DIAGNOSIS AND TREATMENT OF CHRONIC INFLAMMATORY RESPONSE SYNDROME-CIRS

Karen D. Johnson M.D., ABOIM, IFMCP
www.karendjohnsonmd.com
503-371-3232

Have you been sick for a long time without any improvement in spite of multiple medical visits to different clinicians and a multitude of tests and treatments? You may have CIRS.

CIRS, as the name implies, is a chronic illness. It is a cluster of symptoms that affect multiple systems in the body. It was first described by Dr. Ritchie Shoemaker, who continues to do extensive research on diagnosing, treating and understanding the syndrome down to a genomic level. (1) (5)
CIRS is caused by exposure to a biological agent (biotoxin) in your environment that your body cannot clear in part because of your genetics.

The biotoxin can be exposure to:
1. Mold from a water damaged building (CIRS-WDB). Up to 50% of buildings in the US have a history of water damage,
2. Lyme or co-infections from a tick bite (CIRS-LYME), resulting in inability to clear the biotoxin after antibiotic treatment
3. Exposure to a dinoflagellate such as *Pfiesteria* or *Ciguatera*. This can occur after eating tropical reef fish contaminated with Ciguatoxin or exposure to infected fish or water,
4. Exposure to blue-green algae (*Cylindrospermopsis* or *Microcystis)* in infected waterways,
5. Bite from recluse spider.

Returning to the genetics I mentioned above, you may ask, why am I sick and nobody else that lives or works in the WDB is sick? Why did I not get better after I was treated with antibiotics for Lyme and other people who were treated are not still sick?

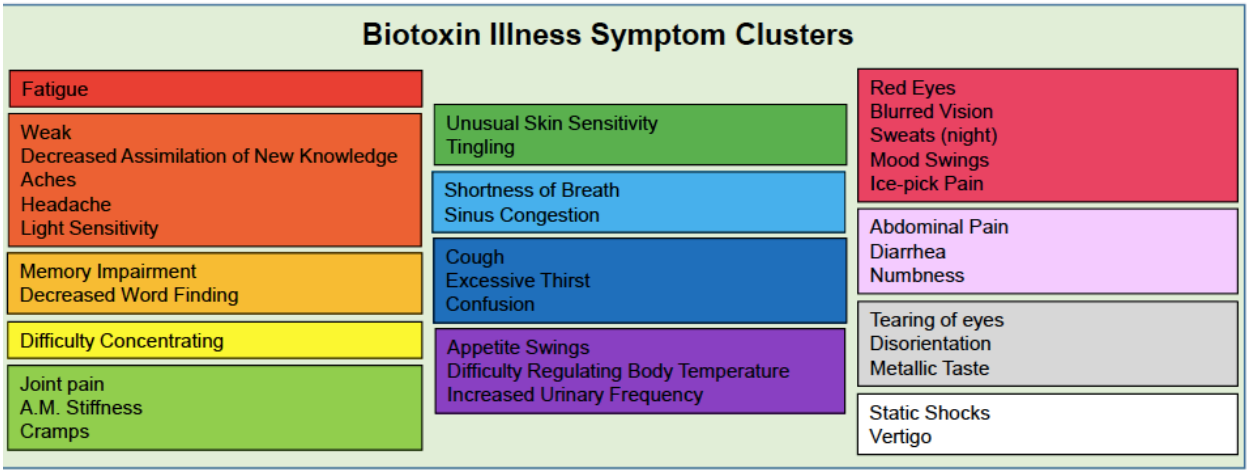
This is explained by your HLA (Human Leukocyte Antigen) profile. Each person has an individual profile that allows our immune system to recognize or not recognize biotoxins. Some people can be mold sensitive, some can be Lyme sensitive and some can have multiple sensitivities. Each individual profile indicates whether your body can efficiently clear that biotoxin or not clear it. Approximately one-quarter of the population is susceptible to mold toxins. A blood test can determine your HLA profile.

