Chronic Inflammatory Response Syndrome Diagnosis and Treatment

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What is Chronic Inflammatory Response Syndrome?

Chronic Inflammatory Response Syndrome (CIRS) is a multi-symptom, multi-system illness caused by exposure to biotoxins, or neurotoxins produced from a biological source. The most common sources of biotoxins are toxic metabolic products and cell wall fragments from filamentous molds (many incorrectly refer to this as mold toxin illness) that occur in water damaged buildings, tick-borne illnesses including Lyme Disease, cyanobacteria, dinoflagellates like ciguatera and red tide, *Pfiesteria*, and poisonous spiders like Brown Recluse and Mediterranean Recluse. Exposure to these sources can create acute illness, and in some individuals who have long-term exposure or who are genetically unable to clear the biotoxins can create a chronic illness.[1, 2 (Ch. 3,4), 3(Ch. 2)]

The acute illnesses caused by exposure to biotoxins typically have a sudden onset and are most often characterized by severe malaise, fatigue, anorexia, chills, fever, headache, muscle pain, joint pain, nausea, vomiting, abdominal pain, and shortness of breath. However, each biotoxin has a slightly different acute presentation:

- Lyme Disease: Stage 1 Lyme disease is classically characterized by erythema migrans (bulls-eye rash) and an undifferentiated febrile illness. One-third of patients do not exhibit erythema migrans, but may have flu-like symptoms including fever, chills, malaise, myalgia, arthralgia, headache, and neck stiffness. Symptoms can very depending on the presence or absence of co-infections as well. Stage 2 of Lyme disease is defined as symptoms occurring 3-10 weeks after inoculation. Classic symptoms of Stage 2 include, fever, malaise, arthritis, arthralgia, neuropathy, and headache.[4, 5]
- Cyanobacteria: The most frequent exposure to this biotoxin is by swimming or drinking water containing cyanobacteria. Symptoms from exposure can include skin irritation, rashes, blisters in the mouth and nose, abdominal pain, vomiting, nausea, diarrhea, fever, sore throat, headache, muscle pain, and joint pain.[6]
- Ciguatera: Exposure to ciguatera toxin is caused by eating contaminated reef caught fish. Ciguatera is an odorless and tasteless toxin that cannot be removed by cooking. Typical symptoms include diarrhea, nausea, vomiting, flu-like symptoms including myalgia, arthralgia, malaise and fatigue, neurological symptoms like numbness and tingling, headache, shortness of breath, tachycardia, severe localized itching.[7, 8]
- *Pfiesteria*: Exposure to this biotoxin can cause eye and respiratory irritation, skin rashes, headache, stomach cramps, nausea, vomiting, and neurocognitive changes.[9]
- Recluse Spider Bites: Symptoms arising after a bite by a Mediterranean Recluse or Brown Recluse often include rash or itching, pain at the site of the bite, blistering of the skin at the site of the bite, muscle pain or cramping, fever, shortness of breath, headache, nausea, vomiting, and chills.[10]
- Mold: Acute reactions to mycotoxins and cell wall fragments from filamentous molds can include headache, eye irritation, nose bleeds, nasal and sinus congestion, cough, flu-like symptoms, gastrointestinal complaints, and shortness of breath.[3 (Ch. 2), 11]

Even when properly treated, not everyone who becomes ill from an exposure to a biotoxin will fully recover from the acute illness, creating a chronic illness. This is in part due to immune activation and genetic variations in immunity. Twenty -five percent of the general population has a HLA DR DQ haplotype that leads to decreased antigen presentation, which results in the reduced clearing of toxins from these biological sources. The resulting increased level of biotoxins causes the simultaneous and progressive activation of inflammatory pathways including TH1, TH2, TH17, complement immunity, and coagulation cascades. Ultimately this creates symptoms across many (minimum of four) or all body systems. Some symptoms that have been found to be associated with CIRS include the following: [2 (Ch. 4, 7, 11), 3 (App. 1), 12]

- Headache
- Light sensitivity
- Memory issues
- Word searching
- Difficulty concentrating
- Difficulty comprehending new knowledge
- Unusual skin sensations
- Numbness and/or tingling
- Confusion
- Red eyes
- Blurred vision
- Mood disturbances
- Icepick-like pains
- Vertigo
- Disorientation
- Metallic taste
- Tearing of the eyes
- Difficulty regulating body temperature
- Night sweats
- Tremor
- Weakness
- Body aches
- Joint pain
- Muscle pain
- Morning stiffness
- Muscle cramping
- Shortness of breath
- Sinus issues
- Cough
- Increased thirst
- Urinary frequency
- High or low appetite
- Abdominal pain
- Gastrointestinal issues
- Static shocks
- Low-grade fever
- Fatigue

How do we diagnose CIRS?

