CIRS- Chronic Inflammatory Response Syndrome

The Shoemaker Protocol

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The hidden disease of chronic inflammatory response syndrome (CIRS) is a multisystem, multi-symptom illness acquired following exposure to environmentally produced biotoxins. According to Dr. Ritchie Shoemaker about 80% of the sources of biotoxin emanate from water damaged buildings where fungi, bacteria, volatile organic compounds, endotoxins and actinomycetes abound. Additionally, biotoxins are produced by tick-borne illnesses like Lyme from Borrelia burgdorferi, Babesia microti, and the spider venom of Loxosceles recluse. Other sources include consumption of contaminated reef fish (Ciguatera) and direct inhalation or contact to contaminated water (Pfiesteria and Cyanobacteria). Living in Minnesota many of these sources of biotoxin are prevalent and I am well aware of the prominent possibility that this list is not complete and only represents a growing of potential biotoxin exposures to be discovered.

The mechanism of illness created by biotoxins has caused much confusion among a suffering population and their treating practitioners. After more than 30 years of research discovering the layers of pathophysiology in this disease, through genetics, proteomics and newer transcriptomics, we are able to clarify that chronic illness occurs among a subset of the population who are deemed to be genetically susceptible. About 24% of people who are exposed to a biotoxin will experience an inability to have their immune system recognize and react appropriately to that biotoxin, thereby misdirecting inflammation within the body. Many symptoms are associated with CIRS that would appear to be random and unrelated, hence the confusion for treating practitioners. Because we are certain about ¼ of the population is vulnerable to this syndrome, the following evaluation, diagnosis and treatment protocol has been developed, the importance of which cannot be overestimated.

Evaluation

In a recently published report in the Internal Medicine Review (2018) CIRS case definition includes:

1) Potential for exposure, to a damp indoor space or other biotoxin source
2) Identification of a multisystem, multi-symptom illness seen in peer-reviewed publications
3) Laboratory testing results similar to those seen in peer-reviewed, published studies
4) Documentation of response to therapy

There are 37 identified symptoms within these 13 clusters as follows.

- Age 0-11y.o. 5 systems or greater + symptom evaluation
- Age 11y.o. + 8 systems or greater + symptom evaluation

Diarrhea	Congested sinuses	Trouble concentrating	Joint pain

Abdominal pain Numbness	Shortness of breath		Morning stiffness Muscle cramps
Disorientation Metallic taste Watery eyes	Blurry vision Night sweats Mood swings	Dizziness Static shocks	Extreme thirst Cough Confusion
Deep, persistent fatigue	Ice-pick pain Blood shot eyes	Impaired memory Difficulty with word finding	Trouble regulating body temperature Frequent urination
Weakness Body aches Sensitivity to light Trouble learning new information		Heightened skin sensitivity Tingling/pins and needles	

In reviewing the above symptoms and system clusters it is easy to understand that patients probably have seen multiple practitioners in their quest to find answers. Some diagnoses may have become attached to patients in error and must be evaluated thoroughly. Starting with a review of past medical records is very important and gives the practitioner time to view previous laboratory results helping to rule out possible differential diagnoses. Building a relationship with the patient and family members will expedite getting accurate information and create a bridge of trust that will be needed not only for treatment of CIRS if identified, but also for the all encompassing discussions of remediation and learning to live in a world where biotoxin exposure is easy.

An initial office visit will include the above mentioned review of records, history of present illness and evaluation of symptoms, personal, social, family histories, a review of systems, current medications and supplements, a discussion of potential environmental exposures and thorough physical exam. Next creating the differential diagnoses, ruling out other possible disease, and identifying next steps in laboratory evaluation which are specific to CIRS inflammatory markers and probably will not have been considered by other consulting practitioners.

DIAGNOSIS

Diagnosis of CIRS can be complex and many faceted with each data point contributing to the constellation of evidence to treat these very sick CIRS patients. Starting with an in office visual contrast sensitivity (VCS) test which has been shown to be a reliable screening tool about 92% of the time for patients with CIRS. A failed VCS is indicative of decreased neurological integrity in the visual pathways running between the retina and the cortex of the brain. Some patients may have participated in an online screen for VCS but a hard copy test will be the most accurate and reproducible as this will be used at each step in the treatment protocol.

An initial laboratory test is called HLA DR by PCR. The following key (Rosetta Stone) helps both practitioner and patient/family understand the genetic basis for this life changing diagnosis.