There are 2 main components to our immune system. The innate immune system is what we were born with. It is the initial defense against foreign invaders. When confronted with an invader, the immune system releases signals to the body that there is danger. The body responds quickly producing chemicals as the first line of defense to destroy the invader. This is nonspecific and could be compared to dumping "bleach" on the invader. These chemicals (not really bleach) are what make us feel so ill when we are "coming down with something". It is usually not the bug itself that makes us feel this way but the host response to the illness.
The second part of the immune system is the adaptive immune system. This is a much more precise system and rather than dumping bleach everywhere, produces antibodies to specifically remove the invader. It takes time for our body to make antibodies specific to the invader and therefore we have the innate immune system as the frontline of defense.
Now, some people lack the ability to make antibodies against certain biotoxins. This is what I was referring to above with HLA types that cannot recognize certain biotoxins. If this happens, the toxins cannot be removed by the adaptive immune system and persist in our body. Our body does have a backup plan which is not very efficient. Our liver secretes the biotoxin into the bile which is dumped into the gut, however these biotoxins are very tiny and 95% of them are quickly reabsorbed in the gut. This is further compounded if our problem is mold toxicity from a water damaged building (WDB) and we have ongoing exposure.
So, what happens? The innate immune system continues to do its job in the only way it knows how and keeps dumping "bleach" on the problem and the person becomes more and more ill with time.

How do you know if you have CIRS?

Dr. Shoemaker has specific case criteria for CIRS diagnosis and these include:

1. **Exposure history** that includes one of the following: living or working in a WDB, history of a tick bite, onset of symptoms after becoming ill from eating reef fish or exposure to blue algae or dinoflagellates. Exposure to WDB can be verified by presence of visible mold growth, musty smells or a positive ERMI (Environmental Relative Moldiness Index). ERMI is a test done on the building in question by obtaining dust samples that are then evaluated for the presence of mold fragments or spores that were in the air and settled in the dust. ERMI testing can be ordered from https://www.mycometrics.com.
2. **Your symptoms cannot be explained as the result of any other illness**. This includes taking a complete health history and doing a thorough physical exam.
3. You need to have **multiple symptoms in multiple systems of your body** to be diagnosed with CIRS. Dr. Shoemaker has developed a symptom chart to evaluate patients for multisystem, multi-symptom illness:



You need at least 1 symptom in at least 6 of the 13 symptom clusters to be considered for CIRS. 8 of 13 symptom clusters indicates a high probability of CIRS.

If these criteria are met, additional testing will be done.
A simple additional test includes **Visual Contrast Sensitivity** testing. This test is done in my office and is not the same as a vision test to assess your near and far vision, but is a test that measures your ability to discern contrast. Visual contrast perception is impaired in a significant number of

people with CIRS as a result of the effect the biotoxin has on reducing the flow of blood in the blood vessels around the optic nerve.

Lab tests are then ordered. Most people have had extensive lab tests done already, however tests for CIRS specifically look at how your immune system is responding to a biotoxin. The tests can indicate if your innate immune system is being over stimulated. Standard lab tests done are typically normal in CIRS and if abnormal usually are the result of some other problem.

Five of the following lab tests ordered need to be abnormal to diagnose CIRS:

1. **HLA haplotype** determination (as discussed above). 24% of the population have an HLA type that makes them susceptible to CIRS-WDB. However, having the haplotype does not mean you will get CIRS. You still need the exposure. 95% of people with CIRS have a susceptible haplotype.

2. **MSH** (alpha melanocyte stimulating hormone) level. This is a protein released from the hypothalamus and pituitary gland in the brain. It controls melatonin and hormone levels including sex hormones and cortisol. MSH affects mucus membrane integrity (think leaky gut), regulates our immune system and controls inflammation. If MSH is low, many symptoms will be experienced including headache, brain fog, chronic fatigue, sleep disruption and chronic pain. Chronic pain can be a major symptom with CIRS and results from reduction in our natural endorphin production in addition to the inflammatory effects of cytokines (signaling molecules that result from stimulation of the innate immune system).
   Normal MSH range: 35-81 pg/ml

3. **MMP-9** (Matrix Metalloproteinase-9). Its release is triggered by the innate immune system. MMP-9 contributes to increased permeability (leaky membranes) by dissolving a protein in tissue to allow molecules to pass more readily out of blood vessels, into joints, the lung, nerves and the brain (2). This is needed in an acute injury to get the fighting

power to the site of injury, but is very dangerous long term as there will be ongoing delivery of inflammatory compounds into the above tissues.
Normal MMP-9 range: 85-332 ng/ml

