Chronic Inflammatory Response Syndrome (CIRS)

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WHAT IS CIRS-WDB?

CIRS stands for Chronic Inflammatory Response Syndrome. WDB stands for Water-Damaged Building. The two are grouped together because CIRS develops by way of exposure to a myriad of bacterial and fungal fragments commonly found in water-damaged buildings.

In 2008, the United States Government Accountability Office (US GAO) produced a peer-reviewed report identifying a working definition for CIRS-WDB. This report was later amplified by the Expert Mold Treating Physicians Consensus Report of 2010. [1]

The consensus report for WDB includes the following criteria:

1. There must be potential for exposure to a building with water damage and subsequent amplified microbial growth. Amplified growth is documented by any of the following:
    a. The presence of visible mold.
    b. The detection of musty smells.
    c. Commercial testing which demonstrates amplified mold growth by species known to flourish on damp indoor building materials.

In order for a case to be confirmed CIRS-WDB, the following additional criteria must also be included:

2. There must be multiple symptoms involving multiple body systems.
    a. These symptoms must be consistent with what is reported in the published peer-reviewed literature.
3. There must be laboratory abnormalities that are similar to those found in the peer-reviewed, published studies.
4. There must be improvement with therapy similar to that reported in the peer-reviewed, published studies.

Symptoms of CIRS patients were refined over 1,829 cases compared to 500 healthy controls.

Remediation of WDB is currently done to industry standard. This may not be adequate to protect occupants with CIRS. At this time, there are no governmental standards that consider the special needs of occupants with CIRS – even though they make up more than 20% of the population.[2]

[1] https://www.survivingmold.com/MEDICAL_CONSENSUS_STATEMENT_10_30_15.PDF

[2] https://www.survivingmold.com/docs/Linkage_disequilibrium_in_alleles_of_HLA_DR.PDF

Case Definition of CIRS

CIRS is defined as a multi-symptom, multisystem illness caused by exposure to biotoxins or neurotoxins.[3] [4] It is associated with a well-defined set of abnormal biochemical disorders and test results in genetically susceptible individuals derived from a biological source.

In a 2013 paper, CIRS was described as a chronic, progressive, multi-system, multi-symptom syndrome characterized by: [5] [6]

- Exposure to biotoxins
- HLA genetic predisposition
- Altered innate and adaptive immunity
- Peripheral hypoperfusion at multiple sites
- Multiple hypothalamic-pituitary-end organ immune dysregulation

Federal Agency Case Definition

In 2008, the GAO a federal agency approved case definition. The Federal agency case definition is as follows:

- Potential for exposure.
- Symptoms like those seen in the published, peer-reviewed literature.
- Laboratory findings similar to those seen in the published, peer-reviewed literature.
- Improvement in objective parameters through treatment.

[3] https://www.survivingmold.com/docs/Sick_Building_syndrome_in_water_damaged_buildings.PDF

[4] https://www.survivingmold.com/docs/VIP_published_3_2013.pdf

[5] https://www.survivingmold.com/docs/Resources/Shoemaker%20Papers/Johanning_book_5_06.pdf

[6] https://www.survivingmold.com/docs/VIP_published_3_2013.pdf

A Quick Primer on the Human Immune System

The human immune system is composed of two unique divisions:

1. The Innate Immune System
2. The Adaptive Immune System

The innate immune system is non-specific. Whereas the adaptive immune system is specific. Vertebrates are born with innate immune system intact. Their adaptive immune systems develop after birth.

The innate immune system

The innate immune response occurs immediately after infection. Whereas the adaptive immune system takes much longer.

The innate immune system is non-specific. Meaning it reacts in the same manner regardless of the infectious agent.

The innate immune system does not provide long-lasting immunity.

The innate immune system communicates with the adaptive immune system by way of antigen-presenting cells. Dendritic cells are the primary facilitators of this role though it can also be done by macrophages and monocytes.

The adaptive immune system

The adaptive immune system provides long-term immunity by creating a memory after exposure to a specific pathogen.

Adaptive immunity involves T cells teaching B cells to recognize and respond to invading toxins. If re-exposure should occur, antibodies produced by the B cells can mount an appropriate attack.

The CIRS patient

Just over 20% of the population has a genetic mutation on specific chromosomes of their HLA haplotype. This leads to an upregulation of their innate immune system. The genetic mutation also creates a poor ability to present antigens to the adaptive immune system.[7]

This is the foundational response of the CIRS patient's immune system – an upregulated activation of the innate immune system due to specific environmental triggers combined with defective activation of the adaptive immune system.

The resulting effect is a chronic inflammatory response or, CIRS.

[7] https://www.survivingmold.com/docs/Transcriptomic_Signatures_in_Whole_Blood.PDF

BIOTOXINS 101

Biotoxins are extremely small, fat-soluble molecules capable of going from cell to cell through membranes without being carried directly into the bloodstream rendering them impossible to find in the bloodstream. Biotoxins can enter through inhalation, direct contact with contaminated water, ingestion, tick bites and spider bites. These biotoxins, in genetically susceptible people whose immune system (antibodies) do not recognize and tag them, lead to chronic inflammation and long-lasting chronic illness. Biotoxins bind to certain surface receptors, particularly those on white blood cells (macrophages, monocytes and dendritic cells) called antigen-presenting cells.

Pattern recognition receptors (PRRs) are a primitive part of the immune system. They are proteins expressed by cells of the innate immune system to identify two classes of molecules: pathogen-associated molecular patterns (PAMPs), which are associated with microbial pathogens, and damage-associated molecular patterns (DAMPs), which are associated with cell components that are released during cell damage or death.

The microbe-specific molecules that are recognized by a given PRR are called pathogen-associated molecular patterns (PAMPs) and include bacterial carbohydrates (such as lipopolysaccharide or LPS, mannose), nucleic acids (such as bacterial or viral DNA or RNA), and bacterial peptides, peptidoglycans, lipoproteins, and fungal glucans and mannans.

Endogenous stress signals are called damage-associated molecular patterns (DAMPs) and include uric acid and extracellular ATP, among many other compounds.

This binding releases specific amounts of inflammatory molecules, cytokines, complement and TGF beta-1- this is the innate immune system's activation sequence. This inflammation is not specific and cannot remove the biotoxins but results in persistent inflammation and a syndrome now known as CIRS.

Unlike bacterial or viral pathogens, which can be identified in blood work, biotoxins cannot be identified by routine blood tests and therefore one needs to rely on identifying them via the damage they inflict on the immune system, neuropeptide hormones and end-organ hormone systems.

Cell membranes depend on ion channels to transport potassium sodium, and calcium ions in and out of cells. Biotoxins show the structural forms of amphipathic ionophores, creating ion channels that disrupt cell electrodynamics and hence the battery-like charge, rendering the cell incapable of performing its energy-producing functions derived from the ion pumps.

Biotoxins have both water and fat-soluble capacities. Biotoxins nestle on the inner fat-soluble membrane of cells, thus showing a predilection for fatty tissue like the brain, nervous tissue, and the autonomic nervous system. Thus, they disrupt cell function without destroying the cell; as opposed to pore-forming toxins which create large holes in cell membranes, which are enough to kill the cell itself.