Cause	DRB1	DQ	DRB3	DRB4	DRB5	
Multisusceptible	4	3		53		**DREADED**
	11/12	3	52B			**DREADED**
	14	5	53B			

Mold susceptible	7	2/3		53		Stacybortrys Aspergillus Penecillium Wallemia Chaetomium
	13	6	52 ABC			
	17	2	52A			
	18	4	52A			
Borrelia, PLS	15	6			51	Borrelia Babesia Bartonella Anaplasma Erlichia
	16	5			51	
Dinoflagellates	4	7/8		53		Cyanobacteria Pfiesteria Cylindrospermopsis Microbystis Ciguatera
MARCoNS	11	7	52B			Biofilm Staph
Low MSH	1	5				
Not recognized as significant	8	3,4,6				
Low risk mold	7	9		53		
	12	7	52B			

The following laboratory tests are collected, some of which will be markers unique to CIRS and be followed as objective evidence to their healing progression.

- **aMSH** (alpha melanocyte stimulating hormone)- a neuro-regulatory hormone which helps to regulate proper immune system function. In CIRS this will be low (normal levels 35-81 pg/ml) and result in abnormal regulation of cytokines, endorphins, melatonin, sex hormones, cortisol and ACTH. Symptoms of low MSH can include chronic fatigue, chronic unusual pain syndromes, headache, decreased concentration, temperature instability, muscle aches, sleep disturbance, gluten intolerance, ADH/Osmolality imbalance and wt gain potentially due to leptin resistance.
- **MMP-9** (matrix metalloproteinase-9)- is produced by elevated cytokines delivering inflammatory elements from blood into extra cellular spaces of the brain, muscles, lung, peripheral nerves and joints (normal levels 85-320ng/ml). Some symptoms seen may include headaches, neurological issues, cognitive issues, muscle pain, lung function, static shocks and urinary frequency.
- **C4a** is a complement split anaphylatoxin which mediates chemotaxis, contraction of smooth muscle, increased vascular permeability and histamine release from mast cells (normal levels 0-2830 ng/ml). This is elevated in CIRS and acts also as an early indicator of re-exposure.
- **VEGF** (vascular endothelial growth factor) a growth factor produced to stimulate angiogenesis, vasodilation and neuroprotection (normal levels 31-86 pg/ml). At first in

CIRS this indicator will be elevated but later suppressed. Symptoms may include shortness of breath, decreased cognitive function, fatigue or muscle cramps.

- **TGF b-1** (transforming growth factor beta-1) regulates immune and tissue cell growth and proliferation. This biomarker has a dual role of either creating or suppressing inflammation (normal range <2382 pg/ml). Elevated levels of TGFb-1 may damage normal T-regulatory cell functions that prevent autoimmunity by turning on TH 17 cells thus converting T regulatory cells in tissue to pathogenic T cells. Th17 cells have been identified as a lineage distinct from Th1 and Th2 cells, and are required for induction of several autoimmune diseases. With high levels of TGF beta-1 you may see lung symptoms, neurological problems, autoimmune disease, learning disability, MS, resting tremors and unusual seizures.
- **VIP** (vaso intestinal polypeptide) is a neuroendocrine peptide distributed in the central and peripheral nervous systems as well as in peripheral tissues, such as various areas of the skin. VIP helps reduce inflammatory reactions, hormonal regulation and oxygen delivery to tissues (normal levels 23-63 pg/ml). Deficiency is common in CIRS patients who may exhibit shortness of breath especially with exertion, inflammation, and capillary hypoperfusion**.**
- **ADH** (antidiuretic hormone-vasopressin) acts on the kidneys to control free water. Measured in conjunction with osmolality. Symptoms potentially include chronic dehydration, increased urinary frequency, thirst, edema, wt gain, and shocks (normal ADH 1.3-8 ng/ml with normal Osmolality 275-295 mOsm/kg).
- **C3a** another complement split anaphylatoxin which when elevated indicates exposure to microbial cell membrane (like B. burgdorferi) and like C4a, mediates chemotaxis, contraction of smooth muscle and increased vascular permeability (normal levels 60-200 ng/ml).
- **Anti-gliadin antibodies**- evaluation of gliadin intolerance with potential of celiac in light of possible autoimmune triggers
- **Anticardiolipins**- IgA, IgG
    - autoantibodies seen in collagen vascular diseases (lupus, scleroderma)
    - High titers= increased intravascular coagulation (tx heparin, coumadin)
    - Low titers = hypercoagulability
- **ACTH** (adrenocorticotropic hormone) is a hormone produced in the pituitary gland in the brain (normal levels 8-37pg/ml). The function of ACTH is to regulate levels of the steroid hormone cortisol, which is released from the adrenal gland.
- **Androgens** (testosterone, androstenedione and DHEAs) often develop imbalance in biotoxin illness due to up-regulation of aromatase.
    - Normal ranges men-
        - 75-205 ng/ml androstenedione
        - 350-1030 ng/ml testosterone
        - 70-218 ng/ml for DHEAs
    - Normal range- pre menopause
        - 60-245 androstenedione
        - 10-55 Testosterone
        - 48-247 DHEAs