4. **TGF-beta-1** (Transforming Growth Factor beta-1) is a conductor of our immune system (3). If TGF-beta is in the normal range it keeps balance between the side of our immune system that needs to be alert to fight an intruder (pathogenic T cells), but yet not be so active that our immune system attacks our own tissue. This control is managed by beneficial T regulatory cells (T-reg) and T helper cells. When there is imbalance and deficiency of T-reg cells, auto-immune disease can develop. Elevated TGF-beta not only signals our body to keep making cells to fight the intruder but these same cells have a positive feedback and stimulate the production of more TGF-beta. High levels of TGF-beta can lead to remodeling of tissue in lung leading to shortness of breath and asthma like symptoms. Other organs in the body such as liver, heart and kidney can also be affected.
   Normal level TGF-beta-1 is under 2380 pg/ml

5. **ADH** (Anti Diuretic Hormone) and **osmolality**- ADH assists in controlling the salt and water balance in our body. In a normal situation, if we are dehydrated, ADH output increases to prevent diuresis (urination), and this will therefore conserve fluid. ADH is produced in the brain and stored in the pituitary gland. Its release is controlled by MSH. The dysregulation in normal production of MSH affects ADH levels. This results in symptoms of headaches, increased thirst, frequent urination and if severe enough, our body tries to sweat out the excess salt resulting in increased susceptibility to static shocks from the sodium present on the skin.
   Normal range ADH: 1-13.3 pg/ml;
   Osmolality: 280-300 mosmol

6. **VEGF** (Vascular Endothelial Growth Factor). VEGF is produced by the body to stimulate the growth of new blood vessels. Initially VEGF levels rise as a result of decreased blood flow to the tissue as the result of cytokines attracting sticky substances to the lining of blood vessels causing white blood cells to become trapped, blocking the blood vessel.

There is however, a subsequent decline in VEGF as a result of prolonged elevation of TGF-beta-1. Unfortunately, the blockage in the blood vessels persists, worsening an already compromised blood flow to the tissue.
Normal range VEGF: 31-86 pg/ml

7. **C4a and C3a.** These are split products of the complement system. They both are anaphylatoxins (cause allergic reaction). Biotoxins stimulate the innate immune system to produce these substances. Complement split products can result in swelling, histamine release, contraction of smooth muscles… essentially all the symptoms of an allergic reaction. High levels result in increased symptoms. In order to produce C3a, you need a microbial cell membrane present. This then requires looking for an infective agent. Lyme is one infection that needs to be considered with elevation of C3a
   Normal range C4a: less than 2830 ng/ml;
   Normal range C3a: less than 940 ng/ml

8. **VIP** (Vasoactive Intestinal Peptide) is made in the gut, pancreas and brain. It is involved in reducing the inflammatory response by regulating the immune response (4). Treatment with this substance can restore many of the imbalances and symptoms seen with CIRS.
   Normal range VIP: 23-63 pg/ml

9. **Cortisol and ACTH** levels. MSH controls release of ACTH from the pituitary gland. ACTH is released in response to stress and stimulates the adrenal to produce cortisol. There is an initial rise in cortisol in CIRS, however as the stress of the illness persists, dysregulation is seen in both levels of ACTH and cortisol.
   Normal range: ACTH: 8-37 pg/ml;
   AM Cortisol: 4.3-21 ug/dl

10. **MARCoNS** (Multiple Antibiotic Resistant Coagulase Negative Staphylococcus). MARCoNS is frequently cultured from the back of the nose in people with CIRS. It does not usually cause symptoms and is not to be confused with MRSA. It is not an infection in the true sense of the word, however it turns on further damaging cytokines. Low MSH

predisposes to development of MARCoNS by impairing mucosal immune function. MARCoNS can then interfere with production of MSH, compounding the problem. MARCoNS can reside in biofilm which protects it from our own natural defenses and from antibiotics. MARCoNS can also affect genetics by controlling which genes are turned off or on. Culture for MARCoNS is obtained by taking a 2-3 inch DEEP nasal culture and sending it for API Staph culture.
Normal result: Negative culture

Additional lab tests that also can be abnormal in CIRS include:

1. **Leptin** is a hormone produced by the fat cells. Leptin controls our appetite and also allows our fat cells to be burned for energy. Leptin attaches to the leptin receptor in the hypothalamus of the brain and is responsible for controlling the production of MSH and beta endorphin (a substance that is our natural pain reliever). Cytokines cross the blood brain barrier and bind to receptors preventing leptin from binding. The body tries to compensate by producing more leptin. This cycle can result in weight gain and inability to lose body fat in spite of dieting and exercise.
   Normal range: Women: 1.1-27.5 ng/ml;
   Men: 0.5-13.8 ng/ml

2. **Von Willebrand's Panel**. von Willebrand's disease can be acquired as a result of elevated C4a level in CIRS. It results in easy bleeding, in particular nosebleeds. This complication is rare.
   Testing involves a von Willebrand's panel and normal results indicate absence of the disease.

3. Screening for presence of **auto-immune antibodies**. There are several that can be abnormal as a result of elevation of TGF-beta-1. Two examples are anti-gliadin antibodies which, if present, result in gluten sensitivity and anti-cardiolipin antibodies which can cause clotting disorders.

4. **CD4+ CD25++** T-regs. These are immune cells with these specific markers on the cell surface. These cells increase as MSH levels rise and indicate an improving immune system (3). Low levels of T-regs increase the chance of allergy and autoimmunity. The levels of these cells can monitor progress of treatment.

CD4+ CD25++ levels should be greater than 18%

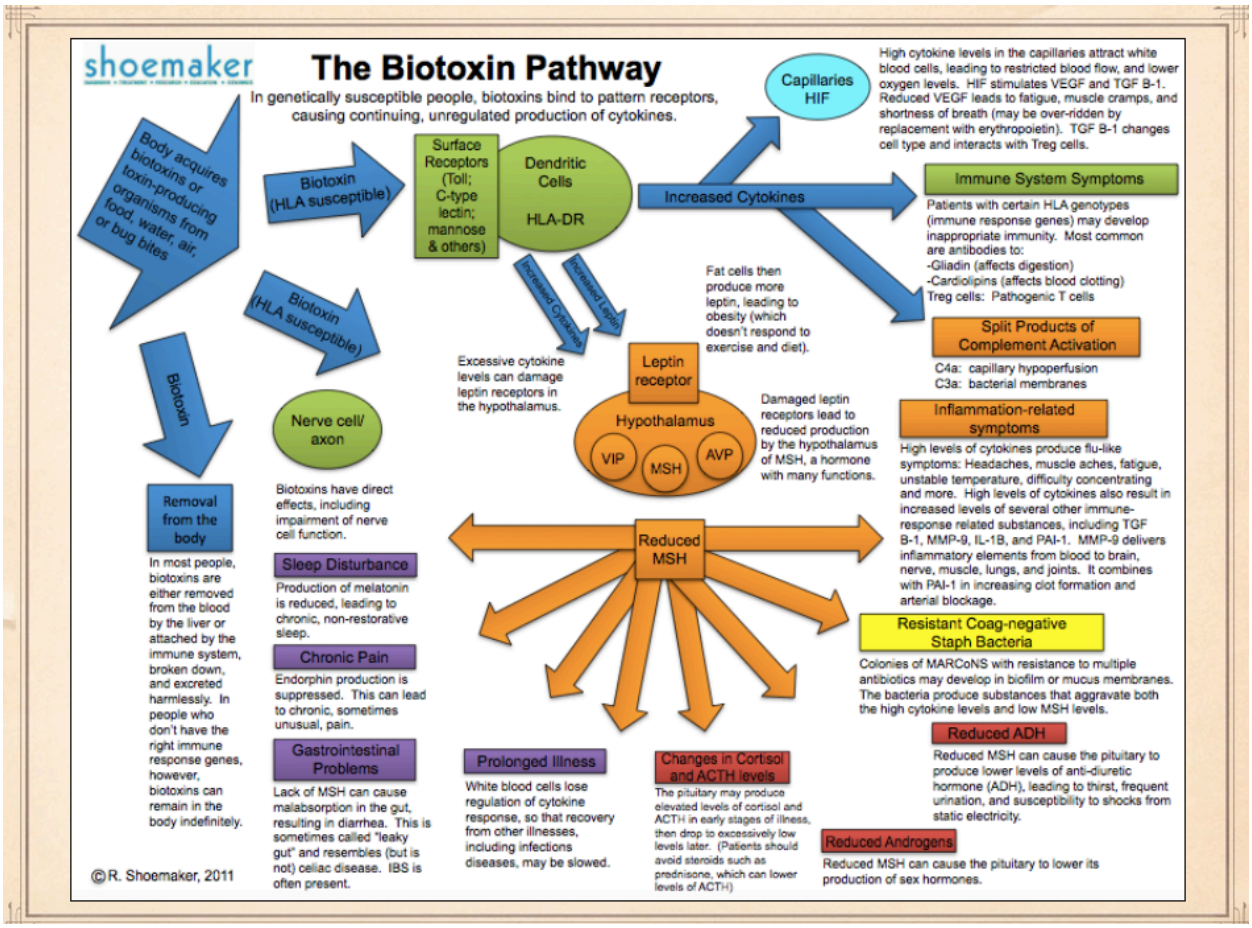
5. **Hormone testing**. Testosterone levels may be low as a result of decreased production of LH (Luteinizing Hormone) and FSH (Follicle Stimulating Hormone) from the pituitary. Testosterone level falls even further as a result of increased aromatase levels in CIRS. Aromatase is an enzyme that converts testosterone to estrogen. Testosterone levels may be low and estrogen levels elevated with symptoms of testosterone deficiency and estrogen excess in both men and women. Testing includes DHEA-S, testosterone and estradiol levels.
   Normal levels vary for sex and age.