Cell-signaling is disrupted inside the cell by the disruption in the ion movement. The cell then triggers a defensive response by activating genes that code for inflammatory cytokines, on top of the already overworked innate immune system driven by CIRS. Elevated TGF beta-1 is a sign that the body is over-revving from both an innate and an adaptive immune system T cell response.

CIRS biotoxins are first and foremost neurotoxins due to the fatty acid predilection with the brain being a common site, especially if there is porous blood-brain barrier. Cardiovascular and GI sites are also common organ sites due to the rich nervous innervation and the fact that these biotoxins reside intracellularly in the fatty acid membrane,

not accessible in the bloodstream. They are difficult to dislodge particularly when the adaptive immune system is not adequately working.

Originally, the case definition criteria included tier one and tier two criteria. All tier-one criteria had to be met and three of the six tier-two criteria had to be met to confirm the condition. As research progressed and deeper insights were gained, Dr. Shoemaker updated his case definition in 2006 by including tier three criteria which described the response to successful treatment.

In 2008, the Government Accountability Office (GAO) issued its case definition, which was largely reliant on the published work of Dr. Shoemaker. It is the definition commonly used today. Dr. Scott McMahon at the 2016 Surviving Mold Conference in Irving, California, recommended that the GAO case definition be used in clinical practice.

The Clinical Case Definition of CIRS

CIRS is defined as a chronic, progressive, multi-symptom, multi-system illness characterized by exposure to biotoxins, HLA genetic predisposition, altered innate and adaptive immunity peripheral hypoperfusion, and multiple pituitary end organ dysregulations. [8]

Biotoxins are small, fat-soluble molecules. Biotoxins may enter through inhalation, direct contact with contaminated water, ingestion, tick bites, and spider bites. The biotoxins capable of triggering CIRS include:

- Filamentous fungi
- Bacteria
    - Actinomycetes
    - Mycobacteria
        - Hemolysins
        - Beta-glucans
        - Mannans
        - Spirocyclic drimanes
- mVOCs are suspect though their role in the pathogenesis of CIRS is still ill-defined.

There are at least 30 known entities found within water-damaged buildings that individually or collectively can trigger CIRS.

In genetically susceptible individuals, the biotoxins are not recognized nor handed off to the adaptive immune system. The resulting effect is a chronic inflammatory response from the innate immune system.

[8] https://www.survivingmold.com/docs/VIP_published_3_2013.pdf

As of 2019, the case definition of CIRS has been expanded to include: [9]

- Abnormal proteomics;
- Abnormal regulation of immune functions and hormonal feedback loops;
- Loss of neuropeptide regulation of the above;
- Now also abnormal transcriptomics;
- Together with suppression of ribosomal and nuclear encoded mitochondrial genes.

Differential Diagnosis

Essential to any proper diagnostic workup is the differential diagnosis. In the context of CIRS, a water-damaged building is the most common source. However, there are other triggers the clinician needs to consider. These include:

- Consumption of ciguatoxic fish
- Exposure to fresh water blue-green algae bloom
- Recluse spider bites
- Post-Lyme syndrome

Other diseases

CIRS patients are often misdiagnosed with a myriad of other conditions. Some of the more common misdiagnosis that are actually CIRS include:

- Chronic Fatigue Syndrome
- Fibromyalgia
- Depression
- Anxiety
- ADHD
- Alzheimer's
- PTSD
- Allergies
- Multiple Chemical Sensitivities

The above diagnosis contains symptoms common in the CIRS symptom cluster. Of which we will now turn our attention to.

Conventional laboratory testing

Inflammatory markers like C-reactive protein and ESR are often in the normal ranges with CIRS patients. Additionally, seeing pathology in a CBC is unlikely.

[9] https://www.survivingmold.com/Publications/CIRS_diagnostic_protocol_final_5_1_2018.pdf

Thyroid function can be abnormal (unpublished). Total IgG, IgE, IgM are normal. ANA antibodies are typically normal.

CIRS patients will also present with normal EKG, pulse oximetry, and normal chest x-rays.

Physical examination

Upon physical examination of a CIRS patient, it is common to find a resting tremor of the hands. Hypermobility is another symptom commonly seen in the physical exam.

THE CIRS SYMPTOM CLUSTER

To better make sense of the multi-symptom, multi-system illness that is CIRS, practitioners have grouped 37 symptoms into 13 different clusters. Each cluster has between 1-5 symptoms. The clusters were organized by statisticians in order to maximize predictive capabilities.

A patient presenting with at least one symptom lasting for at least two weeks in 8 or more of the clusters, is considered consistent with biotoxin illness. In children, if symptoms are present in 6 or more clusters, biotoxin illness should be explored further.

The CIRS symptom Cluster

1. Fatigue/weakness

2. Headache

3. Aches, cramps

4. Unusual sharp, clawing, electrical or icepick pain(s)

5. Light sensitivity; red eyes; blurring, tearing

6. SOB; cough; sinus issues

7. Abdominal pain, secretory diarrhea; bile acid reflux

8. Joint pain; Morning stiffness

9. Issues w. memory, concentration, word assimilation, confusion, disorientation

10. Mood swings; appetite swings, sweats; temperature regulation (hypothalamic functioning)

11. Thirst; frequent urination; static shocks

12. Numbness, tingling, taste abnormalities

13. Vertigo; tremors; skin sensitivity to light touch

>8 out of the above 13 clusters is consistent with biotoxin illness.

LABORATORY FINDINGS

Consistent with the published, pee- reviewed literature, the CIRS patient will present with the following lab abnormalities:

- Abnormal visual contrast sensitivity (VCS) test
- Confirmation of HLA susceptibility
- MSH levels <35pg/ml
- Elevated levels of C4a
- Elevated levels of MMP-9
- Elevated levels of TGF beta-1
- Dysregulation between ACTH and Cortisol
- ADH/Osmolality abnormalities
- Low or high VEGF
- Abnormal Von Willebrand's profile
    - Occurs in ~66% of cases
- Nasal culture showing MARCoNS
    - This occurs in 80% of cases with low MSH

Additional abnormalities include:

- Depressed V02 Max
- Reduced anaerobic threshold
- Elevated pulmonary artery pressure at rest
- During exercise, pulmonary artery pressure rises >8mm over baseline
- Neuroquant brain MRI
    - Lateral ventricle enlargement
    - Atrophic grey matter in 2.4/6 regions
- Transcriptomics
    - Suppression of ribosomal DNA
    - Suppression of nuclear-encoded mitochondrial genes

Laboratory findings are an essential part of a CIRS workup because:

- There must be an accurate ongoing differential diagnosis.
- Laboratory changes will show internal improvement with therapy or worsening with re-exposure.
- Lab results objectively demonstrate the physiology behind CIRS to interested third parties.
- Lab results provide the opportunity for further study.

