

CHRONIC INFLAMMATORY RESPONSE SYNDROME (CIRS)

Overview, Diagnosis, and Treatment

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INTRODUCTION

This overview is designed to be a practical synthesis and overview for Chronic Inflammatory Response Syndrome (CIRS). It will be used in Rezilir Health's clinical practice as an operational guide and we will commit to update it on an annual basis as a "living document". It is not meant to be comprehensive or encyclopedic as that has been done elsewhere. Updates will reflect new changes based on front line practice and advances in the scientific literature.

OVERVIEW

The WHO estimates that 50% of buildings in Western countries have some degree of water damage. 90% of environmental exposure in Western civilizations now occur from indoor environments rather than outdoor environments. 24% of people have a HLA susceptibility in how they process toxins from water damaged buildings. When these patients get exposed to biotoxins from water damaged buildings, they have an upregulation of their innate immune system and a defective adaptive immune response. This creates a multi-symptom, multi-system which can be readily diagnosed by the aware clinician.

The intersection of these risk factors creates an enormous public health challenge, compounded by the fact that most physicians do not think about CIRS on their differential diagnosis.

The opportunity for patients is that despite the multi-system, multi-symptom nature of CIRS, it is eminently treatable if managed by a clinician skilled in the diagnosis and treatment of CIRS. Hope is available. Cures are possible.

CASE DEFINITION OF CIRS

CIRS is defined as a chronic, progressive multi-symptom, multisystem illness caused by exposure to biotoxins (or neurotoxins derived from a biological source). The Government Accountability Office (GAO) in their 2008 reportⁱ described multiple elements for determining causation of symptoms to biotoxins. These elements are used in the current tiered definition of CIRSⁱⁱ

- Potential for exposure to biotoxins from water-damaged buildings of a given person to those findings already published (CIRS Tier 1 – exposure)
- History and symptomatic findings of a given person to those findings already published (CIRS Tier 1 – other diseases, symptoms)
- Lab findings of a given person to those seen in published studies on humans and animals (CIRS Tier 2 – laboratory tests)
- Response to therapy (CIRS Tier 3- response treatment)

Tier 1 – History (All 3 of exposure, other diseases, symptoms must be met)

- **Exposure** – Patient must have a history of an exposure to a biotoxin. This can include multiple sources including biotoxins from water damaged buildings, lyme & other related infections; Invertebrate species and insect bites.

- **Other diagnoses** need be ruled out – patients may carry misdiagnoses including chronic fatigue, allergies, fibromyalgia, depression, anxiety, attention deficit disorder, PTSD, somatization, irritable bowel syndrome, Parkinson’s, Alzheimer’s and somatization.
- **Symptoms** – There are 37 symptoms that are grouped into 8 organ system categories including general fatigue, muscles, general symptoms, eyes, respiratory, gastrointestinal, neurologic and cognitive. Symptoms in 4 out of 8 system categories are considered diagnostic.

Tier 2 – Laboratory Testing – 3 or more of 6 laboratory criteria must be met

3 out of 6 of the following laboratories need to be abnormal: visual contrast sensitivity (VCS), HLA testing, MMP-9 (matrix-metalloproteinase 9), ACTH/ Cortisol, ADH (antidiuretic hormone) / Osmolality and MSH (melanocyte stimulating hormone). The detailed results of the lab and explanations are in the subsequent lab section including many other labs that are measured routinely in CIRS but not in the classic criteria including: TGF-Beta 1 (transdermal growth factor beta one), VEGF (vascular endothelial growth factor), C4a, AGA (antigliadin antibody) and MARCoNS (multiple antibiotic resistance coagulase negative staphylococcus).

Tier 3 – Response to Treatment

Improvement in symptoms & VCS and lab markers are necessary (leptin, MMP-9 were used in the 2006 case definition). Other changes in tests including imaging, proteomics are not part of the definition but are practically used.

PATHOPHYSIOLOGY

The pathophysiology of CIRS is complex; it certainly involves many parts of physiology that may less familiar to many physicians.

Biotoxins (or neurotoxins derived from a biological source) are fat soluble molecules that can go from cell to cell *without being carried directly in the blood stream*. It can be difficult to impossible to measure them in blood tests. Instead we need to identify them via the damage they inflict on the body. There are multiple ways that people can get exposure to biotoxins.

1. **Inhalation in Water Damaged Buildings:** 50% of buildings in the US may have some water damage according to a 2011 report from the National Institute for Occupational Safety and Health. Water damaged buildings can harbor a toxic mix of fungi (mold and its fragments), bacteria (and its fragments), actinomycetes, mycobacteria, volatile organic compounds, and inflammagens such as endotoxins, beta glucans, mannans, hemolysins and proteinases. Mold species particularly associated with CIRS include *Aspergillus penicilloides*, *Aspergillus versicolor*, *Chaetomium globosum*, *Stachybotrys chartarum* and *Wallemia sebi*. This accounts for 80% of the CIRS-related illness burden.
2. **Tick or Spider Bite** – Ticks can carry *Borrelia burgdorferi* (Lyme disease), *Babesia microti* (Babesiosis) and other infections (*Bartonella*, *Anaplasma*, *Ehrlichia*). The Brown Recluse and Mediterranean Recluse spiders can also cause biotoxin illness.

3. **Ingestion** Ciguatera is the most common fish poisoning in the world; it is most often found in reef fish such as barracuda, grouper and snapper that have eaten smaller fish that consumed toxin producing *dinoflagellates*.
4. **Direct Contact with Contaminated Water** There are additional invertebrate species in water that produce neurotoxins including *Pfisteria* and cyanobacteria (*Cylindrospermopsis* and *Microcystis*). Patients can be exposed through direct contact with water contaminated by toxins in areas of fish kills or inhalation of airborne toxins from this source.

Biotoxins show a structure known as an amphipathic ionophore, which creates ion channels that can disrupt cell electrodynamics and cell function without destroying the cell. They reside primarily in the fatty acid membrane; as a result, they can directly impair nerve cell function and have a predilection for the brain, heart, and gastrointestinal sites.

In most people, biotoxins do not cause chronic illness. They are recognized by the immune system, broken down and removed by the immune system. The immune system has 2 major components – innate (nonspecific) and adaptive (specific).

