Chronic Inflammatory Response Syndrome: Assessment & Management

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Definition

Chronic Inflammatory Response Syndrome, or CIRS, is a multi-symptom, multi-system illness, resulting from the body's impaired ability to properly clear biotoxins acquired from specific microorganisms. These biotoxins are produced by dinoflagellates, algae, bacteria and molds. Such organisms can be found in water damaged buildings, reef fish, algae blooms, and insect & arthropod vectors, to name a few. Typically, people who have do not have a genetic predisposition to CIRS can recover from exposure to biotoxins. Unfortunately, for many, research has demonstrated that nearly 25% of the population can be potentially impacted by CIRS.

As a multi-symptom, multi-system syndrome, there are many ways in which the body can express the illness. In general, patients with CIRS experience neurological, immune, endocrine and circulatory dysfunction. Symptoms may be so severe that their quality of life is greatly depreciated.

Initial exposure to biotoxins results in acute illness, generally including but not limited to: fatigue, muscle pain, headache, fever, chills, respiratory distress, abdominal pain, nausea, vomiting and generalized pain. If a patient is not genetically susceptible, and is treated properly, improvement and resolution occurs. However, in those who are genetically susceptible to CIRS, this initial exposure begins the cascade of uncontrolled inflammation leading to the eventual full expression of the CIRS illness. Moreover, with each additional exposure, it is expected that the patient becomes sicker, quicker; this being a result of an innate immune system dysfunction.

In a healthy immune system, the biotoxin is identified by the adaptive branch of the immune system and is removed appropriately through production of cytokines and antibodies. However, in those with the CIRS susceptible HLA haplotypes, there is an error in the functioning of the adaptive branch of the immune system. The adaptive immune system should be able to appropriately process the biotoxin and then present it to other immune system cells. T cells awaiting "instruction" from the antigen presenting cell, will then pass on the information to B cells who will then produce the antibodies necessary to properly sequester and clear the threat from the system. In patients who are genetically susceptible to CIRS, the process of presenting the biotoxin to the T cells has been rendered dysfunctional. Therefore, the antigen presenting cell continues to produce an abundance of inflammatory cytokines, effectively calling the immune system to attention, but ultimately unable to present the threat appropriately for necessary eradication. The continual elevation of inflammatory cytokines, without resolution, is the key to CIRS.

These inflammatory markers are evolutionarily in place to aid the immune system in identifying a threat, recruiting the defense and eradicating the hazard. They were only ever intended to be raised for defensive purposes for a short period of time. When such inflammatory markers are chronically elevated we see the development of multi-symptom, multi-system complaints correlative with CIRS.

Diagnosis

The diagnosis begins clinically, in the discussion with the patient. A list of common symptoms has been developed through cluster analysis, with research showing that biotoxin illness patients typically

report positives in eight symptom clusters. Therefore, it is clinically suggested that patients reporting 6 or more of the symptom clusters be tested for CIRS. The symptom clusters are as follows: fatigue; weakness, decreased assimilation of new knowledge, aches, headache & light sensitivity; memory impairment & decreased word finding; difficulty concentrating; joint pain, morning stiffness & cramps; unusual skin sensitivity & tingling; shortness of breath & sinus congestion; cough, excessive thirst & confusion; appetite swings, difficulty regulating body temperature & increased urinary frequency; red eyes, blurred vision, sweats (night), mood swings & icepick pain; abdominal pain, diarrhea & numbness; tearing of eyes, disorientation and metallic tastes; static shock & vertigo. Confirming reproducibility of reported symptoms is always necessary.

In addition to symptom data acquisition, it is mandatory that a thorough history of present illness is collected including medical record review, along with personal, social, familial history, and detailed review of symptoms. Environmental exposure to the suspected source of the biotoxin should be discussed at this time- eg. Mold exposure in water damaged building; or ciguatera exposure by the consumption of reef fish, etc. Following the collection of subjective data, an objective detailed physical exam must occur. A differential diagnosis is then to be developed, with rule outs to be considered. It is of utmost importance that all possible confounding morbidities must be ruled out as a cause of illness before CIRS is to be suspected. It is at this time that lab assessments should be employed, as to rule in or rule out confounding disease states. Such labs are based on an individual case-to case basis, however these labs may include, but are not limited to investigations of Lyme disease, liver functioning, kidney functioning, complete blood counts, general inflammatory markers (CRP, ESR), lipid levels, auto immunity panels, full thyroid panels, hormonal & other endocrine assessments, and various coagulation panels among others.