    - Normal range post menopause
        - 30-120 Androstenedione
        - 7-40 Testosterone
        - 48-247 DHEAs
- **MARCoNS** (multiple antibiotic resistant coagulase negative staphylococcus)
    - Nasal culture to determine colonization of MARCoNS
    - This bacteria form a biofilm (slime dome) sending out hemolysin proteins which trigger cytokines 24/7
- **T reg cell assays**- to assess for improvement in correlation with MSH and TGFb-1.
- **Von Willebrand's panel**- with elevation of C4a acquired hypocoagulation state may occur.
- **PAX Gene testing**- data collection of transcriptomics with use of VIP treatment.
- **NeuroQuant**- correlative edema of cortical grey matter and forebrain parenchyma along with atrophy of caudate is captured through brain MRI with NeuroQuant and is helpful in determining type and presence of biotoxin.

TREATMENT

#1	**Remove patient from exposure!** Educate pt/family Provide resources for remediation assistance	Once identified CIRS treatment will be less effective if the patient has ongoing exposure. This is one of the most difficult steps in treatment due to the potentially overwhelming nature of remediation. Therefore working hand in hand with a trained IEP is imperative. In home testing: MSQCPR (mold specific quantitative polymerase chain reaction) fungal DNA test QPSR-DNA method of identifying and quantifying molds ERMI- (environmental relative moldiness index) tests for 36 species- for pts with CIRS/WDB, ERMI scores < 2.1 is recommended. HERTMI-2- identifies 5 organisms from ERMI and stratifies-a score of >10 can indicate potential for relapse problems. Because this initial step is often fraught with fear, denial and confusion…I have begun to incorporate a recommendation to my patients to purchase a wonderful handbook to walk them through the complexity of living with CIRS. MOLD ILLNESS: SURVIVING AND THRIVING A Recovery Manual for Patients & Families Impacted By CIRS by Paula Vetter MSN, Cindy Edwards RN and Laurie Rossi IEP
#2	Reduce biotoxin load May be used prophylactically for re-exposures PRN	The medication Cholestyramine is a positively charged binder which attracts negatively charged biotoxin and removes it in stool. Possible side effects include constipation and gastric reflux. (see appendix) Cholestryamine 4 grams QID (taken on an empty stomach-may need to titrate up slowly with sensitive patients) Or Welchol 2 tablets TID with food (for those who aren't able tolerate Cholestyramine) VCS- when pt passes VCS move onto next step of protocol
#3	MARCoNS	Obtain nasal culture- if API-Staph culture specific for coagulase negative staph shows resistance to 2+ distinct classes of antibiotics, treat with