- The innate system is nonspecific and recognizes toxins with *pattern recognition receptors (PRRs)*. The molecular components of pathogens recognized by PRRs are called pathogen-associated molecular patterns (PAMPs). The molecular components of cell components released during cell damage or death are called damage-associated molecular patterns (DAMPs). The innate system communicates with the adaptive immune system via macrophages and dendritic cells and recruits immune cells via TGF beta 1 and other cytokines. It also results in coagulation and complement activation.
- The adaptive system provides long term immunity and immunologic memory to specific antigens. T cell responses are controlled by antigen presenting cells (e.g., dendritic cells). T cells are activated and have distinct functional categories depending on the cytokines excreted. T cell subsets have designations such as Th1, Th2, T reg and T17. T cells teach the B cells to recognize and respond to invading toxins and to mount an appropriate antibody response.

For the genetically susceptible population, exposure to biotoxins causes an upregulation of the innate immune system followed by a defective adaptive immune response. 24% of the population has changes in their HLA system that makes them genetically susceptible to the biotoxins. In these patients the immune system does not recognize the biotoxins and fails to remove them. As a result, the biotoxins can circulate in the body indefinitely.

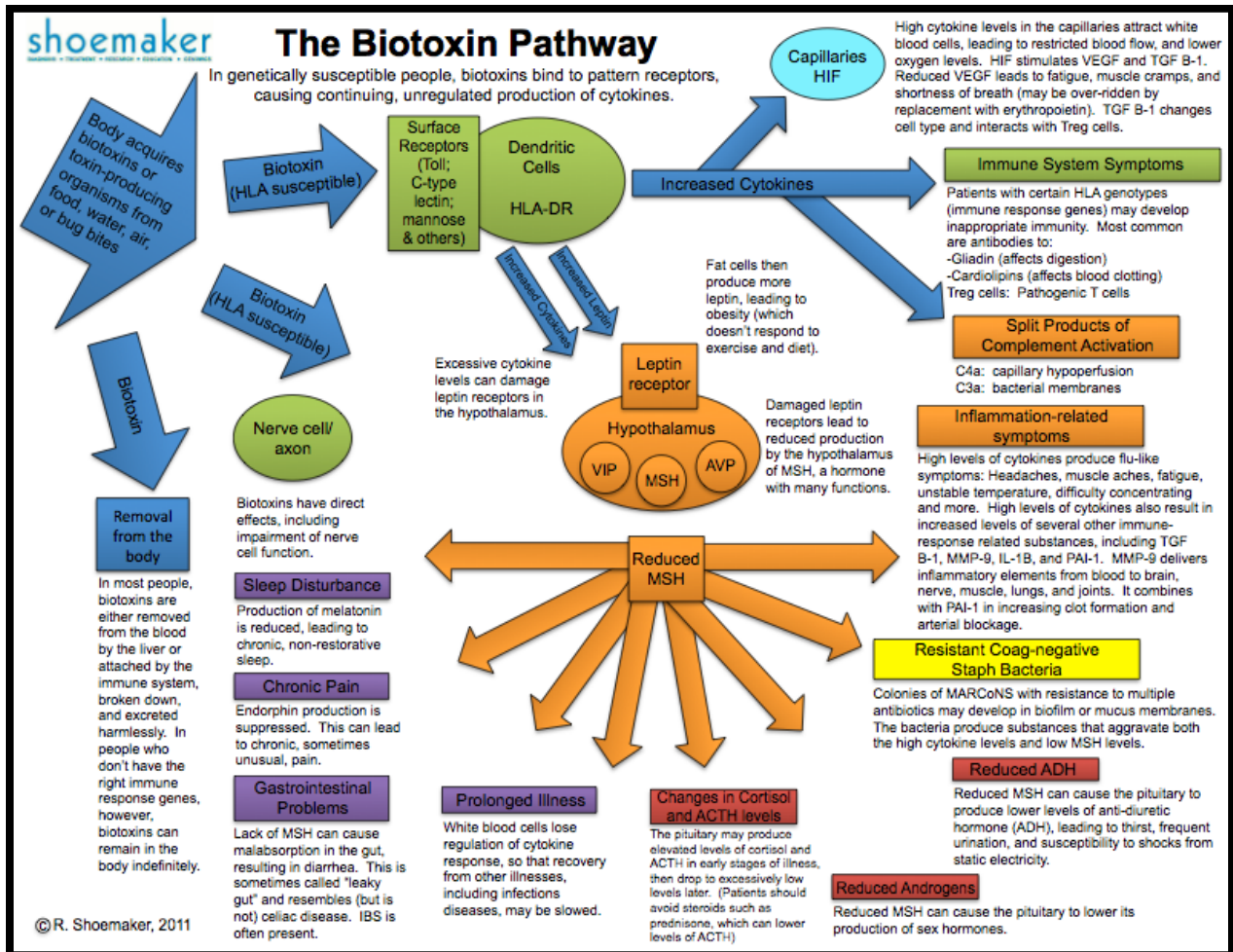
The upregulated innate immune system results in high levels of multiple cytokines (TGFB-1, VEGF, MMP-9) and complement activation (C4a, C3a), which can cause a plethora of symptoms.

Excessive cytokine levels can damage leptin receptors in the hypothalamus which increases leptin and reduces production of MSH and VIP. The impact on these regulatory neuropeptide hormones have cascading effects on the body including changes in cortisol, ACTH, androgens, ADH dysregulation, immune cell / innate immune functions (MARCoNS).

CIRS patients usually have low levels of T reg cells as a result of high TGF-Beta 1 levels. T reg cells are not usually measured directly in clinical practice. They normally suppress inflammation and autoimmunity – low levels of T reg cells therefore create ongoing inflammation and autoimmunity.

Post Treatment Lyme Syndrome occurs in about 20% of Lyme patients and has been a controversial topic since it was first identified in the mid-seventies, particularly because (until now) there had been an absence of reliable biomarkers. Research shows that 22% of population is genetically susceptible and more likely to develop PTLS through a similar inflammatory immune responseⁱⁱⁱ. A recently published paper shows similar results from the treatment of PTLS through the CIRS protocol as treatment of CIRS-WDB^{iv}. Further research needs to and will be done on the outcomes of PTLS treated through the CIRS protocol.