Positively diagnosing a person with CIRS includes taking a thorough history, conducting an extensive physical examination, creating a differential diagnosis and using appropriate laboratory tests to assess the patient's condition. A thorough history is necessary to discover possible sources of exposure to one or more of the known biological agents that can cause CIRS. The comprehensive physical exam allows the physician to observe how the illness is presenting physically in multiple body systems and to find possible evidence of confounding illness. Using general and specific laboratory testing can both lead to a diagnosis of CIRS, concomitant causes of symptoms, or rule out other causes of multi-symptom, multi-system illnesses. Other illnesses that can create multiple symptoms in multiple body systems include a variety of autoimmune diseases, diabetes mellitus, liver disease, renal disease, neurodegenerative diseases and other infectious causes of disease.[1, 2 (Ch. 4), 3 (Ch. 4, App. 4), 12, 13, 14]

The following is a list of lab markers indicative of CIRS:

- HLA DR DQ: Genetic markers associated with certain haplotypes (or patterns) that prevent people from being able to appropriately clear biotoxins due to decreased antigen presentation. [2 (Ch. 4,18, App. 2), 3 (Ch. 4), 14, 15]
- C3a and C4a: Markers of the activity of a person's complement system of innate immunity. One or both of these markers may be abnormal with exposure to certain biotoxins. Both C3a and C4a are anaphylatoxins. They cause smooth muscle contraction, histamine release from mast cells, increase vascular permeability, and mediate chemotaxis. C3a is only elevated when the innate immune system is presented with a microbial cell membrane. If C3a is elevated Lyme disease and other tick borne illness must be ruled out. C4a is the split product of the mannose-binding pathway of complement system and becomes elevated when a patient is exposed to a biotoxin. The level of elevation of C4a translates to the severity of the patient's condition. [1, 2(Ch. 4, 5), 16, 17, 18]
- Matrix Metalloproteinase-9 (MMP-9): An enzyme that becomes elevated due to an increase in a person's cytokines, or inflammatory chemicals released by the immune system. It is directly released by the endothelium into the bloodstream and aids in bringing chemokines to the brain, nerves, muscles, lungs, and joints. [1, 14, 19, 20]
- Anti-diuretic hormone (ADH) and Osmolality: ADH is a hormone that controls the body's ability to hold on to free water. Osmolality is the concentration of solutes like blood urea nitrogen, glucose, and sodium that are in the serum portion of the blood. Together these tests indicate if the body is having trouble with regulating water due to inflammatory and hormonal changes that occur as a result of biotoxin exposure. [1, 2 (Ch. 4, 7)]
- Alpha-Melanocyte stimulating hormone (MSH): A neuro-regulatory hormone produced in the hypothalamus and pituitary gland that is low in 95% of CIRS patients. Low levels of MSH prevent multiple neuro-immune pathways resulting in abnormal regulation of ACTH, cortisol, androgens, melatonin, endorphins, and cytokines. [2 (Ch. 2, 4, 6), 21, 22, 23]
- Vascular endothelial growth factor (VEGF): A growth factor that impacts the oxygen delivering capacity of the body. Normally, VEGF stimulates blood vessel growth in response to Hypoxia Inducible Factor (HIF), leading to dilated blood vessels and increased oxygenation to tissues. In CIRS, VEGF is suppressed by cytokine elevation, which leads to capillary hypoperfusion, or low oxygen deliver to tissue beds. This can lead to post-exertional fatigue and cognitive difficulties. [1, 2 (Ch. 4, 6), 14]
- Transforming growth factor beta-1 (TGFβ-1): An inflammatory marker that impacts the oxygen carrying capacity of the body, remodeling of connective tissue, and creates imbalance in T cell immunity. [1, 2 (Ch. 4, 6)]
- Vasoactive Intestinal Polypeptide (VIP): A neuro-regulatory peptide that regulates cytokine response and pulmonary artery pressure. Abnormalities create issues with hormonal regulation, oxygenation and inflammation.[1, 2(Ch. 4, 6, 16)]
- Visual Contrast Sensitivity (VCS): A visual test that detect defects in the ability to distinguish changes in contrast due to neurological changes in vision.[2 (Ch. 4, App. 7), 13, 24]
- Multiply antibiotic resistant coagulase negative staphylococcus (MARCoNS) Nasal Swab: A deep nasal culture that identifies if a person has a colonization of