   6.**PAX Gene testing** is being developed by Dr. Shoemaker to further understand the effect of the biotoxin on our genes and the response to treatment at a genetic level to further assist in diagnosis and treatment (5).

ADDITIONAL SCREENING-
NEUROQUANT CRANIAL MRI

An MRI of the brain that is additionally interpreted with a software program called NeuroQuant. NeuroQuant measures the volume of different areas of the brain (6). This can be very diagnostic because the abnormalities seen with CIRS-WDB are different from CIRS-LYME.
People with CIRS-WDB will have shrinkage (atrophy) of an area called the caudate nucleus accompanied by swelling in other areas. CIRS-LYME, however results in atrophy of the putamen. This test can also monitor progress of treatment. NeuroQuant is also being used in the Bredesen protocol to monitor patients with cognitive impairment.

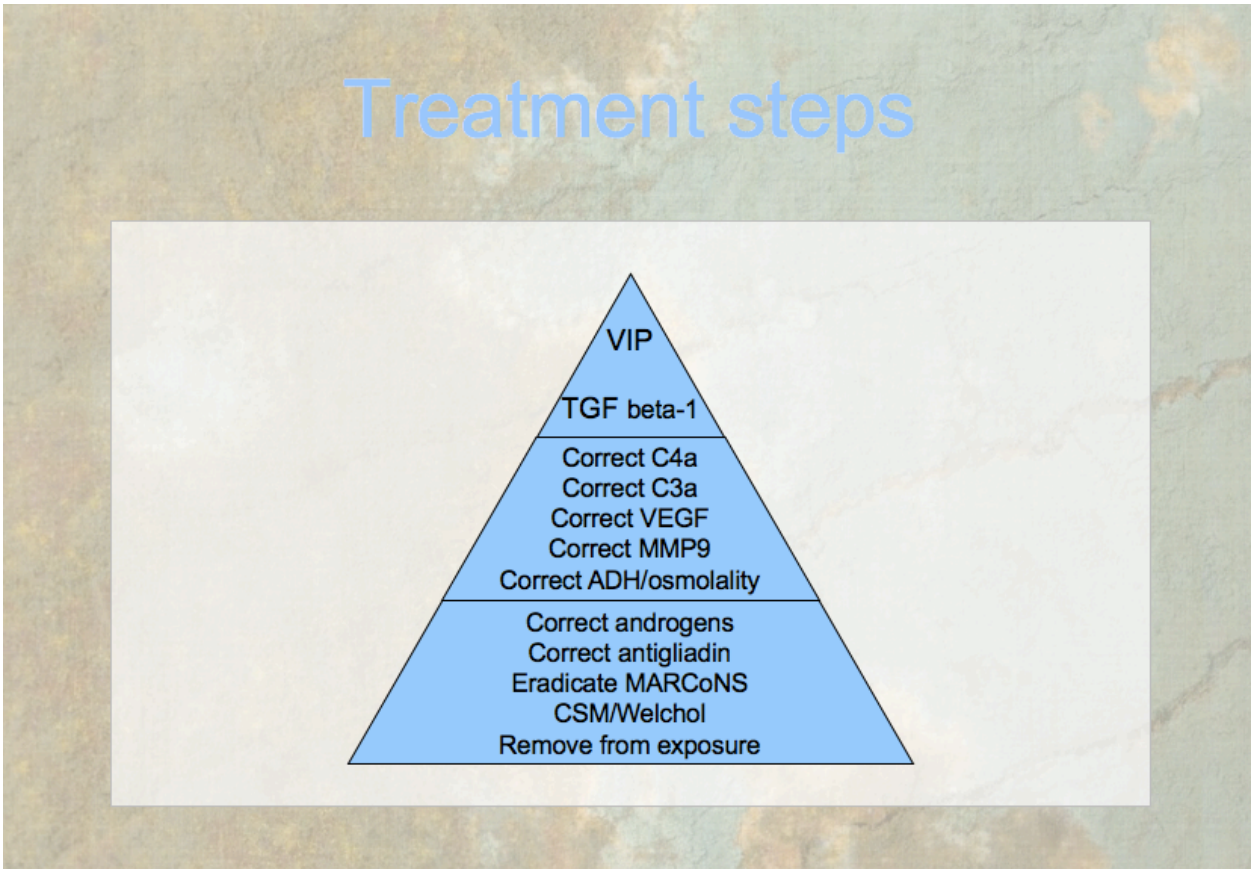
This is an excellent flow chart Dr. Shoemaker developed to understand the course of CIRS:



TREATMENT - YES THERE IS HOPE!

Treatment is stepwise, starting at the bottom of the pyramid and moving up. Jumping steps will not assist in more rapid recovery and may actually interfere with recovery.

Dr. Shoemaker uses this treatment pyramid in correcting abnormalities in CIRS:



At each step retesting of VCS and innate immune markers such as MMP-9, C4a, TGF-beta-1, CD4+ CD25++ T-regs and any previous abnormalities can be monitored to assess progress.

1. The first step is **removal from exposure** and this primarily applies to CIRS-WDB. This is the most difficult for patients for multiple reasons including cost and attachment to personal items. ERMI testing is

indicated to determine where exposure is occurring. The workplace may need to also be tested. Symptomatic improvement will not occur if ongoing exposure to the biotoxin continues. The professional assistance of an Indoor Environmental Professional (IEP) is strongly recommended to assist in evaluation and remediation (7). The affected person should not occupy the affected building during remediation. Repeat testing, either with ERMI or HERTSMI-2 which stands for Health Effects Roster of Type Specific Formers of Mycotoxins and Inflammagens (see https://www.mycometrics.com) is required before re-entering the affected building. Inflammagens are chemicals that trigger an inflammatory response in the body.

2. **Removal of biotoxins**. It is important to understand if you have CIRS-WDB that you DO NOT have mold growing in your body. Instead, you have toxins from mold exposure. You DO NOT take anti-fungal medications to treat this illness.

   Cholestyramine (CSM) is a drug that is approved for cholesterol lowering and is being used off label in this treatment application (that means it does not have FDA approval to treat this condition). CSM has a positive charge and structure that attracts the negatively charged biotoxins that are present in the bile. The biotoxins are irreversibly bound and eliminated in the stool. CSM is not absorbed however does have side effects of constipation, gas and bloating. The dose is 4 grams in 6 oz of water followed by another 6 oz of water, 4 times daily 30 minutes before meals. It can bind to prescription meds and supplements and these should be taken 1 hour prior to CSM or 2 hours after. Constipation must be avoided. Dietary fiber, magnesium and other bowel stimulants may be required to prevent constipation. An alternative treatment is a prescription drug, Welchol 625 mg and is dosed 2 tablets three times daily with meals. This drug is also FDA approved to treat elevated cholesterol. Welchol is only 25% as effective as CSM as a binder, however it causes fewer GI side effects. It is also much more expensive. Some people become ill with binders and this is likely the result of their mobilization of more cytokines, especially MMP-9. Side effects can be reduced with high dose (3-4 grams) omega-3 supplementation daily starting 1 week before starting CSM.