The following chart gives a visual representation of the pathway:



The scientific research behind the pathophysiology continues to strengthen on an ongoing basis. Three examples:

- A **time series analysis** study of volunteers with CIRS-WDB documented changes in symptoms and biomarkers at 5 time points – at baseline, after 2 weeks of CSM therapy, after 2 weeks of mold avoidance without CSM therapy, after 3 consecutive re-exposure to mold-toxic building

and after CSM therapy^v. This strength of this ABB'AB design helps to clearly demonstrate causality of exposure.

- A study of **brain volumetrics** through MRI and NeuroQuant show reversal of brain atrophy after VIP treatment in patients with CIRS^{vi}. The degree to which neuroplasticity can occur with effective treatment is considerably underappreciated by the medical community today.
- A study of **gene transcriptomics** through PAX genomics methodology that allows for stabilization of mRNA and miRNA in serum samples. This particular study showed reversal of gene upregulation with VIP treatment. This is the cutting edge of medicine, well beyond the ability to measure SNPs alone with a promise to create more personalized medicine that will improve patient outcomes over time.^{vii}

HISTORY AND PHYSICAL

History. The most important aspect to the history and physical is for the clinician to have the right mindset around CIRS. Do not assume. Prevalence of CIRS has the potential to be extraordinarily high (24% of population with HLA risk factors, 50% of buildings are water damaged). Many patients have been misdiagnosed and carry with them a history of chronic fatigue syndrome, chemical sensitivity, fibromyalgia, post Lyme treatment syndrome and cognitive decline.

Patients do not always understand whether they have been exposed to mold (it can be revealed after multiple visits and questions). Attention should be paid to worsening of symptoms when in certain buildings or locations.

A history of eating tropical reef fish or exposure to bodies of water associated with fish kills or overgrowth of algae can identify other biotoxin exposures.

Attention should be paid to the timeline of illness presentation as well as antecedents, mediators and triggers.

Symptom clusters: The clinician needs to assess the 37 symptoms that are associated with CIRS through the use of 13 symptom clusters. Patient derived questionnaires are not sufficient, the clinician needs to question the patient directly. Clusters are a more practical approach at the bedside versus the organ system category approach initially used in the case definition. 8 or more positive clusters for adults is diagnostic [In adults, sensitivity 98.4%]. The absence of clusters can help to rule out CIRS. Absolute number of symptoms can help to rule in CIRS(13+ out of 37). Clinicians should track these symptoms every visit to see how they evolve.

- Fatigue
- Weakness, decreased assimilation of new knowledge, aches, headaches, light sensitivity
- Memory impairment, decreased word finding
- Difficulty concentrating
- Joint pain, AM stiffness, cramps
- Tingling, tremors, unusual pain, unusual skin sensations
- Shortness of breath, sinus congestion
- Cough, excessive thirst, confusion

- Appetite swings, difficulty regulating body temperature, increased urinary frequency
- Red eyes, blurred vision, night sweats, mood swings, ice-pick pains
- Abdominal pain, diarrhea, numbness
- Tearing of eyes, disorientation, metallic taste
- Static shocks, vertigo

Physical exam: a complete examination is necessary. Signs will include

- HEENT: Red eyes
- Skin: pallor
- Musculoskeletal: unilateral weakness in the shoulder anti-gravity muscles, strength of arms, forearms, grip. Hyper-flexibility is tested
- Extremities: Cool or discolored hands & feet
- Neurological: cognitive testing, resting tremor

A practical diagnostic approach: The case definition criteria are inherently retrospective since they describe response to treatment; therefore, it cannot be used in the first visit. Clinicians need to use alternate means. Scott McMahon^{viii} has done a review of 371 included patients to determine practical strategies. Here are the results for adults (additional data for other age groups are available in his report)

- **Clusters** – 8 or more out of 13 symptom clusters for adults is diagnostic [In adults, sensitivity 98.4%]
- **Screens** - 3 of the following screens: Symptoms (13+ out of 37 symptoms – not the clusters), VCS test, measure of shoulder anti-gravity muscles/ grip /shrug [In adults, 3 out of 3 screens has a specificity 86.7%, positive predictive value 97.4%]
- **Labs** – 5+ abnormal tests of the following 10 tests: HLA, MSH, TGF-β1, MMP-9, MARCoNS, VIP, C4a, ADH/osmolality, ACTH/cortisol, ACLA/AGA [In adults, specificity 73.3%, positive predictive value is 97.7%, the likelihood by chance alone is <1 in 1x 10¹⁰)

Thanks to this analysis, clinicians can take a practical, yet highly accurate diagnostic approach on the first visit and follow-up:

- **We can use few or absent symptom clusters to help rule out CIRS.** This can help the clinician who is taking CIRS into account on the differential.
- **We can use 3 screens or 5+abnormal laboratory tests to help rule in CIRS.** If the 3 screens is positive, the clinician can start to take practical steps towards treatment after the first visit while labs are still pending.

LABORATORY TESTING

Insights into the laboratory tests and biomarkers help elucidate and diagnose the patient's specific pathophysiologic condition and helps to track improvement over time. We will start with the 11 tests used to in the diagnostic approach mentioned above and then review additional testing.

1. **Human Leukocyte Antigen (HLA) Genetic Testing** (76% of population not susceptible to CIRS)

Human Leukocyte Antigen genes are found on surface of cells and provide instructions for making proteins called the HLA complex. These proteins help the immune system distinguish between the body's proteins and foreign proteins. DR (Antigen D related) & DQ are closely linked and very involved in autoimmune mechanisms as they present foreign cells to T lymphocytes. There are over 50 different HLA types.

Reading the HLA LabCorp report through the Rosetta Stone^{ix} There are five categories of line entries: DRB1, DQ, DRB3, DRB4, and DRB5. Everyone will have two sets of three alleles, **unless the DRB1 is 1, 8 or 10. Those patients will only have a DQ and won't have DRB 3, 4, 5.** Each individual with a DRB1 other than 1, 8 or 10 will have a DQ and one other allele from DRB 3, 4, 5. If you find only one in DR 3, 4, 5, the patient is homozygous for that allele and only one allele will appear on the PCR.