After thorough lab work-up has occurred, allowing a physician to rule out confounding morbidities, the CIRS specific labs and investigations may occur. The initial investigation for CIRS starts with a Visual Contrast Sensitivity test (VCS). The VCS test has been shown to be a reliable screening tool, as 92% of CIRS patients fail this test, and the rate of a false negative is 8%. A failed VCS test is indicative of deceased neurological integrity in the visual pathways running between the retina and the cortex of the brain. Although this test is available online it is best done in office, where administration can be properly supervised by a trained physician.

The remaining CIRS specific labs are collected through venipuncture, with the exception of MARCoNS. The following is a list of the labs acquired, and their rationale:

- HLA DRB and DQ- genetic screen that correlates with abnormal adaptive immune system functioning, thus leading to an increased risk of susceptibility to CIRS
- C4a- an inflammatory marker produced by the innate immune system with exposure to biotoxins. It is an anaphylatoxin which mediates chemotaxis, contraction of smooth muscle, increased vascular permeability and histamine release from mast cells. During exposure to a biotoxin, the mannose binding pathway of complement system is activated and C4a is produced. Clinical severity is directly correlated with C4a; the higher the elevations, the worse the patient feels.
- C3a- an inflammatory marker produced by the innate immune system with exposure to a microbial cell membrane, such as B. burgdorferi. Elevations in C3a are therefore indicative of a microbial source of biotoxin illness, and thus necessitates investigation and eradication of the infective agent. Like C4a, C3a is an anaphylatoxin which mediates chemotaxis,

contraction of smooth muscle, increased vascular permeability and histamine release from mast cells

- MMP-9- (Matrix Metalloproteinase-9)- an enzyme of the innate immune system, produced by blood vessel endothelium. Elevation in MMP-9 results in increased vascular permeability, thus assisting the delivery of inflammatory products to the local tissues- including lungs, nervous system and musculoskeletal system.
- α-MSH (Alpha-Melanocyte Stimulating Hormone)- a neuro-regulatory hormone, which at normal levels helps to regulate proper immune system functioning in the body. Low levels result in abnormal regulation of cytokines, endorphins, melatonin, sex hormones, cortisol and ACTH.
- ADH- (Anti Diuretic Hormone)- a hormone that is produced by the body to maintain proper osmolality (free water-solute balance). When normal, ADH is typically reflective of osmolality levels and vice versa- meaning when ADH is elevated, as is osmolality. Incongruent levels, such as low ADH paired with high osmolality may be caused by abnormal a-MSH functioning as a result of biotoxin exposure.
- VEGF (Vascular Endothelial Growth Factor)- a growth factor produced by the body to stimulate angiogenesis. Initially, VEGF will be increased in patients with CIRS in response to hypoperfusion of the capillary bed. However, after time, the cytokines produced by the biotoxin exposure will work to suppress VEGF, further exacerbating hypoperfusion and decreased oxygenation of tissues.
- TGF-beta-1 (Transforming Growth Factor beta-1)- an inflammatory marker with widespread effects. TGF- beta-1 is typically used by the immune system to produce T regulatory cells, which keep downstream subtypes of T helper (Th) cells in balance. When TGF-b-1 is elevated above normal levels, there is a hydrolysis of T regulatory cells to pathogenic effector T cells. These cells in turn produce more TGF-b-1, thus further depleting the T regulatory cell count. Low levels of T regulatory cells increase the likelihood of a Th1, Th2, and Th17 imbalance. Such imbalances can increase predilection to allergies, autoimmunity, and decreased functionality of the protective measures of the immune system.
- VIP- (Vasoactive Intestinal Polypeptide)- a neuro-regulatory peptide indicative of blood flow. Decreased levels of VIP, found in 98% of CIRS patients (and only 10% of controls), are reflective of abnormal pulmonary artery pressure and capillary hypoperfusion. When levels are normal, VIP assists in the proper management of inflammatory reactions, hormonal regulation and oxygen delivery to tissues. Specifically stated in regards to CIRS patients, when VIP levels are corrected it: raises T regulatory cell levels, regulates Th17 balance, supports proper circadian rhythm, dampens innate immune system over activation, improves PASP and inhibits TGF-b-1.
- MARCoNS- (Multiple Antibiotic Resistant Coagulase Negative Staphylococcus)- an exotoxin producing antibiotic resistant staphylococcus collected from the posterior nasopharynx. A positive culture result is determined by antibiotic resistance to 2 or more drug classes. These specific bacteria release toxins into the surrounding tissues of the nasopharynx. These toxins can interfere with the production of α-MSH, thus exacerbating low levels. MARCoNS also produce hemolysin which causes disruption of endothelium, and red blood cell membrane integrity, thus potentiating bleeding and clotting disorders.