Treatment with binders is continued until VCS test results are normal, symptoms are the same as controls and lab results have normalized.

A low amylose diet is very helpful in reducing insulin levels, reducing inflammation and assisting in weight loss. (8) This diet is recommended along with CSM.

3. **Eradication of MARCoNS**. If MARCoNS testing by API Staph swab is positive it needs to be treated after one month of treatment with CSM. The treatment for MARCoNS is with BEG nasal spray that is made by a compounding pharmacy. It contains Bactroban 0.2%, EDTA 1% and Gentamicin 0.5% in a base that improves adherence to mucous membranes. Dosing is 2 sprays each nostril 3 times daily for 1 month. The spray is irritating and can result in nasal burning, congestion and nose bleeds. This will all resolve after completing treatment. Repeat culture needs to be done post treatment. If the culture remains positive, other family members or dogs may be the source of re-infection. Cats are off the hook here!

4. **Gluten free diet** should be followed if gluten antibodies are present. This diet should be followed for a minimum of 3 months. Retesting should be done and if antibodies are still positive, the likelihood of celiac disease needs to be considered. Eliminating gluten also reduces amylose in your diet. Many people are gluten sensitive as a result of leaky gut and most feel better eliminating gluten even if testing is negative. It is worth a trial with no risk.

   It is important to allow healing to occur on many levels and the food we eat provides information to our cells that can be good or bad depending on our choices. Avoiding toxic exposure to the best of one's ability reduces the overall toxic burden in the body. Eat organic whenever possible. Pay attention to what you eat, the air you breathe and what you put on your skin.

5. **Correction of hormone levels**. This is done carefully with the addition of DHEA. Estrogen and DHEA-S levels need to be monitored while on treatment and DHEA will be discontinued when levels return to normal.

DHEA is a hormone that is converted to testosterone. Less conversion to estrogen occurs with DHEA than with testosterone supplementation. If testosterone is given directly, it will be converted to estrogen, worsening the imbalance in both men and women. This imbalance will resolve once the underlying overstimulation of the innate immune system is corrected.

6. **Correct ADH/osmolality**. DDAVP is a prescription form of ADH and can be used cautiously 0.2 mg every other night for 2 weeks. This, again, is off label use. Daily weights, monitoring blood pressure and for edema needs to be done while on treatment. ADH/osmolality and electrolyte levels need to be retested in 2 weeks after starting treatment.

7. **Correct elevated MMP-9**. This involves reducing inflammation with a low amylose diet and 3-4 grams of omega-3 daily for one month. If there is no improvement Actos 45 mg daily for 10 days can be used. Actos works by reducing insulin resistance and inflammation. Its use has lost favor because of a black box warning by the FDA of developing bladder cancer with long term use of over 1 year.

8. **Correct VEGF**. Treatment with low amylose diet and high dose omega-3 supplementation should be continued if VEGF abnormalities persist. The final step in treatment with VIP nasal spray will also address this.

9. **Correct elevated C3a**. The underlying cause needs to first be addressed. If it is due to Lyme, this needs to be treated. Auto-immune diseases such as lupus also result in elevation of C3a. After the underlying cause has been addressed, inflammation and C3a levels are reduced with high dose (80 mg) statins. Pre-treatment with Co-Q 10 200 mg daily starting 10 days before the statin reduces the risk of side effects. Muscle pain, fatigue and elevation of liver enzymes can occur with high dose statins.

10. **Correct elevated C4a** with VIP nasal spray 50 mcg/0.1 ml, 1 spray in alternating nostrils 4 times daily for minimum duration of 4 months. When symptoms improve and lab values normalize, dosage can be reduced to 50 mcg twice daily for 1 month. Before VIP can be used, the following requirements must be met: VCS testing must be normal,

MARCoNS testing is negative, lipase level is normal and ERMI is less than 2 or HERTSMI-2 less than or equal to 10. The first dose should be administered in the office and patient monitored with pre and post labs. If no adverse reaction, lipase, C4a, TGF-beta-1, MMP-9 and any abnormal labs should be checked in 1 month. VIP needs to be discontinued if lipase elevates or abdominal pain or rash develops.