Translate these categories into B1, DQ, 52 (A, B, C), 53 and 51 respectively. Write down only the first two numbers in each line.

- **For DRB1**, when you see 03 as one of the two genes, an allele, for DRB1, rewrite it as 17.
- **For DRB3** by converting the 01 to A, the 02 to B and the 03 to C; this will give you 52A, 52B and 52C, respectively:
- **DRB4 is 53**, if you see Labcorp read a dash (-) leave it blank
- **DRB5 is 51**, if you see Labcorp read a dash (-) leave it blank
- **DRDQ does not need additional translation**

	DRB1	DQ	DRB3	DRB4	DRB5	Clinical notes
Multi-susceptible <i>Unable to clear any / all toxins from system</i>	4	3		53		3%, highest C4a, TGFB1 DRB1- 0401, 0402, 0403 worst
	11/12	3	52B			1% Get sicker, quicker
	14	5	52B			
Mold <i>Unable to recognize or clear mold toxins</i>	7	2/3		53		7-2-53 associated with celiac
	13	6	52A ,B, C			
	17	2	52A			52 A, B, C associated with celiac
	18*	4	52A			
Borrelia , Post Lyme	15	6			51	
<i>Unable to clear Lyme toxins</i>	16	5			51	
Dinoflagellates	4	7/8		53		
MARCONS – Inability to recognize / attack MARCONS	11	7	52B			
Low MSH	1	5				
No recognized significance	8	3,4,5,6				
Low risk mold	7	9		53		
	12	7	52B			
	9	3,9		53		
Less common additional haplotypes	1	3,4,8				
	4	4		53		
	7	4,9		53		
	9	2,7,9		53		
	10	5				
	11	4,5,8	52B			
	12	5	52B			
	13	3,7	52A, B			
	14	3,7	52B			
	15	5			51	
	16	6			51	
	17	2	52B,C			
	17	3,4	52 A,B,C			
	103	5				

If a patient is in a low HLA risk category, they can still get CIRS, but it will likely be less severe with a rapid response to therapy.

2. Visual Contrast Sensitivity (VCS) (normal: 7 or greater in column C, 6 or greater in column D)

This test measures the neurologic function of the optic nerve from the retina to the cortex. Contrast is the ability to see an edge; the test measures contrast sensitivities for five different spatial frequencies. The curve is the highest level of contrast a patient can see, with higher contrast being better. CIRS patients have lower contrast sensitivity.

VCS is a highly useful test. Defects in VCS are due to capillary hypoperfusion to the nerve induced by the inflammatory response. Occupational exposure to heavy metals, solvents, petrochemicals and hydrocarbons are all known to create deficits in visual contrast.

VCS is early, highly sensitive (92%), persistent, cheap and readily measured. VCS will be used to follow response to cholestyramine before advancing to the next part of the protocol.

Only rows C & D count for scoring pass or fail. (C 7 or greater, D 6 or greater).

Visual acuity must be better than 20:50 in both eyes, lighting must be sufficient, and patients must sit 18 inches away for contrast sensitivity.

Use the following online link <http://www.survivingmoldstore.com/store1/online-screening-test> or use a hand-held chart.

3. Melanocyte Stimulating Hormone (MSH) (normal: 35-81 pg/ml)

MSH deficiency is a critical step in CIRS. MSH is made primarily in the hypothalamus. In CIRS, cytokines block leptin receptors in the pituitary which decreases the production of MSH. MSH is usually made by the splitting of pro-opiomelanocortin (POMC) into alpha-MSH, ACTH and beta-endorphin.

Low MSH has multiple impacts on the body:

- Intestinal permeability in the gut.
- Dysregulation of the HPA axis specifically ACTH / cortisol and ADH / osmolality.
- Upregulation of aromatase causing androgen abnormalities.
- Dysregulation of T cells resulting in inflammation and autoimmune disorders. This also results in nasal colonization with MARCoNS (which then further decreases MSH a positive feedback loop)
- Anti-gliadin antibody formation in some individuals
- High leptin which then promotes weight gain

4. Transforming Growth Factor Beta – 1 (TGF Beta-1) (normal <2380 pg / ml)

TGF Beta-1 has an important role in the innate immune system. It is a potent suppressor of T cell activation and can decrease T cell proliferation and cytokine production. It also helps control growth and differentiation of cell, cell motility, cell death. It can damage T reg cells as well as TH1, TH2. It also

decreases the number of IL-1 receptors, thereby making cells less sensitive to other cytokines. If it is elevated, it indicates that the body is trying to down regulate an overactive T cell adaptive immune system.

Elevated TGF beta-1 can cause tissue remodeling in liver, heart, CNS, kidney, and lungs usually at levels greater than 5,000. When levels get above 10,000 patients can get interstitial lung disease, pulmonary hypertension, tremor, cognitive issues, and joint pain. Hair loss is common.

5. Multiple Antibiotic Resistance Coagulase-Negative Staph (MARCoNS) (normal – not present)

MSH deficiency is highly correlated with presence of MARCoNS; less than 1% of patients with normal MSH have MARCoNS. MARCoNS release endotoxin A and B which cleave MSH and make it ineffective.

MARCoNS produce biofilms which are barriers that protect the bacteria from the immune system. They live in the deep aerobic spaces of the nasal cavity and can also be isolated from dental cavitations.

Proper testing of MARCoNS requires the use of API Staph Isolate, often ordered through Microbiology Dx. It is not necessary to order the fungal culture or the biofilm routinely as part of the testing. Fungus is a colonizer in the sinus rather than a pathogen. Biofilms can be measured on a special basis if there is an ongoing problem with eradication. A more cost-effective approach is to order the bacterial culture and if positive, treat. The culture must be redone after treatment is complete to assure eradication.

6. C4a (normal: 0-2830 ng/ml)

C4a is a product of the mannose binding lectin pathways of the complement system, which is activated by the innate immune system. It helps antibodies and phagocytic cells remove toxins and infections from the body and participate in the membrane attack complex.

