help ease the symptoms of constipation.

In patients who are unable to tolerate CSM due to its gastrointestinal side effects, Welchol might be used. Like CSM, Welchol is a bile acid binding resin, but it has fewer side effects. Welchol is less effective than CSM because it only has 25% of the binding sites found in CSM. Hence, it will take longer to normalize lab values and symptoms when treating with Welchol compared to CSM.

In his research, Dr. Shoemaker tried other binding agents such as cholestipol, charcoal, clay such as bentonite, chitosan, and pectin. Unfortunately, he has not seen the same change in lab values using these binders.

Treatment with CSM or Welchol must be continued for a minimum of 30 days and until the patient's VCS score has normalized.

Step 3: Treat MARCoNS

After the first month of treatment with CSM, patients whose nasal culture tested positive for MARCoNS (Multiple Antibiotic Resistant Coagulase Negative Staph) need to be treated until colonization is gone. MARCoNS secrete toxins that lower MSH (Melanocyte Stimulating Hormone), produce substances that destroy red blood cells (hemolysins), and raise cytokine levels. A nasal spray called BEG (Bactroban/EDTA/Gentamicin) is used to destroy MARCoNS. Bactroban and Gentamicin work together against the MARCoNS while EDTA dissolves the protective biofilm that the bacteria produces. Biofilm is a slime-like substance created by bacteria to help them attach to a surface, stick to each other to form colonies, and to protect themselves from immune attack or antibiotics. The biofilm created by the MARCoNS bacteria is part of what creates its antibiotic resistance. When first beginning treatment for MARCoNS, some patients may feel their symptoms get worse in the beginning. The reason is because as the biofilm is broken down, the encased bacteria is exposed along with its toxins, resulting in a temporary increase in toxin levels.

MARCoNS treatment continues for 30 days, followed by a new nasal culture test to make sure the MARCoNS colonization is gone. If the culture is still positive for MARCoNS after the first 30 days of treatment, other sources must be investigated. A few sources of continued MARCoNS exposure include the family dog,

infected root canal teeth, or a deep-seated jawbone cavitation (weakened area of the jawbone that harbors bacteria, eventually killing the bone tissue and leaving enclosed spaces of decomposing bone and teeming with bacteria). A biological dentist will often need to be consulted regarding any suspected infections in root canal teeth or potential cavitations.

Step 4: Correction of Anti-Gliadin Antibodies

In patients with biotoxin illness who have low MSH, there is an increased risk of inflammation and autoimmune disease. If those patients also have high levels of Anti-Gliadin Antibodies, they need to remain on a gluten-free diet for at least three months, potentially longer. These patients should also be evaluated for celiac disease.

MARCoNS and Your Dog

In Dr. Shoemaker's research, he discovered that dogs can also be carriers of MARCoNS. Cats, however, are not MARCoNS carriers and are unaffected by it.

Step 5: Correction of Androgens

Patients with biotoxin illness often develop an imbalance of their androgen-based hormones, such as dehydroepiandrosterone (DHEA) and testosterone. Current research suggests this imbalance could be caused by an increase in an enzyme called aromatase, which changes testosterone to estradiol (a form of estrogen). Recommended treatment would be supplementation with high quality DHEA or human chorionic gonadotrophin (HCG). Vasoactive Intestinal Peptide (VIP) treatment could be considered at this step to stabilize the aromatase enzyme.

Step 6: Correction of ADH/Osmolality Dysregulation

Desmopressin (DDAVP) is a synthetic form of ADH (Anti-diuretic Hormone) that helps correct water loss and dehydration for patients with biotoxin illness. DDAVP is available as a nasal spray or tablet medication. Blood serum osmolality (concentration of chemicals in blood serum or plasma) and blood sodium levels need to be monitored with extreme caution while on this medication.

Step 7: Correct MMP and VEGF

The treatment to correct MMP and VEGF depends on the patient's leptin level. If the patient's leptin level is less than 7, supplementing with high dose Omega-3 fatty acids (2.4 gm EPA and 1.8 gm of DHA) works to correct the imbalance. If the patient's leptin level is higher than 7, the patient may be prescribed Actos (45 mg once daily) for 30 days. Actos may cause low blood sugar and also has a black box warning of increased risk of bladder cancer with long-term use.

Patients must strictly follow a low amylose diet during this step of the protocol. Amylose is a type of starch made of long chains of glucose (sugar). The diet calls for avoiding many starches and forms of simple sugars. See Appendix 2 for a list of foods to eliminate while on a low amylose diet.