11. **Correct elevated TGF-beta-1**. Losartan (a drug to lower blood pressure) produces a degradation product that lowers TGF-beta. Dosage is 12.5 mg daily and increased to 25 mg twice a day if tolerated. If a person already has low blood pressure, it may not be tolerated and VIP nasal spray, with the above directions and guidelines can be substituted. Note that other blood pressure medications do not have the same effect as Losartan.

12. **Correct low VIP**. If recovery has not yet occurred, VIP nasal spray is to be continued with the above guidelines and dosage.
VIP nasal spray has many beneficial effects. VIP downregulates cytokines, raises VEGF, CD4+ CD25++ T-regs, restores circadian rhythm (sleep), regulates auto-immunity, restores normal hormone levels by downregulating aromatase, increases endorphins, improves exercise tolerance and has been shown to normalize genomics.
VIP can also help people with multiple chemical sensitivities by down regulating olfactory driven neurons.

Avoiding re-exposure is critical, however sometimes unavoidable. People do not want to live in terror of travelling outside of their “safe bubble”. If re-exposure occurs, identifying the source is beneficial to prevent repeat exposure.
Retest VCS and lab markers and if abnormal, retreat with CSM/Welchol. Continue up the pyramid until symptoms resolve and markers are back in the normal range. People who have had CIRS have a tendency to become “sicker, quicker” upon re-exposure. Prevention is best.

CIRS is a very misunderstood disease at best and denied by many at worst. Thanks to the research and dedication of Dr. Shoemaker, who

followed the evidence, there is now clinical validation supported by thousands of cases for the diagnosis and treatment of CIRS.

It is important to understand the pathway the biotoxin takes in our body which results in a cascade of symptoms. This understanding provides the knowledge of the how and why these treatment steps are taken in order to reverse the disease.

This diagnosis is not made easily. As outlined above, multiple criteria must be met. The diagnosis is then validated with numerous tests which analyze the effect of the biotoxin on multiple systems of the body. Tests range from VCS testing, multiple lab tests including determining genetic susceptibility, MRI volumetric imaging, and now Dr. Shoemaker is on the cutting edge with his genomic research. This will "personalize" diagnosis and treatment by understanding what the biotoxin is doing in your body at a cellular/genetic level.

This is an exciting frontier to be part of. For me, it provides a very important piece to a puzzle of chronic illness.

References:

1. Shoemaker: "Surviving mold-What is CIRS" December 2014. http://www.survivingmold.com/news/2014/12/what-is-cirs/

2. Al-Sadi, Rawat, Ma: Inflammatory Bowel Diseases: February 2017. MMP-9 Modulation of Intestinal Epithelial Junction Permeability. http://journals.lww.com/ibdjournal/Abstract/2017/02001/P_272_MMP_9_Modulation_of_Intestinal_Epithelial.275.aspx

3. Noack, Miossec: Autoimmunity Reviews, June 2014. Th17 and T-reg cell balance in autoimmune and inflammatory disease. http://www.sciencedirect.com/science/article/pii/S1568997214000081

4. Ganea, Hooper, Kong: Acta Physiologica, December 2014. The neuropeptide vasoactive intestinal peptide: direct effects on immune cells

and involvement in inflammatory and autoimmune diseases. http://onlinelibrary.wiley.com/doi/10.1111/apha.12427/full

5. Ryan, Wu, Shoemaker: BMC Medical Genomics, April 2015. Transcriptomics in CIRS/Ciguatoxin https://www.ncbi.nlm.nih.gov/pubmed/25889530

6. Shoemaker, House, Ryan: Neurotoxicology September 2014, Structural brain abnormalities in patients with inflammatory illness acquired following exposure to water damaged buildings: A volumetric MRI study using NeuroQuant . https://www.ncbi.nlm.nih.gov/pubmed/24946038

7. Berndtson, McMahon, Ackerly, Rapaport, Gupta, Shoemaker: Medically sound remediation of water damaged buildings in cases of CIRS. January 2016.

https://www.survivingmold.com/docs/MEDICAL_CONSENSUS_1_19_2016_INDOOR_AIR_KB_FINAL.pdf

8. Maier: The No-Amylose diet. August 2013

http://www.livestrong.com/article/335261-the-no-amylose-diet/#ixzz18n8hXyTi