It can cause smooth muscle release, activate mast cells, increase histamine, increase basophils and increase vascular permeability – all part of anaphylaxis pathways.

Cleavage of C4-C4a by MASP2 is the critical part of the “quicker / sicker” phenomenon that happens with many CIRS patients on re-exposure to biotoxins.

Critically, C4a can create capillary hypoperfusion in the CNS – this creates increased lactate levels and suppression of the glutamate / glutamine ratio, which can be directly measured on MR spectroscopy. Cognitive functions improve when the C4a drops. C4a therefore becomes an important measure when evaluating patients with Alzheimer’s and cognitive decline.

7. Matrix Metalloproteinase 9 (MMP-9) (normal: 85-332 ng/ml)

MMP-9 is activated by macrophages as part of the innate immune system response. It is an enzyme that destroys the basement membrane of endothelial cells. This increases permeability of the blood brain

barrier and allows cytokines to penetrate tissues such as muscles, lung, joints, brain and the nervous system. It correlates with a high toxic / cytokine load and disease burden.

8. Vasoactive Intestinal Peptide (VIP) (normal: 23-63 pg/ml)

There are VIP receptors in the hypothalamus, nerve endings, gut and pancreas. Low levels of VIP are found in 98% of patients with CIRS. These levels are associated with capillary hypoperfusion and abnormal pulmonary artery pressure at rest or in response to exercise – which creates post-exertional fatigue and shortness of breath.

9. ACTH / Cortisol

ACTH and cortisol are biomarkers for hypothalamic-pituitary axis dysfunction. They can be measured through blood tests as part of the Shoemaker protocol. HPA axis dysregulation occurs in 50% of people with low MSH. Both absolute or relative dysregulation can be seen. ACTH is released with the breakdown of POMC causing the adrenals to release cortisol, the classic “stress hormone.”

- Absolute high: ACT>45 or cortisol > 21
- Absolute low: ACTH < 5 or cortisol < 4
- Relative: ACTH < 10 when cortisol < 7 or ACTH > 15 when cortisol > 16

Doing a DUTCH (dried urine comprehensive hormone test) can help the clinician look for dysregulation in the usual early morning awakening response of cortisol, but this is not part of the Shoemaker protocol.

There can be a number of different patterns seen in CIRS over time.

- Early – elevated ACTH and elevated cortisol
- Low ACTH relative to cortisol
- Late, high symptoms – low ACTH and low cortisol

10. ADH / Osmolality

ADH and osmolality are also biomarkers for hypothalamic-pituitary axis dysfunction and together manage serum osmolality. The hypothalamus contains osmoreceptors that shrink when serum osmolality is high and release ADH from the posterior pituitary. Dysregulated ADH / osmolality levels occur in 80% of patients with CIRS.

As mold is remediated, low ADH will normalize in many cases on its own.

Both absolute or relative dysregulation can be seen.

- Absolute high: ADH > 13 or osmolality > 300
- Absolute low: ADH < 5 or osmolality <275
- Relative: ADH<2.2 when osmolality 292-300 or ADH > 4.4 Osmolality 275-278

11. Antigliadin Antibodies (AGA) (normal 0-19)

Low MSH can result in T reg cell dysregulation and is associated with high antigliadin antibodies and gluten sensitivity. High AGA shows an inflammatory response to gluten and can contribute to intestinal permeability. 33% of adult CIRS patients have high AGA. If AGA is positive would rule out celiac by measuring HLA DQ2/DQ8 genes and serum tissue transglutaminase levels.

12. Vascular Endothelial Growth Factor (VEGF) (normal: 31-86 pg/ml)

VEGF is a growth factor which stimulates blood vessel growth in response to hypoxia inducible factor (HIF) and dilates blood vessels.

Early in CIRS, there can be an increase in VEGF as the body tries to compensate for low oxygen delivery. Later in CIRS, inflammation and cytokines can suppress VEGF and create capillary hypoperfusion. This creates anaerobic mitochondrial metabolism which results in decreased muscle endurance, poor recovery from exercise, fatigue and a low VO₂max. While not on the diagnostic approach list of tests, VEGF correction is part of the Shoemaker Treatment Protocol so it needs to be routinely measured as part of the protocol.

13. MRI with NeuroQuant

NeuroQuant volumetrics has been FDA-cleared since 2006. It provides the reliability of software algorithms in accurately measuring the volume of different parts of the brain and has a deep database in which to understand percentile volumes compared to age-sex matched distributions. Importantly for CIRS (and Alzheimer's) patients – serial NeuroQuant testing has shown in multiple studies that there is significant plasticity of the brain with an ability to heal. There is also a competitive software algorithm product that is also FDA-cleared known as Neuroreader, which has easier to interpret outputs. Their software is also available on the web. However, the Neuroreader database is not as extensive at NeuroQuant at this time.

Patients with CIRS due to mold have a specific pattern of abnormalities

- Increase in: forebrain parenchyma, cortical gray, hippocampus, and pallidum
- Decrease in: Caudate (reversible through use of VIP in published papers)

Patients with CIRS due to borrelia / Lyme have following pattern

- Increase in: Thalamus, cerebellum
- Decrease in: Forebrain parenchyma, putamen

14. HERTSMI-2 and ERMI (normal < 11)

The Health Effects Roster of Type Specific Formers of Mycotoxins and Inflammagens (HERTSMI-2) is a cost-effective result of the Environmental Relative Moldiness Index (ERMI). Importantly the HERTSMI-2 scores have been effectively shown in published research to guide safe exposure for patients with CIRS.

ERMI is an objective, standardized DNA Mold-Specific Quantitative Polymerase Chain Reaction (MSQPCR) method for identifying and quantifying molds. All national standards represent measurements from the living room and bedroom (rather than the basement). Collection processes with vacuuming or swiffer cloths emphasize dust collection which gives a quantitative based exposure rather than a single point in time estimate that occurs with air samples. Indoor environmental professionals may find value in the ERMI to guide remediation as that gives more data on issues with the buildings, while the HERTSMI-2 is specific for health care issues.