Additional labs and imaging may also be drawn to help assess the prognosis of the disease state and the efficacy of treatment. These labs may include, but are not limited to:

- T-regulatory cell assays- to assess for improvement in T reg function with correction of MSH and TGF-b-1
- Von Willebrand's panel- to assess for acquired von Willebrand's syndrome as a result of elevated C4a.
- Anti-cardiolipin antibodies-to assessing hypercoagulation states.
- Anti-gliadin antibodies- to rule out celiac disease as a cause of GI dysfunction, as low α-MSH and elevated TGF-b-1 can cause GI dysfunction. Additionally, anti-gliadin antibodies can develop because of T-regulatory cell dysfunction, but can be corrected with avoidance of gluten, thus distinguishing it from a true celiac reaction.
- PaxGene testing- initial research has demonstrated changes in gene transcription with VIP use. Such information aids in the understanding of the efficacious mechanism of action of VIP treatment, and thus additional elucidation of the genetic etiology of CIRS.
- NeuroQuant- research reveals correlative interstitial edema of cortical gray matter and forebrain parenchyma, while also demonstrating caudate atrophy. Imaging may aid in the diagnosis, prognosis and determination of treatment efficacy in CIRS cases.

Treatment

Step 1- Removal from exposure

As each step in the treatment of CIRS builds on the previous step, it is therefore mandatory that each step be completed before moving forward. Following such logic, the most critical step is the first, which is the removal of biotoxin exposure. When CIRS develops as a result of exposure to biotoxins in water damaged buildings (CIRS-WDB), either proper remediation or full avoidance is required. Many people do not have the luxury to completely avoid a water damaged home, work place, school, or car. Instead these CIRS-WDB patients need to navigate the process of remediation, which because of varying industry standards, can be overwhelming and often incomplete. Therefore, it is suggested that patients contract with an Indoor Environmental Professional (IEP) who has experience with CIRS clientele. A desirable IEP will not only test the indoor air quality appropriately, but will also suggest a thorough remediation, and will outline the instructions accordingly in detail. As complete remediation is required for the safety of CIRS patients, a higher standard of care, and attention to detail is required throughout the remediation process. Therefore, it is also advised that the CIRS experienced IEP guides the remediation process. It is imperative that the ill patient does not remediate their own space, nor live in the space as it is being remediated—as they risk exacerbation of CIRS-WDB. Instead, an IEP may suggest a remediator with which they have previously worked. If the IEP is not local, it is advised that the patient screens local remediators by asking if the company would be willing to work in conjunction with the CIRS IEP. After remediation, a third-party assessment of the indoor air quality (not done by the remediators) is necessary. It is also suggested that clients work with the IEP to set standards of indoor air quality that need to be met following remediation work. These standards should be set forth in a contractual agreement with the remediators.

Once the remediating process has occurred it is not frowned upon for a patient to keep their home at 35% humidity or less. Additionally, patients may choose to employ various air filtrations devices, however doing so should be done with caution, as not all air filters, scrubbers, sanitizer or purifiers are created equal. Additionally, some may exacerbate complaints, while others may act as reservoirs

if not maintained, and some may even fail in their filtration ability over time. Making an informed decision based on the individual's needs with the oversight of the CIRS IEP is suggested.