VISUAL CONTRAST SENSITIVITY TESTING

The visual contrast test measures the neurologic function of the optic nerve from the retina to the cortex by measuring the least amount (threshold) of luminescence difference between adjacent areas (contrast) necessary for an observer to detect a visual pattern.

The test measures contrast sensitivity for five sizes (spatial frequencies) of light, gray and dark bar patterns (sinusoidal gratings). The VCS eliminates near, far, color, motion and peripheral vision variables.

There are spatial frequencies measured amongst healthy individuals which is the curve formed by the highest level of contrast the patient will see, versus the CIRS patients who will have lower contrast sensitivities and their curves will fall below the healthy control line. Higher contrast sensitivity is better.

In the presence of biotoxin illness, visual contrast sensitivity decreases. Only rows C and D count for scoring pass or fail. One must see 7 in each eye on C and 6 in each eye on D. Rows D and C show improvement with clearing of biotoxins. With an intensification reaction to cholestyramine, there will be a fall in column E followed by a fall in column D. and not the other eye, still constitutes a fail.

VCS appears to be an early, persistent, highly sensitive, inexpensive and easily measured indicator for biotoxin illness. Only 8% of people with CIRS will have a normal VCS test. Thus, 92% of people with biotoxin illness will fail the VCS. [10] [11]

98% of patients who fail the VCS test and who have 8 of the symptom clusters will have biotoxin illness.

A few people (~10%) will pass the VCS but still show signs, symptoms, and inflammatory markers suggestive of biotoxin illness such as artists and professional baseball players with extra keen vision. Occupational exposure to solvents, hydrocarbons, and petrochemicals can cause a person to fail the VCS test and not have biotoxin illness.

For accuracy, the following conditions need to be met:

1. Visual acuity must be better than 20:50.
2. Patients must wear their corrective eyewear
3. Lighting must be sufficient
4. Patients must sit 14 inches away from the screen for visual acuity, 18 inches for contrast sensitivity.

If a patient either passes or fails the VCS test and there is still a high index of suspicion for biotoxin illness based on a history of exposure, symptom cluster analysis and/or signs on physical examination, it is still advisable to proceed with HLA and inflammatory biomarker testing.

[10] https://www.survivingmold.com/docs/Use_of_visual_contrast_sensitivity.PDF

[11] https://www.survivingmold.com/docs/Results_of_health_screening.PDF

THE BIOTOXIN PATHWAY

For the majority of the population (~75%), exposure to biotoxins does not result in lasting symptoms. For this demographic, biotoxins are removed from the blood via the liver or picked up by the immune system, broken down and excreted.

But in those with HLA susceptibilities, (~23% of the population), exposure to biotoxins results in the binding of said toxins to pattern receptors. This causes a continuous, unregulated production of cytokines.

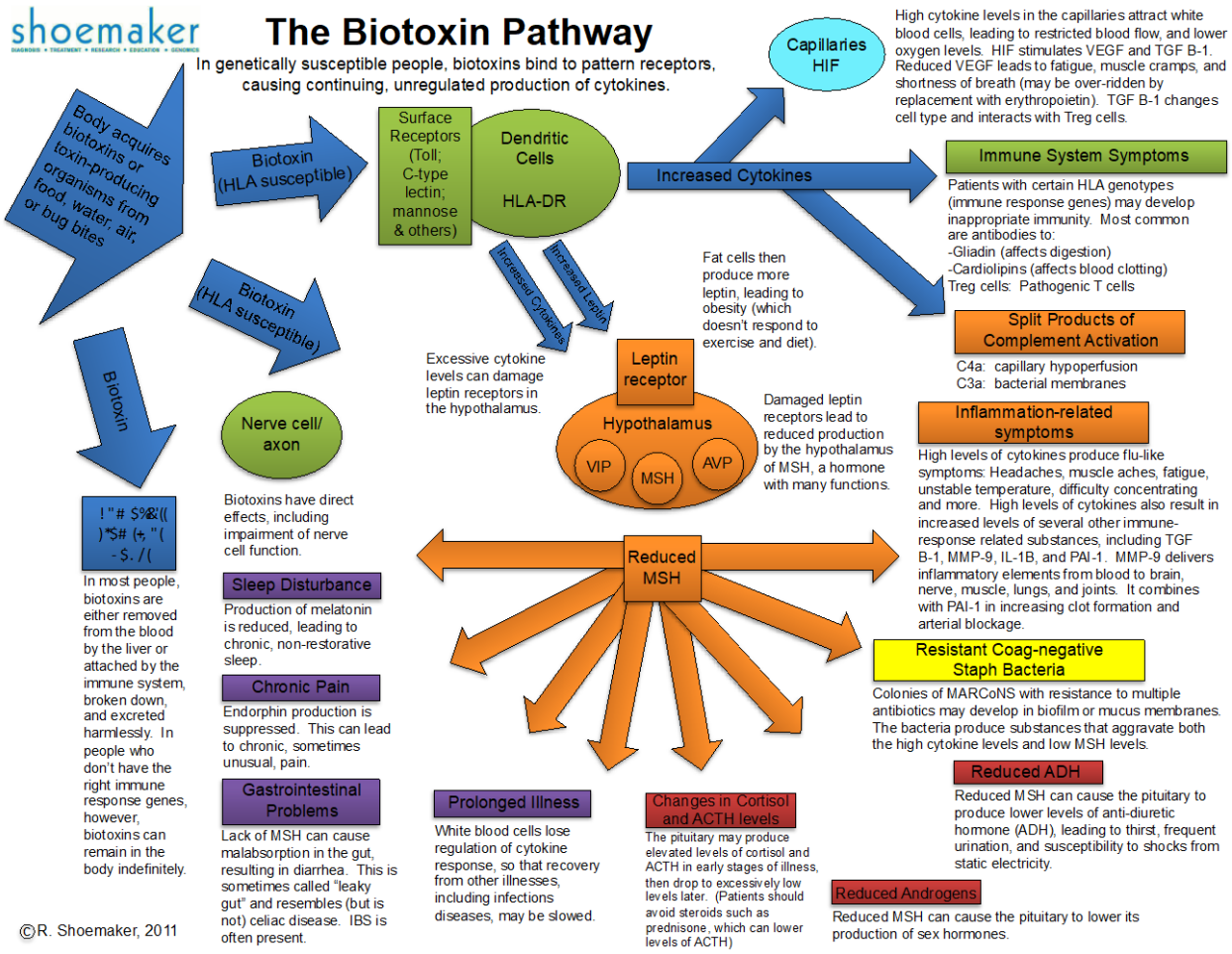
Elevated cytokines in the peripheral capillaries will attract WBCs. This results in restricted blood flow and lowered tissue oxygenation. Capillary hypoperfusion stimulates VEGF and TGF beta 1. VEGF is a signalling protein that stimulates the formation of blood vessels. Lowered VEGF results in fatigue, shortness of breath, and muscle cramps.

In the genetically susceptible, biotoxins will bind to pattern receptors on the surface of cells. This then causes an increase in both leptins and cytokines. Excessive levels of cytokines are known to damage leptin receptors in the hypothalamus.