The HERTSMI-2 roster was based on the results of 738 consecutive ERMI tests. It uses values of five specific molds – *Aspergillus penicilloides*, *Aspergillus versicolor*, *Chaetomium globosum*, *Stachybotrys chartarum* and *Wallemia sebi*.

10 points are awarded for (all units in spore E/mg)

- *Aspergillus penicilloides* > 500
- *Aspergillus versicolor* >500
- *Chaetomium globosum* >125
- *Stachybotrys chartarum* >125
- *Wallemia sebi* >2500

6 points are awarded for

- *Aspergillus penicilloides* > 100
- *Aspergillus versicolor* >100
- *Chaetomium globosum* >25
- *Stachybotrys chartarum* >25
- *Wallemia sebi* >500

4 points are awarded for

- *Aspergillus penicilloides* > 10
- *Aspergillus versicolor* >10
- *Chaetomium globosum* >5
- *Stachybotrys chartarum* >5
- *Wallemia sebi* >100

All points are added up

- Any score over 15 is too dangerous for previously sickened patients to occupy.
- Score 11-15 is borderline. Building needs to be treated
- Score < 11 had a recurrence rate of CIRS of < 2% (N=807)^x
- Some individuals may need a score of under 8 to not relapse (e.g., C4a >20,000)

Pertinent negative tests There are a great deal of objective tests that are not abnormal in CIRS. This would include ESR, C-Reactive protein both measures of inflammation, as well as immunoglobulins and ANA.

Tests done for particular indications

C3a (normal: 55-486 ng/ml)

C3a is generated at the same time C4a and C2a are made. It should be ordered when suspecting a tick-borne illness as an etiology of CIRS. It elevates within 12 hours of a tick-bite. If the HLA is a Lyme susceptible pattern, the patient will likely need longer than 3 weeks of antibiotics. If it persists after antibiotic therapy, statin therapy is necessary.

Transcriptomics

Pax genomics allows for direct measurement of messenger RNA allowing us to look at ribosomal RNA and mitochondrial RNA transcription patterns in serum. Research on patients before and after VIP treatment in the standard CIRS protocol has shown dramatic changes in up and down regulation of Ribosomal genes and Mitochondrial genes^{xi} This provides significant promise in measuring ultimate cures and return to normal function. Transcriptomics will be the wave of the future. Reductions in the costs of the tests following the cost curve of other sequencing tests and potential coverage by insurance will help to make this more available over time. Research in this area should be closely monitored by the clinician.

Leptin (normal: 0.5-13.8 ng/ml in men, 1.1-27.7 in women)

Leptin regulates the proopiomelanocortin (POMC) pathway and low leptins contribute to low MSH, ADH, VIP and ACTH. It was initially used as a marker for treatment 10 years ago, but now is not considered a major marker. High levels of leptin will result in weight gain.

Von Willebrand's Profile

High C4a can result in acquired von Willebrand's syndrome and increase bleeding tendencies. If this is the case, this should be documented by measuring Factor VIII activity, von Willebrand antigen, Ristocetin Cofactor, von Willebrand Factor, PT, PTT, INR.

PFT's, Stress Echo, VO2 Max

Patient's with unusual shortness of breath and post exertional fatigue warrant a workup for etiologies due to CIRS. Differential diagnosis can include capillary hypoperfusion, interstitial lung disease and pulmonary hypertension. Sequence of testing would be PFT's first, then VO2 max and Stress Echo

- **Pulmonary Function Tests** PFTs can show a restrictive pattern consistent with interstitial lung disease.
- **VO2 Max** It is important to understand that a low VO2 max for these patients may not represent cardiopulmonary function but rather capillary hypoperfusion due to low VEGF. VO2 max > 35 is

normal; CIRS patients have VO₂ max < 20. By comparison stage IV heart failure is VO₂ MAX OF 12-15.

- **Stress Echocardiogram** This can be used measure pulmonary artery pressure through the Bernoulli equation. This would be done at baseline and after maximal exercise with a 90% of maximum predicted heart rate. Any rise in PA systolic pressure over 8 is abnormal and can be clinically used as an indication for VIP as a treatment

TREATMENT AND RESPONSE

A brief summary of the multi-step CIRS treatment protocol is below:

1. Remove from exposure
2. Remove biotoxins with cholestyramine and monitor with VCS
3. Treat MARCoNS
4. Correct anti-gliadin antibodies
5. Correct abnormal androgens
6. Correct elevated MMP-9
7. Correct low VEGF
8. Correct elevated C3a
9. Correct elevated TGF-B1
10. Correct low VIP & elevated C4a
11. Recheck labs and VCS

This protocol has evolved over time based on published research and input from a community of practicing CIRS physicians. It reflects the experience from thousands of patients. It is critically important to follow the pathway in the order prescribed; if this is done the success rate is around 90%.

1. Removal from exposure

Removal from exposure addresses the root cause of the issue and cannot be overemphasized. The patient cannot effectively progress past the first steps of the protocol unless the root cause of the problem is addressed. If the source is from Lyme, the underlying infection needs to be treated. HLA haplotypes may indicate a longer course of treatment. If the exposure is from ciguatera or cyanobacteria exposure, the patient needs to be removed from the source of exposure.

Mold remediation: If biotoxins from water-damaged buildings are the source, a HERTSMI-2 test should be done and a qualified indoor air specialist needs to do a visual inspection.

There is a detailed consensus statement on the prevention, assessment and remediation of water damaged buildings and the maintenance of indoor environmental quality.^{xii} Treating clinician and the indoor environmental professionals (IEP) should be aware of the detail within this consensus statement. The clinician needs to develop relationship with reliable IEPs that can help patients in assessment and remediation.

Medically sound remediation will differ from traditional remediation in several ways: Use of DNA analysis; greater reliance on small particle cleaning; systematic calculation of a WDB's propensity for growth and control of mold and bacteria; and assessment of organization within the living space. Ideally the area is assessed by a qualified IEP and done by a separate contractor who does not deviate from the IEP's plan.

The remediation process follows 3 phases

- Inspect and investigate to detect water intrusions and leaks. Investigate HVAC system for cross contamination issues. Develop a plan for correcting problems and preventing recurrences.