Although curiously now considered to be investigational by the EPA, the ERMI is one of the best ways to determine "livability" of a water damaged space. The ERMI is available through mycometrics, and is an assessment of quantities of various species of mold, as determined through DNA analysis. When a space has been properly remediated, an ERMI under 2 should be safe for those patients who have a C4a below 20,000 and an α-MSH less than 35. For those with an C4a over 20,000 and an α-MSH under 35, and ERMI level of -1 is the only safe space. A HERTSMI-2 evaluation may also be used to indicate safety of a WDB. A HERTSMI-2 score of 11 or below indicates a safe space for CIRS-WBD patients. However, patients who are more sensitive, may require a HERTSMI-2 below 8 for optimal health.

Step 2- Sequester Biotoxins

Cholestyramine (CSM) is used in CIRS patients to sequester biotoxins from the body. Originally used as a lipid lowering drug, it is now used for its off label ability to bind to negatively charged particles using its quaternary ammonium structure. This binding affinity prevents enterohepatic recirculation of the biotoxins via the bile. Goal dosing of CSM is four grams four times per day, thirty minutes before a fat containing meal. All other supplements and medications should be taken away from CSM dosing, preferably one hour prior to dosing, or two hours following dosing. As CSM exerts its medicinal benefit in the gut, and it is not absorbed, it is not uncommon for patients to have side effects of constipation, gas and bloating. If CSM is poorly tolerated Welchol is an alternative option, however it is less efficacious in its binding affinity compared to that of CSM's. Additionally, for those who are food and chemically sensitive, a pure resin form of CSM is available, without added sugar, artificial sweeteners, or flavoring. Pairing CSM with the low amylose diet is necessary for best outcome. If a patient is having difficulty tolerating CSM initially, treatment is stopped, and a loading dosage of three to four grams of combined EPA & DHA for approximately one week may be suggested prior to re-starting the CSM treatment. Tracking efficacy of treatment with repeat VCS is suggested.

Step 3- Eradication of MARCoNS

If the MARCoNS nasal swab is positive, it should be treated with BEG spray. BEG spray is a combination of Bactroban, EDTA and Gentamycin. The EDTA acts as a driver delivering the antimicrobial Bactroban and Gentamicin into the biofilm. Recent research suggest that EDTA may also impart its own antimicrobial activity. Application should be two sprays in each nostril two times per day. Recent suggestion of using a muco-adhesive polymer for sustained nasopharynx delivery has been studied with positive results. An additional culture needs to be performed following treatment in order to confirm eradication. Patients who have successfully cleared MARCoNS are susceptible to recurrent inoculation from numerous sources, including exposure including dogs, loved ones, and WDBs.

Step 4- Gluten Free Diet

This step is to be carried out if anti-gliadin antibodies are present. A gluten free diet should be maintained for a minimum of 3 months in order to assess for a reduction in anti-gliadin antibodies If

the antibodies remain elevated after 3 months of avoidance, then celiac disease is suspected. If anti-gliadin antibodies improve, then the initial elevations were more than likely due to a T-regulatory cell imbalance, TGF-b-1 elevation and/or α-MSH deficiency. One should also keep in mind that a gluten free diet removes a major source of amylose from the diet, which is mandatory during treatment with CSM.

Step 5- Correction of Androgen Imbalance

Correction of androgen imbalance should be done with caution. As CIRS can upregulate aromatase, unintended testosterone conversion to estrogen must be considered. Supplementation with testosterone is not suggested, as the increased aromatase activity readily depletes testosterone by converting it to estrogen; thus further worsening the androgen to estrogen ratio in both men and women. Instead the preferred initial intervention is DHEA. However, the ultimate resolution comes from the correction of α-MSH depletion.

Step-6- Correction of ADH

Correction of ADH and osmolality occurs with the use of DDAVP, or Desmopressin acetate. Treatment involves .2mg every other day for fourteen days. As DDAVP does impact fluid balance it is imperative to track peripheral edema, weight gain blood pressure, serum osmolality and sodium levels in the blood.