Here lies the crux of the CIRS puzzle, the damage to leptin receptors in the hypothalamus leads to reduced production of Melanocyte Stimulating Hormone (MSH). MSH is one of the lesser-known but more important neuro-regulatory hormones.

Reduced MSH leads to a number of downstream effects including:

- Sleep disturbances
  - Reduced MSH leads to reduced melatonin which then leads to chronic, non-restorative sleep.
- Chronic pain
  - The suppression of endorphins occurs as a result of low MSH. This can lead to both chronic and unusual pains – think “ice-pick pain”
- GI problems
  - Low MSH affects the tight junctions in the gut creating a leaky gut.
- Chronic illness
  - WBCs lose their ability to regulate the cytokine response. This results in a slowed/delayed recovery from other infections/diseases.
- Alterations to cortisol and ACTH
  - Early in the illness, you will see elevated levels of cortisol. In chronic cases, hypocortisolism is present. This is a protective mechanism. It should not be treated by herbs/medications that increase cortisol.
- Reduced androgens
  - Reduced MSH can cause the pituitary gland to lower its production of sex hormones like testosterone and DHEA.
  - There is often due to an upregulation in aromatization where testosterone is converted to estrogens.
- Reduced ADH
  - Reduced ADH results in unquenchable thirst, frequent urination, and an increased susceptibility to static shocks.
- MARCoNS Colonization
  - MARCoNS can cause a lowering of MSH and also occur as a result of low MSH
  - This infection aggravates cytokine levels and prolongs suppression of MSH


shoemaker
The Biotoxin Pathway
In genetically susceptible people, biotoxins bind to pattern receptors, causing continuing, unregulated production of cytokines.
Body acquires biotoxins or toxin-producing organisms from food, water, air, or bug bites
Biotoxin (HLA susceptible)
Surface Receptors (Toll; C-type lectin; mannose & others)
Dendritic Cells
HLA-DR
Capillaries HIF
High cytokine levels in the capillaries attract white blood cells, leading to restricted blood flow, and lower oxygen levels. HIF stimulates VEGF and TGF B-1. Reduced VEGF leads to fatigue, muscle cramps, and shortness of breath (may be over-ridden by replacement with erythropoietin). TGF B-1 changes cell type and interacts with Treg cells.
Increased Cytokines
Immune System Symptoms
Patients with certain HLA genotypes (immune response genes) may develop inappropriate immunity. Most common are antibodies to:
-Gliadin (affects digestion)
-Cardiolipins (affects blood clotting)
Treg cells: Pathogenic T cells
Split Products of Complement Activation
C4a: capillary hypoperfusion
C3a: bacterial membranes
Biotoxin (HLA susceptible)
Biotoxin
Nerve cell/ axon
Increased Cytokines
Increased Leptin
Fat cells then produce more leptin, leading to obesity (which doesn't respond to exercise and diet).
Excessive cytokine levels can damage leptin receptors in the hypothalamus.
Leptin receptor
Hypothalamus
VIP
MSH
AVP
Damaged leptin receptors lead to reduced production by the hypothalamus of MSH, a hormone with many functions.
Inflammation-related symptoms
High levels of cytokines produce flu-like symptoms: Headaches, muscle aches, fatigue, unstable temperature, difficulty concentrating and more. High levels of cytokines also result in increased levels of several other immune-response related substances, including TGF B-1, MMP-9, IL-1B, and PAI-1. MMP-9 delivers inflammatory elements from blood to brain, nerve, muscle, lungs, and joints. It combines with PAI-1 in increasing clot formation and arterial blockage.
Biotoxins have direct effects, including impairment of nerve cell function.
Reduced MSH
In most people, biotoxins are either removed from the blood by the liver or attached by the immune system, broken down, and excreted harmlessly. In people who don't have the right immune response genes, however, biotoxins can remain in the body indefinitely.
Sleep Disturbance
Production of melatonin is reduced, leading to chronic, non-restorative sleep.
Chronic Pain
Endorphin production is suppressed. This can lead to chronic, sometimes unusual, pain.
Gastrointestinal Problems
Lack of MSH can cause malabsorption in the gut, resulting in diarrhea. This is sometimes called "leaky gut" and resembles (but is not) celiac disease. IBS is often present.
Resistant Coag-negative Staph Bacteria
Colonies of MARCoNS with resistance to multiple antibiotics may develop in biofilm or mucus membranes. The bacteria produce substances that aggravate both the high cytokine levels and low MSH levels.
Reduced ADH
Reduced MSH can cause the pituitary to produce lower levels of anti-diuretic hormone (ADH), leading to thirst, frequent urination, and susceptibility to shocks from static electricity.
Prolonged Illness
White blood cells lose regulation of cytokine response, so that recovery from other illnesses, including infections diseases, may be slowed.
Changes in Cortisol and ACTH levels
The pituitary may produce elevated levels of cortisol and ACTH in early stages of illness, then drop to excessively low levels later. (Patients should avoid steroids such as prednisone, which can lower levels of ACTH)
Reduced Androgens
Reduced MSH can cause the pituitary to lower its production of sex hormones.
©R. Shoemaker, 2011

Formal Diagnostic Criteria for CIRS

Tier 1 Criteria (all 3 must be met)

1) **Exposure**
    - The patient must have a history of exposure to WDB, tick-borne illness, other neurotoxins (ex: Dinoflagellates, Pfiesteria, Cyanobacteria), or recluse spider bites.
2) **Differential diagnosis**
    - Ruling out other common illnesses.
    - See the section on differential diagnosis.
3) **Symptoms**
    - Must be consistent with the peer-reviewed literature.
    - See symptom cluster analysis.
        - >8/13 symptom clusters must be present.

Tier 2 Criteria (3 of 6 must be met)

1) **Abnormal VCS**
    - In the presence of biotoxin illness, visual contrast sensitivity decreases. Only rows C and D count for scoring pass or fail. One must see 7 in each eye on C and 6 in each eye on D. Rows D and C show improvement with the clearing of biotoxins. [12]
2) **Presence of HLA**
    - 95% of the CIRS population will possess genetic susceptibility.
3) **Elevated MMP-9**
    - Activated by macrophages inducing inflammatory cytokines.
4) **Imbalance in ACTH/Cortisol**
    - Both are often elevated early on in CIRS.
    - As disease progresses, low levels in both is often found.
5) **ADH/Osmolality imbalance**
    - In CIRS patients, ADH is usually low while osmolality is usually high.
6) **Low MSH**
    - MSH is low in 95% of patients with CIRS.

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[12] Shoemaker R. State of the Art answers to 500 Mold Questions Question 212.

TIER 3 CRITERIA

1) Symptoms and VCS test improve with treatment
2) Lab markers (MMP9, ACTH, etc.) return to normal levels. [13]

SUMMARY OF THE 3 TIER CRITERIA

In order to make a preliminary diagnosis of CIRS, the clinician must have the following:

- All three of the tier-one criteria
- At least three of the tier-two criteria

Should these two criteria be met, the clinician can proceed with the treatment outlined through the Shoemaker protocol. Treatment will reveal a confirmation of the CIRS diagnosis should symptoms, VCS test, and lab markers improve.