- Perform planned corrections and remediation needs to include in-depth cleaning of all reservoirs of bioactive particulates inside the building. All porous materials should be removed and taken out of the house and discarded. Non-porous items need to be thoroughly and professionally cleaned.
- Perform maintenance procedures to sustain high quality indoor air over the long-term including optimal air filtration, ventilation, and pressurization. Furnace filters should have at least a rating of MERV 6 to 8.

Post remediation testing should occur 3-5 weeks after remediation. Taping large black or green garbage bags on horizontal surfaces to attract new dust for a sample is a practical approach. The building is safe when HERTSMI-2 levels are less than 11 or less than 8 if C4a is > 20,000.

Patients have a learning curve for how to avoid re-exposure in their daily life. Small exposures may not trigger symptoms immediately, but over time the “sicker quicker” phenomenon can surface where brief exposures can lead to reactivation of illness for days. It is important to encourage patients to listen to their body and warnings.

2. Removal of biotoxins with cholestyramine and monitor with VCS

Cholestyramine (CSM) is a bile acid sequestrant which has a positive quaternary structure. It binds negative charged biotoxins which are then excreted in bile while bound to CSM. It comes in generic packets which can be taken ½ hour before and 1 hour after meals, drugs or supplements. Avoid CSM with aspartame. It needs to be taken 4 times a day to be effective.

Recheck the VCS one month after starting treatment. The VCS needs to be normalized. If the patient is exposed to multiple environments, they may require ongoing treatment at a lower dose. Children seem to respond to treatment quicker. Older and sicker patients often cannot tolerate the full dose of cholestyramine and need to be started more slowly. Therapy for older people can take up to several months.

If there are problems with toxin release, pre-treat with Omega 3 (EPA 2.4 gm, DHA 1.8 gm) for a week.

It is practical at this stage to start the patient on a **no-amylose diet** which will be helpful for later steps as well. A low amylose diet also is a gluten-free diet and involves eliminating

- 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.
- Rice. Oats. Barley. Rye.
- Foods with added sugar, sucrose, corn syrup, or maltodextrin.

Foods that are allowed are anything not eliminated. Questions that often come up include

- Corn
- Onions.
- Garlic

- All vegetables that grow above the ground: including lettuce, tomatoes, beans of all types, peas, cucumbers, and celery.
- All fruits except bananas.
- Meat, fish, and poultry.
- Condiments (avoid low-fat varieties as they usually contain added sugar).
- Spices.
- Eggs
- Dairy (avoid sugar-laden products).
- Nuts
- Sunflower, pumpkin, and squash seeds.

Welchol may be better tolerated by patients but is not as effective. It also does not have the same published data to support its use as cholestyramine. Some patients combine Welchol with CSM and take Welchol at lunch and dinner – this can be a practical alternative for those who cannot tolerate cholestyramine 4x a day.

Other binding agents such as charcoal and clays have not been demonstrated to be effective in binding biotoxins.

3. Treat MARCoNS

If the patient has MARCoNS, she should be treated with nasal BEG (Bactroban, EDTA, gentamicin) spray at a dose of 2 sprays each nostril tid for 30 days. The nose should be blown before using. Repeat nasal culture after a month to see if eradicated. If there are problems with resistance, colloidal silver should be added. (EDTA 0.5% Silver 25 ppm in Mucolox 2 sprays each nostril tid for 30 days.)

A thorough periodontal and dental examination should be undertaken preferably by a dentist referral. We have uncovered several underlying dental infections in patients that were not immediately apparent under initial physical examination.

If MARCONS persists with correct treatment, the clinician needs to rule / out canine exposure, colonization in another person in house, ongoing environmental exposure to biotoxins.

4. Correct Anti-Gliadin Antibodies

AGA antibodies are done at the beginning of the evaluation. If positive, patients need to be completely gluten free for at least 3 months. At that point, the anti-gliadin antibodies are retested and need to be negative to move to the next step in the protocol. If the patient feels better off gluten or if they have celiac disease, they should stay off gluten for life.

If the patient completes the protocol and wishes to test gluten it can be reintroduced carefully with monitoring for GI symptoms and retesting the AGA.

Many of these patients have other GI issues such as SIBO, dysbiosis that will need to be taken into account through steps not on the protocol.

5. Correct abnormal androgens

Low MSH can lead to abnormal androgens, particularly low testosterone via upregulation of aromatase. Testosterone should be avoided in these patients as it can lead to high levels of estradiol when aromatase levels are high. DHEA 25-75 mg qd in men and 5-25mg qd in women is a better alternative. DHEA needs to be measured before treatment. Patients estradiol levels need to be monitored.

6. Correct ADH / osmolality

When osmolality is high with a concurrent ADH, DDAVP should be used. Symptoms connected with ADH are recurrent headaches, static shocking, polyuria, polydipsia, orthostatic hypotension.

0.2 mg every other night should be used as an initial dose. Clinician needs to be sure that there are no side effects with edema and rapid weight gain due to fluid retention.

After 5 doses – repeat labs should be checked including serum osmolality, ADH and electrolytes verifying normal sodium and not too low. After 10 days repeat electrolytes and osmolality should be checked.

If symptoms persist, then the dose should be increased to 0.2mg qd. Some may require it twice a day.

When the endpoint of normal ADH for a given osmolality is reached, then the DDAVP should be tapered. In many patients the ADH abnormalities correct over time. Treatment will also help reduce MMP-9, C4a and correct von Willebrand syndrome if present.

7. Correct elevated MMP-9

Therapeutic options to upregulate PPAR-gamma production and reduce MMP-9 expression include pioglitazone (Actos), omega 3 fatty acids, and a low amylose diet. Leptin levels can guide options – if leptin < 7, pioglitazone is contraindicated. If leptin is high or normal can use pioglitazone with a low carb, low-amylose diet.

Pioglitazone is 45 mg qd for 30 days – it is used for type 2 diabetes mellitus treatment as an oral hypoglycemic so need to monitor blood sugar, renal function. It is implicated in bladder cancer with long term use.

Omega 3 acids are high dose at least 2.4mg of EPA and 1.8 mg of DHA daily. Use with a low carb / amylose diet as well. Recheck labs after 30 days.