Step 8: Correct C3a

For patients with high C3a levels, the immune system is being triggered by cell membranes in the presence of microbes that cause Lyme disease. The primary Lyme infection needs to be treated with antibiotics as appropriate before moving to the next step in the protocol. The patient will also be prescribed a high dose cholesterol medication (often Zocor 80 mg) along with a CoQ10 supplement.

Step 9: Correct C4a

C4a is biomarker that shows how severe the patient's case of CIRS is. Treatment with erythropoietin (Procrit) reduces C4a. Procrit has a black box warning due to increased risk of blood clots. The decision whether or not to use Procrit is based on individual patient assessment and requires close monitoring, extreme caution, and the patient's informed consent. If Procrit cannot be used, then VIP should be considered.

Step 10: Correct TGF beta-1

Cozaar (Losartan) can be used to lower TGF-beta-1 and decrease the risk of autoimmune response and illness. Patients with low blood pressure who cannot take Cozaar should be considered for VIP treatment at this step instead.

Step 11: Vasoactive Intestinal Peptide (VIP)

Vasoactive intestinal peptide (VIP) is a 28 amino acid regulatory neuropeptide with many beneficial physiological effects. In his research, Dr. Shoemaker noted low levels of VIP in 98 percent of the patients with biotoxin illness. In contrast, only 10 percent of control patients had low VIP levels.

VIP restores regulation of the inflammatory processes that have gone awry in biotoxin illness. It also normalizes genomics, down regulates aromatase (enzyme that converts testosterone to estrogen), lessens chemical sensitivities, releases endorphins, and reduces the "sicker-quicker" phenomenon. The "sicker-quicker" phenomenon occurs in some patients following re-exposure to water-damaged buildings. VIP is thought to be involved in down regulating C4a production, which may be the key to reducing the "sicker-quicker" phenomenon.

VIP treatment is the very last step in the Shoemaker protocol. By this time, most patients already feel much better but some will require this last step in the protocol. Before starting VIP treatment, all of the prior steps of the protocol must have been completed successfully. Also, it is critical to make sure the VCS test is normal, MARCoNS culture is negative, and in the case of water-damaged buildings, that the source of exposure has been successfully remediated (ERMI result is less than 2 or HERTSMI-2 result is less than 10). If all the steps of the protocol are not completed and if there is ongoing exposure to WDB, the VIP treatment will not work.

If all of the above conditions are met, VIP treatment can begin. VIP administration should be followed by the prescribing doctor. First dose of VIP should be administered in the doctor's office. This part of the protocol includes measuring labs (lipase, TGF Beta 1, C4a) right before VIP administration and 15 minutes after. Labs should be repeated in 30 days. If there is an elevation in the inflammatory markers after VIP administration, this indicates there is an ongoing exposure to biotoxins. If lipase increases or the patient develops abdominal pain, VIP treatment should be stopped.

Dr. Shoemaker and the Shoemaker Protocol

Dr. Ritchie Shoemaker is a pioneer in the research and discovery of biotoxin illness (Chronic Inflammatory Response Syndrome) and the impacts of exposure to water-damaged buildings.

In the time since his first breakthrough in the area of toxin-related illnesses in 1997, he has continued to research, study, test, and develop treatment options for patients commonly misdiagnosed with a long list of illnesses and help them recover. He has published eight books, produced dozens of medical papers in collaboration with other researchers from all over the world, emphasized the concept of evidence-based medicine, and through that evidence created a unique treatment protocol that has helped countless patients recover their health.

Despite being technically retired, Dr. Shoemaker continues to research the connection between biotoxins and genetics, as well as diagnostic and treatment options for biotoxin-related illnesses. Currently, Dr. Shoemaker is using PAX gene testing to research the role of genomics for diagnosis and treatment of biotoxin illness. He is also continuing his research with NeuroQuant analysis of MRI brain scans as a diagnostic tool for identifying specific biotoxins and their impacts on the brain. His persistence and dedication in raising awareness of biotoxin-related illnesses along with their sources and treatments has benefited the lives of countless patients across the globe and will undoubtedly change the course of medicine in the future.