[13] https://www.survivingmold.com/docs/POA_MOLD_7_27_10_final.pdf

DIAGNOSTIC MARKERS FOR CIRS

Human Leukocyte Antigen (HLA) Genetic Testing

95% of CIRS patients are HLA susceptible.
5% of CIRS patients do not have genetic susceptibility.

- 20-25% of the population have HLA gene types that make them susceptible to biotoxin illness. Said another way, this demographic's immune system does not have the capabilities to clear biotoxins after an exposure.
- Those with HLA gene types make up 95% of the CIRS patient population.
- More specifically, the HLA genes occur on chromosome 6.
- HLAs are found on the surface of nearly every cell in the body. Think of the HLAs as instructions for making a group of proteins known as the HLA complex. The HLA complex helps the immune system differentiate self-proteins from proteins made by biotoxins.
- The HLA DR test identifies one's susceptibility to CIRS and many other illnesses. [14]
- The alleles most important for chronic illness expression include:
  - DRB1
  - DQ
  - DRB3
  - DRB4
  - DRB5
- The following haplotypes are associated with these different biotoxin illnesses.
  - Multi-susceptible: 4/3/53; 11/3/52B; 12/3/52B; 14/5/52B
  - Mold specific: 7/2/53; 7/3/53; 13/6/52A, B or C; 17/2/52A; 18/4/52A
  - Borrelia specific: 15/6/51; 16/5/51
  - Dinoflagellate specific: 4/7/53; 4/8/53
  - MARCoNS susceptible: 11/7/52B
  - MSH low: 1/5
  - Mold - low risk: 7/9/53; 12/7/52B; 9/9/53

[14] (Shoemaker RC. Johanning E. Sick Building Syndrome in Water-damaged Buildings: Bioaerosols, Fungi, Bacteria, Mycotoxins and Human Health, pp 66-77, 2005)

Susceptibility	DRB1	DQ	DRB3	DRB4	DRB5
Multi-susceptible	**4**	**3**		**53**	
Unable to clear toxins from system	**11 or 12**	**3**	**52B**		
	14	**5**	**52B**		
Mold Susceptible	**7**	**2 or 3**		**53**	
Unable to recognize or clear mold toxins	**13**	**6**	**52A, B, C**		
	17	**2**	**52A**		
	18	**4**	**52A**		
Chronic Lyme or Post-Lyme	**15**	**6**			**51**
Unable to clear Lyme toxins	**16**	**5**			**51**
Dinoflagellates	**4**	**7 or 8**		**53**	
MARCoNS	**11**	**7**	**52B**		
Low MSH	**1**	**5**			

Melanocyte Stimulating Hormone (MSH)

Normal range = 35-81 pg/ml; 206-478 pmol/L
MSH levels <35 pg/ml are found in 95% of CIRS patients

- MSH regulates the innate immune system. It is incredibly anti-inflammatory. Low levels help to explain the chronic inflammation seen in CIRS patients.
- Inflammatory cytokines bind to leptin receptors, usually activating MSH and beta endorphins. MSH would then control leptin. In biotoxin illness, cytokines block leptin receptors. This results in MSH not being made. Low MSH then disrupts nerves, hormones and immune function.
- MSH is controlled by leptin in the pituitary gland; pro-opiomelanocortin (POMC) is split into three components- alpha-MSH, or adrenocorticotrophin (ACTH) and beta-endorphin.
- MSH functions include:
    - melatonin production,
    - immune surveillance of mucous membranes,
    - intestinal permeability,
    - nasal pathogen protection,
    - regulates ADH and VIP,
    - reduces inflammation,
    - controls cytokine release in skin and gut,
    - prevents Candida infections,
    - controls pain through endorphin release.

- When MSH is abnormal, the result is problems with sleep, pain, gut symptoms, fluid dysregulation due to ADH with increased thirst and increased urination, cortisol dysregulation, fatigue, nasal colonization with MARCoNS, stress management problems, reduced sex hormones.
- Due to leptin issues, weight gain which does not respond to more exercise and less eating, can be a problem.
- Low MSH causes dysregulation of T reg cells leading to inflammation and autoimmune disorders.
- MSH has been shown to regulate the inflammatory cytokines (TNF and nitric oxide) found in inflammatory bowel disease. [15]

C4a

Normal range = 0-2830 ng/ml

- C4a is an innate immune system biomarker.
- If C4a is elevated, it is indicative that the innate immune system pathologically activated. The activation is usually in response to a pathogen-associated molecular pattern (PAMP) caused by biotoxins.
- C4a is a split product of the mannose binding lectin pathways of the complement system of the innate immune system and predicts the severity of CIRS.

[15] Rajora N, alpha MSH Modulates Inflammatory Bowel Disease Peptides Vol 18 Issue 3 pg. 381-385.

- C4a has been associated with elevated levels of mannin-binding lectin serine protease 2 (MASP2) in patients with CFS. [16]
- Complement proteins circulate as inactive precursors but when split into active components they amplify the immune response of the membrane attack complex. [17] MAC kills the outer layer of cells causing cell death.
- C4a are anaphylatoxins which cause:
    - smooth muscle release,
    - activation of mast cells,
    - increased histamine,
    - increased basophils,
    - increased vascular permeability,
    - capillary hypoperfusion with resultant cellular hypoxia resulting in reduced mitochondrial function,
    - increased lactate production from glycolysis, and can
    - increased cognitive dysfunction (memory loss, concentration, word finding difficulties, disorientation, confusion, difficulty integrating new information) and fatigue. [18]
- Cognitive functions improve when C4a drops.
    - C4a can be elevated in Lyme disease and SLE.

Matrix Metallopeptidase 9 (MMP-9)

Normal range = 85-332ng/mL; 28.14-109.89 nmol/L
Elevated levels of MMP-9 are found in CIRS

- MMP-9 is an enzyme activated by macrophages inducing inflammatory cytokines of the innate immune system that destroys the basement membrane of endothelial cells. This provides a barrier between blood and tissue.
- High MMP-9 occurs when the immune system is chronically stimulated. The results in a porous basement membrane allowing inflammatory compounds to penetrate tissues such as joints, muscles, brain, lungs, and the peripheral ANS. [19]
- High MMP-9 increases the permeability of the blood brain barrier. [20]
- MMP-9 increases lipoprotein a and oxidized LDL.
- MMP-9 is increased with head injuries.

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[16] Sorensen B, Jones JF, Vernon SD, Rajeevan MS. Transcriptional control of complement activation in an exercise model of chronic fatigue syndrome. Molecular Medicine 2009 Jan-Feb; 15 (1-2): 34-42

[17] Rapaport S. Evaluation and Treatment of CIRS pg. 7

[18] Ogata RT, Rosa PA, Zepf NE. Sequence of the gene for murine complement component C4a. The Journal of Biological Chemistry, 1989; 264(28): 16565-72.