MARCoNS. MARCoNS is diagnosed if the culture reveals resistance to 2 or more antibiotic classes. MARCoNS contributes to immune dysregulation by interrupting the production of MSH, thus disrupting multiple neuro-immune pathways in the body including those that regulate sleep, pain, and mood.[2 (Ch. 4, 19), 25]

- NeuroQuant MRI: A specialized program that uses a magnetic resonance imaging (MRI) of the brain to determine if there are changes in volume and/or structure of brain matter. The patterns of change in the brain are like a fingerprint that can aid in determining the cause of CIRS. Repeat NeuroQuant MRIs can also monitor the effectiveness of treatment.[26]

Other general labs that may be ordered include, but are not limited to: Complete Blood Count with Differential, Complete Metabolic Panel, Lipid Panel, C-reactive protein, Sedimentation Rate, Anti-Nuclear Antibodies with reflex, TSH, Free T3, Free T4, Reverse T3, Thyroid Peroxidase Antibodies, Anti-Thyroglobulin Antibodies, Estradiol, Sex Hormone Binding Globulin, Free and Total Testosterone, Progesterone, Pregnenolone , Anti-Gliadin Antibodies, cortisol, d-Dimer, Cardiolipin Antibodies, activated Partial Thromboplastin Time, Prothrombin Time, Thrombin Time, Factor VIII Activity, von Willebrand Factor Antigen, Ristocetin Cofactor, von Willebrand Factor Collagen Binding Assay, von Willebrand Antigen.[2 (Chapter 4, 5)] There are other tests that may be indicated based on a person's individual symptoms.

What are the treatment steps?

Although the general treatment steps are outlined below, it is important to remember that treatment is individualized to accommodate each patient, and thus, may vary from patient to patient. In many cases resolving issues in the earlier steps of treatment aids in body's ability to correct abnormal lab results associated with later steps of treatment without specific treatment. Strict adherence to the treatment steps is required in the order prescribed to obtain resolution of symptoms and correction of abnormal lab values.

The Shoemaker Protocol:

1. *Remove from exposure*: Once a positive diagnosis of CIRS is confirmed, the first step in treatment is to ensure that there is no exposure to any biotoxin. This is the most important step in treatment. The most common biotoxin in the U.S. is toxic metabolites and cell wall fragments from mold. For this reason every patient must test their home using an Environmental Relative Mold Index (ERMI) test through Mycometrics Laboratory. Acceptable ERMI result levels vary based on how dysregulated the CIRS Lab Markers are with testing. In general, an ERMI result >2 is considered unsafe for CIRS patients. From the ERMI result, a secondary result, HERTSMI-2, can be calculated. This uses the values of five specific molds from the ERMI test—*Aspergillus penicilloides, Aspergillus versicolor, Chaetomium globosum, Stachybotrys chartarum, and Wallemia sebi*. Based on current literature, a HERTSMI-2 score <11 is considered safe for CIRS patients. Based on clinical experience, more sensitive patients may require an environment with a HERTSMI-2 <8 for improvement of health.[27, 28]
2. *Remove neurotoxins from the body*: Research has found that Cholestyramine (CSM), a bile acid sequestrant, has the correct structure, as a quaternary amine cation, to

bind biotoxins (anion dipoles) and effectively remove them from the body via the digestive tract. The binding of CSM to the biotoxin prevents enterohepatic recirculation from the bile. Effectiveness of treatment is based on the ultimate dose of 4 grams four times per day taken away from food, supplements, and medications. For certain patients, a more gentle bile acid sequestrant, Welchol, can be used. CSM, Welchol or a combination of the two medications should be taken until a person passes the VCS test and/or through the eradication of MARCoNS.[2 (Ch. 29, App.1), 3 (Ch. 4, App. 4), 13, 15, 24, 29, 30]