	Multiple antibiotic resistant Coagulase negative Staphylococcus	• Hydrosol Silver and EDTA nasal spray, 2 sprays each nostril TID for 30 days • Repeat nasal culture after nasal spray is finished • For persistent MARCoNS- EDTA 2 sprays each nostril TID 6-8 weeks • Repeat nasal culture after nasal spray is finished • If MARCoNS persists- check canine, other person or ongoing environmental exposure
#4	Correct antigliadin antibodies (AGA)	Low MSH causes dysregulation of T-reg cells with the potential development of autoimmune disorders. Serum IgA and IgG antigliadin antibodies are checked. If positive running a TTG-IgA will help to rule out celiac disease, but T-regulatory cell dysregulation may show negative result. Avoidance of gluten containing foods for at least 3 months Recheck AGA, i f negative start slowly reintroducing foods Test TTG (tissue transglutaminase) if elevated, gluten free forever
#5	Correct androgens	Abnormal androgens are commonly caused by up-regulation of aromatase. Low DHEA- supplement with up to 25mg TID x 30 days Check estradiol levels 2 weeks after DHEA supplement started Excess aromatase activity will be corrected by VIP later in protocol Do not correct testosterone due to up-regulated aromatase and potential to convert any excess testosterone into estrogen.
#6	Correct MMP-9	MMP-9 increases vascular permeability allowing inflammatory molecules to enter brain, nerves, muscles, joints and lungs with accompanying symptoms. If MMP-9 is elevated > 332 ng/ml High dose fish oil 2.4 gm EPA and 1.8 gm DHA qd Low amylose diet
#7	Correct ADH/Osmolality	We may see symptoms of polydipsia, polyuria, postural hypotension, migraine-like headaches and frequent static shocks. Low ADH is treated with desmopressin (DDAVP) 0.2 mg qod at HS for 2 weeks Check serum Na+ level in 5 days and 10 days to monitor for hyponatremia Daily weights and weekly electrolyte monitoring if on DDAVP Instruction on circumference measurement of calf about 6-8 " up from medial malleolus to monitor developing edema.
#8	Correct VEGF	Symptoms may include brain fog, fatigue, muscle pain, dyspnea with exertion and post exercise exhaustion. Low VEGF (<31 pg/ml) Treat with low amylose diet and high dose fish oil 2.4 gm EPA and 1.8 gm DHA qd
#9	Correct C3a	Complement C3a is elevated in the presence of bacterial membranes such as Borrelia. First treat with antibiotics if that had not been done. If C3a remains elevated Start CoQ10 150 mg qd. On day 10 start Zocor 80 mg qd Check liver enzymes prior to starting statin medication and repeat in 1 month
#10	Correct TGF beta-1	Transforming Growth Factor Beta-1 causes tissue remodeling, down-regulates VEGF and influences T Reg cells inducing autoimmunity. If TGF-B1 is > 2380 pg/ml treat with losartan 12.5mg to 25mg QD (always start low and go slow) When BP is stabilized, increase losartan to 25mg BID x 30 days Monitor BP during therapy especially for pts already on antihypertensives. Test CIRS specific T-Reg Cell Panel (CD4 + CD25 ++ CD 127 lo/-) This will also be addressed with subsequent VIP therapy for patients unable to tolerate

		BP reduction on losartan.
#11	Correct C4a	Complement C4a is a potent anaphylatoxin indicating the severity of the syndrome. If C4a level is >2830 ng/ml treat with VIP (vasoactive intestinal polypeptide) 50 mcg/ml single spray QID (see instructions below)
#12	Correct VIP	If patient is still symptomatic after all above steps, VIP offers hope. There are 4 criteria the patient needs to meet for VIP therapy: 1. MARCoNS culture must be negative. 2. VCS testing is negative or normal. 3. Avoidance of exposure evidenced by ERMI <2 or HERTSMI2 <11 4. and normal fasting lipase levels <60 u/l Monitor baseline labs VIP, MSH, C4a,TGF b-1, MMP-9, VEGF, testosterone, estradiol, CD4+CD25++Tregs and lipase as well as baseline echo to verify positive Pulmonary Artery Systolic Pressure (PASP). Serum lipase level is tested before VIP and monthly during VIP therapy. If there is a significant rise in lipase, determine the cause and consider cessation of VIP therapy. Additionally if pt develops abdominal pain discontinue VIP and check for gallbladder dysfunction. TGF b-1 is drawn prior to administration of VIP and 15 minutes after first dose. If there is an elevation in TGFb-1 it is an indication of hidden mold exposure. First dose of VIP should be administered in office: observe for acute changes in symptoms positive or negative, monitor BP, skin rash or other symptoms. If pt tolerates in office dose, may continue with VIP 50 mcg/ml, 1 spray QID. Redraw labs after 30 days: C4a, TGFb-1 and fasting lipase. If labs are stable and pt is tolerating can continue for 30 more days and taper down to BID, then 30days, then discontinue VIP. VIP must be refrigerated, kept in upright position and will last about 90 days.
	Monitor stability	Monitor clinical symptoms Monitor laboratory tests when off of medications Thorough education to patients about vigilance in avoiding re-exposure Prophylactic use of CSM or Welchol for potential re-exposure