[19] Shoemaker RC. Defining Sick Building Syndrome in adults and children in a case -control series as a biotoxin-associated illness: American Journal of Tropical Hygiene and Health; 2005;73 (6):228

[20] Candelario-Jalil E, Thompson J, Taheri S, Grossetete M, et al. Matrix metalloproteinases are associated with increased blood-brain barrier opening in vascular cognitive impairment. Stroke. 2011 Mar 31.

- MMP9 correlates with high toxic load, total cytokine load, and probability of Herxheimer reaction.
- If MMP9 is high, the patient will likely feel worse with CSM binding – opt for natural remedies.

Transforming Growth Factor Beta-1 (TGF Beta-1)

Normal range = <2380 pg/ml
Symptoms appear = >5000 pg/ml
>10,000 pg/ml = restrictive lung disease, tremor, cognitive issues, joint problems
> 40,000 pg/ml = re-test as specimen was likely mishandled

- TGF beta-1 is a protein that can either produce or suppress inflammation.
- It helps control the growth and differentiation of cells, cell motility and cell death. In utero, it helps form new blood vessels, regulates muscle and body fat development and wound healing.
- Elevated levels are a result of the immune system trying to down-regulate an overactive T-cell adaptive immune system – think, allergies and autoimmunity.
- Elevated levels are also indicative an overactive innate immune system – a hallmark sign in CIRS.
- TGF beta-1 affects autoimmunity through differential gene activation. TGF Beta -1 can damage T reg cells CD4 and CD2 which regulate TH1 (autoimmunity) And TH2 (allergy), and TH17 cells.
    - Together T reg and Th17 cells work to prevent autoimmunity.
    - TGF beta-1 can thus activate or reduce autoimmunity.
- In treatment, the goal is increase T reg cells and lower TGF beta-1.
    - If T reg cells are low, TGF beta 1 is likely to be high (>2380 pg/ml)
- High TGF beta-1 is associated with joint inflammation.
- High TGF beta-1 may result in neurological diseases:
    - Seizures
    - Tremors
    - Parkinson’s
- High TGF beta-1 may result in autoimmune diseases:
    - MS
    - Lupus
    - RA
    - UC
    - Scleroderma
    - Dermatomyositis
- High TGF beta-1 may also result in:
    - Learning disabilities
    - Vocal polyps
    - Nasal polyps
    - Cognitive symptoms

ACTH & Cortisol

Normal Range:
ACTH = 8-37 pg/ml; 1.76-8.14 pmol/l
AM cortisol = 4.3-22.4 ug/dl; 3.07-15.99 umol/l
PM cortisol = 3.1-16.7 ug/dl; 2.21-11.92umol/l

- ACTH and cortisol measure the HPA axis' regulation of the adrenal glands. ACTH stimulates the adrenal glands to release cortisol in response to stress.
- Cortisol release raises blood sugar. Diurnal cortisol pattern is often affected resulting in elevated evening cortisol. This will result in sleep challenges.
- If the CIRS patient is treated early in the disease progression, elevated levels of cortisol and DHEA will likely be present.
- If CIRS has been undiagnosed for a long period of time, the HPA axis will down-regulate production of cortisol and DHEA as a neuro-protective mechanism.
    - Cortisol is a catabolic hormone. Elevated levels over the long-term are not conducive to health.
- ACTH and cortisol have an inverse relationship. As cortisol levels decrease, ACTH should rise.
- CIRS patients will commonly have low ACTH in relation to cortisol.
- As ACTH decreases, presenting symptoms start to increase.
- Very ill patients will show both low ACTH and cortisol.

ADH and Osmolality

Normal range: ADH: 1- 13.3 pg./ml; 0.9-12.28pmol/l
Osmolality: 280-300 mOsm/kg.

High serum osmolality - High ADH = normal
Low serum osmolality - Low ADH = normal
High serum osmolality with low ADH = abnormal.

Absolute or relative ADH dysregulations may be seen:
1) Absolute high: ADH > 13 or osmolality > 300
2) Absolute low: ADH <5 or osmolality <275
3) Relative: ADH was < 2.2 when osmolality was 292-300 - two-tiered test
4) Relative: ADH was > 4 when osmolality was 275-278 - two-tiered test

- ADH and osmolality are pituitary end-organ markers dysregulation markers.
- 80% of CIRS patients show dysregulated ADH/Osmolality levels.
- ADH is a marker of disrupted MSH function.
- Low ADH associated with autistic behavior and social avoidance behavior in people with CIRS.[21]
- When the serum osmolality is high (body fluids/blood concentrated due to dehydration), the osmoreceptors shrink and release antidiuretic hormone from the posterior pituitary where it is stored. ADH is a 9-amino acid peptide. ADH binds to receptors on cells in the collecting ducts in the kidneys and reabsorbs water. Thus, cells become rehydrated and ADH levels fall.

[21] Tansey KE, Hill MJ, Cochrane LE, Gill M, et al. Functionality of promotor microsatellites of arginine vasopressor 1A (AVPR1A): implications for autism. Molecular Autism. 2011 Mar 31;2(1):3

- When serum osmolality falls (overhydrated, more water in the blood), the osmoreceptors swell and block ADH release from the posterior pituitary. ADH levels drop and free water is lost in the kidneys.
- In CIRS patients there is a dysregulation of this mechanism. Most commonly ADH levels are low.
- ADH levels and the osmolality levels do not appear to be synchronous with each other as they should be in a healthy non-CIRS patient
- Patients with CIRS often have increased thirst and increased urination. They are also susceptible to electric shocks from touching door handles. This happening is due to the fact that as salt levels rise in blood due to the dehydration, salt is released onto the skin, through the sweat glands and creates a battery-like effect that increases the electrostatic shock potential. Chloride levels may be higher than cystic fibrosis patients in some cases.
- Dehydration may also produce migraine like headaches. [22]
- ADH also affects VIP and MSH levels in the suprachiasmatic nucleus of the hypothalamus. Without these three hormones, the hypothalamic regulation is significantly affected. Patients with low MSH will most often have low levels of ADH.

VEGF

Normal range = 31-86 pg/ml

- VEGF is growth factor that stimulates blood vessel growth in response to hypoxia inducible factor (HIF); In healthy controls, VEGF dilates blood vessels.
- VEGF is a laboratory marker used to measure capillary hypoperfusion. Low levels of VEGF in skeletal muscle is associated with decreased muscle endurance. [23]
- Inflammatory cytokines bind to endothelial receptors, which release *glues* - adhesion and integrins. These hold the white cells together and narrow the capillaries creating hypoxia. This is sensed by regulatory cells which produce a gene controller hypoxia inducible factor (HIF), which produces VEGF.
- In biotoxin illness, inflammation and cytokines suppress VEGF. This creates a state of persistent capillary hypoperfusion.
- Lowered VEGF results in the following symptoms:

    - Fatigue
    - Cognitive challenges
    - Muscle aches
    - Exercise intolerance

- In lactic acid metabolism, due to low VEGF, one obtains only 2 ATP for every glucose molecule, instead of 38 ATP as is normally the case.