3. *Eradicate MARCoNS*: If the nasal culture is positive for MARCoNS it is necessary to eradicate the bacterial colonization and associated biofilms. MARCoNS leads to immune dysregulation by cleaving MSH with endotoxin A. This decreases the production of MSH and impacts multiple neuro-immune pathways such as ACTH, cortisol, androgens, melatonin, endorphins, and cytokines. Treatment of MARCoNS is achieved by using B.E.G. antibacterial nasal spray, which is comprised of Bactroban (Mupirocin), EDTA, and Gentamicin. Treatment typically lasts for 30 days, followed by a repeat nasal culture to ensure eradication.[2 (App. 1), 25]
4. *Eliminate gluten in AGA positive patients*: For those individuals who test positive for Anti-Gliadin Antibodies (AGA) it is necessary to maintain a 100% gluten free diet for at least 3 months. In these individuals it is also necessary to rule out celiac disease, which would require strict lifelong avoidance of gluten.[2 (App. 1), 14]
5. *Correct ADH/Osmolality dysregulation*: Using Desmopressin Acetate (DDAVP) orally can correct the dysregulation of ADH and osmolality. DDAVP is used over the course of 10-14 days. During this treatment, ensure that there is no excessive weight gain, swelling of the extremities, worsening serum osmolality, and hyponatremia.[1, 2 (Ch. 4, 7, App. 1)]
6. *Correct elevated MMP-9*: This is achieved by following a low-amylose diet and using high doses of fish oil for at least one month. Actos, a medication used to control blood sugar, may also be used in certain cases in which the aforementioned treatments alone do not correct MMP-9. [2(Ch. 4, App. 1), 14, 19, 20]
7. *Correct low VEGF*: Correction of VEGF also occurs by following a low-amylose diet and using high does of fish oil. This step is combined with Step 6. [2 (Ch. 4, 6, App. 1), 14]
8. *Correct elevated C3a*: An elevated C3a can indicate an ongoing exposure to bacterial membranes. For this reason it may be necessary to use antibiotics, statin drugs, and/or CoQ10 supplementation for 30 days. A majority of the time, longer term antibiotic use is unnecessary.[2 (Ch. 4, App. 1), 14, 16, 17]
9. *Correct elevated C4a*: C4a tends to self-resolve as a patient successfully completes the previous treatment steps and avoids re-exposure. The final step in treatment, VIP spray, is used to completely correct C4a. In certain cases Procrit can be used to correct C4a levels, but the side effects of the medication make it a less desirable option for treatment.[2 (Ch. 4, App. 1), 14, 16, 17, 18]
10. *Reduce elevated TGFβ-1*: Losartan, an angiotensin receptor blocker used to treat high blood pressure also can correct elevated TGFβ-1. It is contraindicated for patients who already have low blood pressure to use this medication. In those individuals, VIP spray can be used as an alternative.[1, 2 (Ch. 4, App. 1), 14, 31]
11. *Replace low VIP*: VIP nasal spray is a compounded medication that is used as the last step in treatment. VIP nasal spray restores any lab markers that remain abnormal

after the previous 10 steps have been completed. After using VIP spray without re-exposure for 2-6 months, it also has the added benefit of preventing immune activation upon re-exposure. There are certain criteria that must be met prior to using VIP nasal spray:

a. Passing the VCS test
b. ERMI <2 in ALL areas of exposure.
c. Negative MARCoNS nasal culture
d. MMP-9 <320

VIP Trial: Initiating the use of VIP nasal spray requires laboratory testing, including TGFβ-1, CMP, Lipase, Amylase, and possibly other labs as well as administering a test dose of VIP Nasal Spray. Based on the lab results from the VIP Trial, one can determine if the patient is truly out of exposure. It is necessary that the patient continue to avoid all biotoxin exposures. While a patient is using VIP Nasal Spray, they are required to monitor their blood pressure and pulse daily. Monthly laboratory testing is required and should include at a minimum a CBC with differential, CMP, amylase, and lipase.[1, 2 (Ch. 4, 16, App. 1), 32]

12. *Final check*: Once all of the steps have been successfully completed, it is necessary to re-test all of the CIRS lab markers to ensure are within normal limits.[1, 2 (Ch. 4, App. 1), 33, 34]

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