8. Correct low VEGF

Re-check VEGF levels when you come to this part of the protocol as they may have already improved or corrected especially on the protocol to correct MMP-9.

If they aren't improved, then doing anaerobic threshold exercises for up to 45 minutes a day, 7 days a week is recommended. These exercises are started at very low-level activity and increased gradually. The ideal end routine would be 15 minutes of cardio, 15 minutes of free weights and 15 minutes of core. Once 45 minutes of activity has been achieved, then the intensity of the exercises can be increased. The notion here is to train the muscle beds to extract oxygen more efficiently.

9. Correct elevated C3a

This step is primarily for Lyme patients who have elevated C3a due to activation of MASP2 on bacterial membranes.

C3a is corrected through the use of statins and concurrent Coenzyme Q10. Statins impact on C3a is through reduced T cell activation, macrophage infiltration and vascular wall infiltration in addition to their other effects on HMG Co-A reductase inhibitors. Usual statin precautions apply (e.g., no grapefruit juice, monitor kidney and liver function).

10. Reduce elevated TGF Beta-1

Losartan (Cozaar) will reduce elevated TGF Beta-1 via a breakdown product called EXP 3179 that preventing conversion of T reg cells and lowers TGF beta-1. This effect is independent of the normal inhibitor effect on the angiotensin II receptor. Dosing starts at 12.5 mg bid and can increase to 25 mg bid if needed. Monitor impact on TGF Beta-1 on a monthly basis. Losartan can also have a favorable effect on high pulmonary artery pressures at rest.

11. Correct C4a and VIP

VIP will correct a low VIP and a high C4a (through downregulating MASP2). It will also have a host of favorable effects on the CIRS pathophysiology including favorable effects on:

- Aromatase upregulation (correcting estrogen and testosterone)
- ADH / osmolality
- TGF-beta 1, VEGF, MMP9
- MSH, Circadian rhythm
- Ribosomal and mitochondrial gene regulation
- Brain abnormalities seen on NeuroQuant especially caudate nucleus atrophy
- Correction of PASP during exercise and changes in fatigue and energy

The following factors need to be in place before using VIP:

- MARCoNS must be eradicated, VCS must be normal, Lipase must be normal, and the HERTSMI-2 must be < 10.
- MRI with NeuroQuant needs to be done
- Baseline stress echo to measure PASP and its increase with exercise

- Pre-administration labs drawn: VIP, MSH, TGF-beta1, C4a, VEGF, MMP-9, Vit D-25-OH, estradiol, total testosterone, and lipase

The initial VIP test dose process is the following:

- Draw blood
- Test spray one dose 50 mcg in one nostril
- Vital signs q 5 min x 3 – observe for rash and symptom improvements (changes in joint pain, cognition, shortness of breath)
- Redraw TGF beta-1 and C4a after 15 minutes to rule out hidden mold that would be apparent through a 2x increase in those biomarkers.
- Give second dose of VIP in other nostril, repeat monitoring. If tolerated, patient can then leave the office

VIP dose after the initial test dose is 50 mcg spray qid x 30 days. Repeat evaluation in 30 days including lipase, C4a, TGF beta-1, VCS, blood pressure and stress echo. Dosage can be increased to 2 sprays qid.

Once TGF beta-1, VCS, lipase is normal and symptoms are improving then VIP should be continued for 30 days, then taper to bid and then discontinued. It can be used for up to 4 years without adverse effects.

Cialis can be added to regimen if there is poor response to exercise on VIP alone. Dose is 20mg 3 x week

If there are problems with cognitive functioning, doing NeuroQuant pre and post VIP treatment is a good idea. Adding MRI spectroscopy to the evaluation if the NeuroQuant is not abnormal is an option – would see high lactate and low glutamate / glutamine ratio in patients with high C4a which resolves after treatment.

Erythropoietin is an additional option to reduce C4a at 8000 units twice weekly. Given the advent of VIP, most clinicians elect to use VIP as a first line alternative. If erythropoietin is used, it should be used before starting VIP and before treating TGF Beta-1.

12.Recheck Labs and VCS

Once symptoms are normal, labs and the VCS should all be repeated to insure therapy is complete.

Conclusion

It often is said that it takes 20 years for medical advances to make its way into practice. An example of this was the treatment of *H. pylori* for ulcers – first discovered in the mid-eighties, ultimately resulting in a Nobel Prize in Medicine 20 years later.

The scientific foundation for CIRS is extremely strong, with mapped out pathways, causality and substantial improvement in biomarkers, imaging and gene expression occurring because of adherence to the CIRS protocol. Full randomized clinical trials still need to be done and are dependent on appropriate research funding.

However, today the CIRS diagnosis is often diminished, misdiagnosed, and misunderstood by the clinical community. Yet the opportunity to impact patient outcomes and public health is profound. Here are 3 examples that are neither exhaustive or exclusive but highlight the magnitude of the opportunity for impact.

In patients who are exposed to water-damaged buildings. I am writing this overview one month after recent hurricanes in South Florida and Texas. People with predictably get symptoms of CIRS after they return to water damaged buildings; many of those people's symptoms will be misunderstood and mistreated.

Patients with cognitive decline and Alzheimer's. Advances in the multi-factorial treatment of Alzheimer's are leading to hope for the first time in patients with these symptoms. In a 2016 paper, Dr. Dale Bredesen described a set of patients in the intersection of CIRS and Alzheimer's and estimated the prevalence to be as high as 10% of the Alzheimer's population ^{xiii}. With the right treatment, these patients can respond to the Shoemaker protocol.

Patients with Post Treatment Lyme Syndrome, Chronic Fatigue, and Fibromyalgia. These patients should be evaluated for CIRS to see if they have physiological changes that can be responsive to the CIRS protocol. Ongoing research should elucidate what percentage of these patients have full CIRS that is responsive to the protocol

It requires a deep commitment by clinicians to learn the literature for CIRS and practically apply them to patients in a rigorous matter without taking shortcuts. It also requires the same commitment by patients to strictly follow the protocol. If both sides do this, in what we call at Rezilir Health a "commitment practice" the chances of achieving a return to excellent health are good.

FOOTNOTES

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