[22] Shoemaker R. Biotoxin Illness Treatment Protocol pg. 6

[23] Olfert IM, Howlett RA, Tang K, Dalton ND et al. Muscle specific VEGF deficiency greatly reduces exercise endurance in mice. Journal of Physiology 2009 Apr 15; 587:1755-1767

MARCoNS

MARCoNS positive = resistant to two or more classes of antibiotics plus the presence of a biofilm.

- Multiple Antibiotic Resistant Coagulase Negative Staphylococci or MARCoNS thrive in the deep nasal cavity.
- Biofilms are a goo that surrounds the bacteria. Biofilms protect the bacteria from the body's immune system.
- 80% of patients with MSH deficiency had positive MARCoNS colony. <1% of those with normal MSH had MARCoNS colonies.
- MARCoNS release toxins that cleave MSH, rendering it ineffective. This leads to immune dysregulation.
- Low MSH impairs the body's ability to coordinate dendritic cell responses within the gut and mucus membranes. [24]
- MSH acts as an immune system modulator on the skin and mucus membranes. MSH kills fungi and coagulase-negative staphylococci. If MSH is normal, MARCoNS will not survive. [25]
- MARCoNS colonization produces no symptoms but dysregulates MSH.
- MARCoNS have also been found in dental cavitations.

Antigliadin Antibodies

Normal = 0-19 U

- Low levels of MSH results in T reg cell dysregulation. This can lead to inflammation and possible autoimmunity.
- Serum IgA and IgG antigliadin antibodies are antibodies against the primary protein found in wheat, barley, and rye – gliadin.
- Note that AGA is not specific for celiac disease. TTG-IGA can be used to rule celiac disease in/out.

Androgen Deficiency

Values vary based on age and gender

- Reduced MSH levels can cause the pituitary to lower production of androgens.
- Upregulation of aromatase activity can also see androgens being converted into estrogens.
- HRT is contraindicated as this may cause issues in feedback regulation.

[24] Catania A, Caterina L, Sordi A, et al., The melanocortin system in control of inflammation. The Scientific World Journal 2010; 10:1840-1853

[25] https://www.survivingmold.com/docs/Association_of_nasal_carriage.PDF

Leptin

Normal range in men = 0.5-13.8 ng/ml
Normal range in women = 1.1-27.7 ng/ml

- The leptin hormone determines how fatty acids are stored in adipose tissue. When leptin receptors are disrupted, leptin levels will be elevated.
- When leptin is elevated, fatty acids are stored in fat. The resulting effect is weight gain.

V02 Max

Normal = >35
CIRS patients = <20

- CIRS patients often demonstrate low V02 max.
- Low V02 max reflects the state of capillary hypoperfusion and post-exertional malaise (push-crash).
- During treatment, CIRS patients must stay within their anaerobic threshold.

Von Willebrand's Profile

- Von Willebrand's Disease is a clotting disorder that may be acquired.
- CIRS patients with clotting disorders (nose bleeds, menorrhagia, bleeding gums, etc.) should be evaluated with a panel for von Willebrand's disease.
- Acquired von Willebrand's syndrome can be the result of elevated C4a levels

Neuroquant MRI

- Neuroquant is a software addition to an MRI scan.
- Neuroquant is used to determine if there are changes in brain volume or structure in 11 different regions.
- CIRS patients with exposure to WDBs show: [26]
    - Atrophy of caudate nucleus
- CIRS due to Lyme show:
    - Atrophy of putamen
    - Enlarged right thalamus

Vasoactive Intestinal Polypeptide (VIP)

Normal range = 23-63 pg/ml

- No accurate lab test for measuring VIP
- Before administering VIP, the patient must:
    - Be free from a moldy building
    - Have a normal VCS test
    - Be free from MARCoNS
- VIP is a 28 amino acid regulatory neuropeptide which down-regulates cytokine levels.

[26] https://www.survivingmold.com/docs/Structural_Brain_Abnormalities_in_Patients.PDF

- Low levels of VIP are associated with: [27]
    - Capillary hypoperfusion
    - Abnormal pulmonary artery pressure at rest or in response to exercise
- VIP use has been shown useful in treating brain abnormalities as shown on Neuroquant like caudate nuclei atrophy.
- Low levels of VIP are found in 98% of CIRS patients and only 10% of controls.
- A 2013 study on the use of VIP for CIRS-WDB patients by Dr. Shoemaker found: [28]
    - VIP corrected C4a, TGF beta-1, VEGF, and MMP9
    - Raised VIP and MSH levels
    - Corrected testosterone, estradiol, and vitamin D levels
    - Corrected T reg levels
    - Restored PASP during exercise to normal
    - Enhanced quality of life in 100% of patients from the study.

Environmental Testing (ERMI & HERTSMI-2)

ERMI:
Q1 = -10 to -4 (low relative moldiness)
Q2 = -4 to 0 (low to medium relative moldiness)
Q3 = 0 to 5 (medium to high relative moldiness)
Q4 = 5 to 20 (high relative moldiness)
>20 (very high relative moldiness)

HERTSMI-2:
>15 = building is unsafe for CIRS patient
<10 = building is safe for CIRS patient to occupy
11-15 = Borderline; further remediation should be employed before re-entry

The ERMI Test

- The ERMI test is an objective and standardized DNA-based means to identify and quantify molds.
- ERMI testing was developed by the Environmental Protection Agency as a research tool to standardize mold testing in the United States. [29]
- ERMI tests classify 36 species of mold into two clusters. Cluster one is associated with WDBs and cluster two is common indoor molds.
- ERMI does not provide information regarding bacterial species, actinomycetes, or mVOCs.
- ERMI does not predict safety of a building for CIRS patients. [30]
- ERMI tests are best utilized for indoor environmental professionals. Whereas HERTSMI-2 tests are ideal for healthcare issues like CIRS.

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[27] Berndtson K. Chronic Inflammatory Response Syndrome. Overview, Diagnosis, and Treatment. Pg.7

[28] Shoemaker RC, House D, Ryan J. Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. Health, 2013; 5 (3) 396-401

[29] https://www.epa.gov/air-research/environmental-relative-moldiness-index-research-tool-fact-sheet

[30] Shoemaker and Lark, HERTSMI-2 and ERMI: Correlating Human Health Risk with Mold Specific qPCR in Water-Damaged Buildings, 2016, p1