Step 7- Correction of Elevated MMP-9

Previously Actos was used to help lower MMP-9, however the preferred intervention is now treatment with a low-amylose diet in conjunction with high doses of EPA and DHA omega 3 fatty acids for a minimum of one month. Historically, treatment with Actos was suggested, but has since been reserved for cases that are non-responsive to the aforementioned interventions. Long term use of Actos has been linked to bladder cancer when used chronically for ten years; for this specific treatment protocol 45mg would be used for ten days only.

Step 8- Correction of Low VEGF

VEGF is corrected using the same protocol as was used for the correction of MMP-9. Additionally, in order for VEGF to remain at a healthy level, avoidance of re-exposure is mandatory.

Step 9- Correction of Elevated C3a

C3a is elevated in the presence of a bacterial cell membrane, therefore identification and eradication of the infective agent is necessary. After doing so, elevated C3a is treated using any number of statin medications, at a dosage of 80mg per day. Additionally, supplementation with ubiquinone is suggested as to avoid the possible side effect of rhabdomyolysis. When rhabdomyolysis occurs, muscle fibers are degraded and the metabolites are released into the blood stream, potentially leading to kidney damage.

Step 10- Correction of Elevated C4a

The initial correction of C4a comes in the form of avoidance of exposure. After that is ensured, and all previous steps have been adhered to, a trial of low dose Procrit may occur. Dosing of Procrit occurs every 3 days, for a total of 5 doses. This schedule will allow for an 8,000unit vial to be used completely over the course of 15 days. Procrit, also known as erythropoietin, is an endogenously produced glycoprotein hormone used to stimulate red blood cell production in the bone marrow. Therefore, when exogenous sources are provided, it is possible that a hypercoagulable state may result, as well as an elevation in hemoglobin. Thus hemoglobin and d-dimer labs should be drawn during the course of administration. As risk of cardiovascular events is also included in the listed of side effects, blood pressure should also be closely monitored. Since Procrit has a black box warning, it should be avoided in those with clotting disorders, cancer, and kidney failure treated with dialysis, among others.

Step 11- Reduction of Elevated TGF-beta-1

Treatment of TGF beta-1 occurs with the ARB drug known as Losartan, or Cozaar. The mechanism of action lies in the metabolite known as EXP 139. This degradation product significantly lowers TGF-beta-1. Losartan is the only Angiotensin II Receptor Blocker (ARB) that has this effect. Dosage varies depending of weight, and can range from 25 to 50 mg per day. If a patient presents with hypotension, and they cannot tolerate further reduction in blood pressure via an ARB, then treatment with VIP should be considered, but only if the specific treatment criteria is met.

Step 12- Correct low VIP

VIP is corrected by adherence to the previous steps, wherein attempts to address the innate immune system activation have occurred. For the non-responders of the first 11 steps, VIP is the chosen treatment. There are four criteria which the patient must meet in order to be considered for treatment with VIP, these include: normal VCS testing, continued avoidance of exposure to space with an ERMI >2, or HERTSMI-2 $\geq$ 10, a negative MARCoNS culture, and normal lipase levels. After confirmation of the aforementioned, additional necessary testing includes: VIP, α-MSH, C4a, TGF beta-1, MMP-9, VEGF, testosterone, estradiol, T-regulatory cell assay, and a stress echo; all of which are required in order to procure a treatment baseline. Treatment with an intranasal delivery of 50mcg/ml of VIP in one nostril four times per day can then occur. After thirty days of use C4a, TGF beta-1, lipase should be redrawn. Additionally, another VCS and stress echo should be ordered in conjunction with blood pressure monitoring. If all parameters are within normal ranges, or improving, the dosage can be reduced to two times per day for thirty more days, and then once daily dosing for thirty days. Discontinuation may occur at the ninety-day point if the patient is feeling well. In some instances treatment may be extended. Screening labs and testing should occur at monthly intervals during use, and eventually at the six-month point following discontinuation. Discontinuation must occur with elevated lipase enzymes or abdominal pain.

Step 13- Recheck lab values

Recheck the labs to assess for resolution, and to investigate any additional exposure. It should be noted that if a patient suspects exposure to a WDB, then CIRS relevant labs should be redrawn, and the treatment protocol restarted. Hence the first step being the most important step, and also the most difficult of them all—avoidance of exposure.