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Chronic Inflammatory Response Syndrome (CIRS)	
Start Low Amylose Diet This diet is instrumental in decreasing inflammation and correcting several biomarkers in your laboratory results.	Forbidden Foods • Roots and tubers including white and sweet potatoes, beets, peanuts, carrots and other vegetables which grow underground. Onions and garlic are permitted. • Bananas (the only forbidden fruit) • Wheat and wheat based products including bread, pasta, cakes, crackers, cookies, cereals. • Rice, Oats, Barley, Rye • Foods with added sugar, sucrose, corn syrup or maltodextrin. Allowed Foods • Allowed foods include basically anything that is NOT on the list of forbidden foods including: • Corn • Onions and garlic • All vegetables that grow above ground like lettuce, tomatoes, beans (all types), peas, cucumbers and celery. • All fruits except bananas • Meat, fish, and poultry • Condiments- avoid low-fat foods as they usually contain added sugar. • Spices • Eggs • Dairy (avoid sugar laden products). • Nuts and seeds- pumpkin, sunflower and squash seeds • If you have been advised to be on a gluten-free diet, no changes need to be made in order for you to eat gluten-free. This diet does not allow rice while gluten-free products frequently use rice as a substitute for wheat. You can use garbanzo bean flour as wheat flour substitute in cooking.
Start Omega 3 FAs- strong antiinflammatory	High dose fish oil 2.4 gm (2400 mg) EPA and 1.8 gm (1800mg) DHA /day. About 4000 mg of combined EPA & DHA daily. Can divide doses. Can take with meals.

CSM Patient Instructions

- The Medication you have received contains Cholestyramine Resin Powder.
- Keep this medication in the container it came in, tightly closed, and out of reach of children. Store it at room temperature and away from excess heat and moisture (not in the bathroom).
- Cholestyramine Powder should be discarded after 180 days.
- 1.75 teaspoonfuls provide 4 grams of pure Cholestyramine Resin.
- Mix 1.75 teaspoonfuls with 240ml to 360ml (8oz-12oz) of water, with some apple juice or cranberry juice for flavor. Mix or blend thoroughly. Mixture will settle quickly and may be gritty. (You may add more juice or water, but you need to drink the entire amount.)
- To prevent constipation, drink a full glass of water before and after you take the dose described above.
- Cholestyramine Powder should be taken 30 minutes prior to a meal- on an empty stomach. Take any other medication(s) either 1 hour before or 3 to 4 hours after taking Cholestyramine.
- This medication may cause constipation, bloating, gas, and/or abdominal discomfort. Please contact your prescriber regarding any concerns or issues that may occur after starting this medication.

Sample daily routine.

6am	Get up, immediately take any necessary medication or supplements If you are taking thyroid medication you will need to take supplements about 3 hours later thus missing your first dose of CSM also. High dose fish oil 2.4 gm EPA and 1.8 gm DHA daily ~4000mg total
630 am	Eat breakfast- smoothies with fruits and vegetables are great to keep GI tract moving. Low amylose diet.
730 am	Take dose of CSM- can drink as much water as you want- more is better (If you are sensitive to medications and can only tolerate 3x/day, leave off this dose of CSM)
11:00 am	Take dose of CSM- can drink as much water as you want- more is better
12 pm	Eat lunch-
3 pm	Take dose of CSM can drink as much water as you want- more is better
6-630 pm	Eat dinner - take magnesium citrate 400 mg to keep GI tract moving, also can try senna or smooth move tea. Can take any other supplements or medications as needed.

	High dose fish oil
930 pm	Take dose of CSM If GERD symptom can take GI Encaps by Thorne- or slippery elm and marshmallow paste (made with a little water) this also coats stomach lining. This symptom should resolve within first week or 2 of using CSM.

- The most important thing is to have regular daily bowel movements as this is the way the CSM is taking biotoxins out of your system.
- If you cannot tolerate 4 doses/day, then try 3, but consistency is very important. If you unable to start with 4 doses/day, you can start with 2 doses- 1 in am and 1 in pm, and build up to 4 doses/day.
- If you have constipation, we may need to give you additional medications/supplements to help bowel movements.
- If you have bloating, gas or abdominal discomfort you should let your practitioner know. Adding coconut oil to dose of CSM can help with bloating and gas.
- If you have GI burning or reflux type symptoms you can use GI Encaps by Thorne Research or try over the counter H2 blocker (zantac), or notify your practitioner. These are usually temporary as the body gets used to CSM.
- If you are not tolerating CSM at all after 1 week of trial, contact your practitioner.
- Remember, this is a marathon, not a sprint. Pushing through adverse reactions may lead to more problems.