APPENDISES

APPENDIX 1

Biochemical Stew

The components of the “biochemical stew” found in water-damaged buildings can be a complex mixture of a variety of the following:

Fungi-related	Mold, Conidia, Hyphal Fragments, Spirocyclic Drimanes, Mannans, <i>Aspergillus penicilloides</i> , <i>Aspergillus versicolor</i> , <i>Wallemia sebi</i> , <i>Stachybotrys chartarum</i> , <i>Chaetomium globosum</i>
Bacteria-related	Gram-negative bacteria, Gram-positive bacteria, Actinomycetes, Mycobacteria, Mycoplasma, Actinobacteria, Chlamydia, Nocardia, Hemolysins
Inflamagens	Bioaerosols (organic dust), Beta Glucans, Inorganic Xenobiotics, Siderophores
VOCs	Microbial Volatile Organic Compounds, Chemical Volatile Organic Compounds, Building Material Volatile Organic Compounds
Particulates	Coarse Particulates, Fine Particulates, Ultrafine Particulates, Nano-sized Particulates
Other	Cell Fragments, Cell Wall Components, Endotoxins, Proteinases, Chitinases, Inflamagens, Lipopolysaccharides

APPENDIX 2

Dr. Shoemaker’s No-Amylose Diet

The list of foods below should be completely eliminated while the patient is on Dr. Shoemaker’s No-Amylose Diet during Step 7 of the Shoemaker Protocol.

Foods to Eliminate:

- Bananas
- Grains: Wheat, Rice, Rye, Oat, Barley, and Millet
- Hidden Sugars: Glucose, Dextrose, Sucrose, Maltodextrin, Sugar, Corn Syrup, High Fructose Corn Syrup
- All Foods Grown Underground: Beet, Carrot, Parsnip, Radish, Potato, Sweet Potato, Yam, Peanuts (Exception: Garlic and Onions are allowed.)
- Processed Foods: Fast Food, Soft Drinks, Commercial Fruit Juic

RESOURCES

1. Berndtson K, McMahon S, Ackerley M, Rapaport S, Gupta S, Shoemaker RC. Medically sound investigation and remediation of water-damaged buildings in cases of CIRS-WDB: Consensus Statement Part 1. *Center for Research on Biotoxin Associated Illness*. 2015.
2. Berry Y. A Physician's Guide to Understanding and Treating Biotoxin Illness: Based on the work of Ritchie Shoemaker, M.D. Presentation: April 3, 2014.
3. Clayton EW, Alegria M, Bateman L, Chu L, Cleeland CS, Diamond B, Ganiats T, Keller B, Klimas N, Lerner AM, Mulrow C, Natelson B, Rowe P, Shalanski M. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness: Report Guide for Clinicians. *Institute of Medicine*. 2015.
4. Greenblatt JM, Brogan K. *Integrative Therapies for Depression: Redefining Models for Assessment, Treatment, and Prevention*. CRC Press: Boca Raton FL, 2016.
5. Kane PC, Foster JS, Kane E. *The Detoxx Book: Detoxification of Biotoxins in Neurotoxic Syndromes – Physician's Guide*. BodyBio: Millville NJ, 2009.
6. McMahon SW, Shoemaker RC, Ryan JC. Reduction in Forebrain Parenchymal and Cortical Grey Matter Swelling across Treatment Groups in Patients with Inflammatory Illness Acquired Following Exposure to Water-Damaged Buildings. *Journal of Neuroscience and Clinical Research*. 2016;1:1.
7. Shoemaker RC. *Desperation Medicine*. Gateway Press: Baltimore MD, 2001.
8. Shoemaker RC, Schaller J, Schmidt P. *Mold Warriors: Fighting America's Hidden Health Threat*. Gateway Press: Baltimore MD, 2005.
9. Shoemaker RC, Hudnell HK, House DE, van Kampen A, Pakes GE. Atovaquone Plus Cholestyramine in Patients Coinfected with *Babesia microti* and *Borrelia burgdorferi* Refractory to Other Treatment. *Advances in Therapy*. Jan/Feb 2006;23:1.

10. Shoemaker RC. *Surviving Mold: Life in the Era of Dangerous Buildings*. Otter Bay Books: Baltimore MD, 2010.
11. Shoemaker RC, Mark L, McMahon S, Thrasher J, Grimes C. Research committee report on diagnosis and treatment of chronic inflammatory response syndrome caused by exposure to the interior environment of water-damaged buildings. *Policyholders of America*. 2010 July 27:1-161.
12. Shoemaker RC, House D, Ryan JC. Structural brain abnormalities in patients with inflammatory illness acquired following exposure to water-damaged buildings: a volumetric MRI study using NeuroQuant®. *Neurotoxicology and Teratology*. 2014 Sep-Oct;45:18-26.