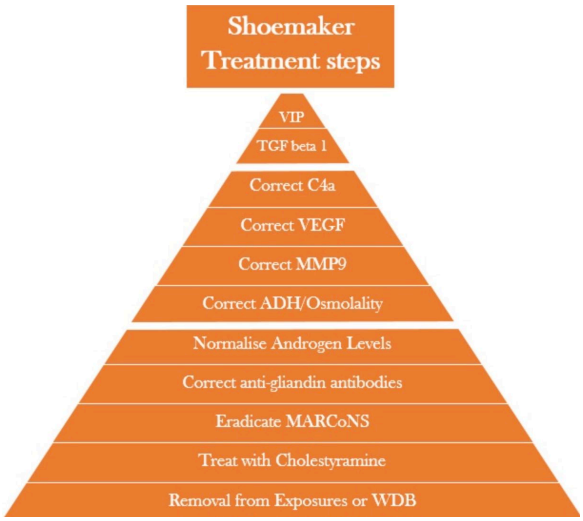
The HERTSMI-2 Test

- HERTSMI-2 test was designed to help CIRS patients and practitioners understand if a particular building is safe for occupancy.
- HERTSMI-2 looks at five specific mold species known to contribute to illness:
  - Aspergillus penicilloides
  - Aspergillus versicolor
  - Chaetomium globosum
  - Stachybotrys chartarum
  - Wallemia sebi
- HERTSMI-2 showed predictive accuracy of over 97% for patients with low or high scores. [31]
- Like the ERMI test, the HERTSMI-2 test does not evaluate bacteria, actinomycetes, or mVOCs.
- HERTSMI-2 accurately predicts safety from re-exposure for patients who had prior CIRS-WDB.
- HERTSMI-2 testing is best utilized for healthcare issues like CIRS.

In clinical practice, start by running the HERTSMI-2. If results come back >10, or, if patient's lab indicate biotoxin exposure, run testing for Actinomycetes. If Actinomycetes come back >9, run endotoxins.

[31] Shoemaker and Lark, HERTSMI-2 and ERMI: Correlating Human Health Risk with Mold Specific qPCR in Water-Damaged Buildings, 2016, p6

TREATMENT - THE SHOEMAKER PROTOCOL IN PRACTICE



Step 1: Removal from Ongoing Exposure

- If this step is skipped, ignored, or not taken seriously, the patient will not get better. No matter the intervention. Practitioners must endeavor to uncover the source of biotoxin exposure. Often, CIRS patients have been exposed to more than one biotoxin.
- The biotoxins associated with a water-damaged building are the most common source of CIRS. Considering 50% of homes in the United States have some form of water damage, [32] proper testing of the patient's home and office space is essential.
- HERTSMI-2 testing needs to be <10 in order for safe occupancy by a CIRS patient. Post remediation testing should occur 3-5 weeks after remediation.
- Personal belongings may need to be discarded. Porous items that can be replaced should be discarded. Valuable porous items will need to be thoroughly cleaned.
- HEPA filters and air purifiers that can remove particles smaller than 0.3 microns should be utilized following remediation.

[32] https://www.survivingmold.com/docs/CONSENSUS_FINAL_IEP_SM_07_13_16.pdf

Step 2: Remove Toxins & Inflammagens

- Patients with the HLA mutations commonly found in CIRS will be unable to effectively eliminate biotoxins on their own.
- Cholestyramine (CSM) is the binding agent of choice. CSM has a quaternary cation structure that binds negatively charged biotoxins which possess an anion dipole.
- Negatively charged binders like charcoal, clay, chitosan, etc. will not bind to biotoxins.
- Biotoxins are excreted in bile into the digestive tract where they are then able to be bound to CSM and eventually removed. The binding prevents enterohepatic recirculation of the biotoxins.
- 4-9 grams (1 scoop) of CSM is to be taken four times per day.
- Pediatric dosing for those under 18 or <120lbs is 60mg/kg/dose TID.
- Take CSM 30 minutes before eating or 1 hour after eating.
- If CSM is not tolerated, Welchol can be prescribed. Worth noting, Welchol has 4x fewer binding sites than CSM.
- Constipation is a common side-effect of CSM. This can be addressed by using magnesium citrate powders or MiraLAX.
- Re-check VCS every 2 weeks after starting CSM treatment.
- If VCS is not passed within 1 month, consider re-exposure or MARCoNS.
- If CSM triggers an inflammatory response, use EPA/DHA (2.4g EPA, 1.8g DHA)

Step 3: Eradicate MARCoNS

- Elimination of MARCoNS is essential before moving on to the next steps of the Shoemaker Protocol.
- Use BEG spray – 2 sprays per nostril TID
    - Bactroban
    - EDTA
    - Gentamycin
- Repeat nasal culture after a 30-day course of therapy.
    - If culture remains positive, consider a pet dog or partner as a source of re-exposure.
- MARCoNS can be the reason why the patient continues to fail the VCS test.

Step 4: Eliminate Gluten in AGA Positive Patients

- Patients positive for antigliadin antibodies will need to abstain from gluten for at least 3 months.
- After 3 months of gluten-free diet, re-check antibodies.
- A gluten-free diet will reduce GI inflammation.

Step 5: Correct Androgens

- In CIRS, androgens typically decrease due to an upregulation of aromatase enzyme. The resulting effect is often low testosterone and elevated estrogens.
- Avoid TRT as this will suppress natural testosterone production.
- Utilize DHEA 25-75mg QD.
- VIP nasal spray can reduce aromatase activity and improve testosterone production.

Step 6: Correct Osmolality & ADH

- Use DDAVP when osmolality is >295 and ADH is low
    - 0.2mg tablet every other night to verify tolerance.
    - After 5th dose, recheck labs.
        - Ensure osmolality and sodium is normal.
    - Daily dose may be required for those with POTS.
- ADH and osmolality issues typically resolve on their own through the Shoemaker Protocol.
- Treatment of ADH/osmolality may also correct acquired von Willebrand's syndrome.
    - Von Willebrand's patients may need to carry DDAVP spray to prevent nasal hemorrhage.

Step 7: Correct Elevated MMP-9

- The objective is to upregulate PPAR-gamma production and reduce MMP-9 expression.
    - This will lower TNF, leptin, and plasminogen activator inhibitor-1, and raise low VEGF levels.
- If leptin levels are <7, do not use Actos.
- If leptin is elevated, consider a low amylose diet combined with Actos.
    - 45mg QD for 30 days
    - Monitor for hypoglycemia
- If Actos is not well tolerated or contra-indicated, use high-dose fish oil.
    - 2.4g EPA, 1.8g DHA daily

Step 8: Correct VEGF

- The steps taken from part 7 often improve VEGF.
- Graded exercise therapy 7x/week below anaerobic threshold is recommended.
    - This should help correct low VEGF.

Step 9: Correct Elevated C3a

- Goal is to get C3a <780
- High dose statin therapy is used until C3a levels return to normal.
    - This typically takes 30 days.
    - If C3a remains elevated after 30 days, this indicates ongoing stimulation of the compliment system.
        - Further investigation is warranted.
- Ensure CoQ10 is taken 10 days before starting statins and continued while taking statin medication.
    - 150-300mg QD
- Avoid grapefruit as this interferes with cytochrome p450 3A4.

Step 10: Correct Elevated C4a

- Goal is to get C4a <2830
- VIP nasal spray is commonly used to lower C4a.
    - Patient to take VIP nasal spray until remaining symptoms improve.
    - 4 sprays per day

- Treatment of C4a should improve cognitive deficits – memory, concentration, word finding, assimilation of new information, etc.

Step 11: Reduce Elevated TGF Beta-1

- Goal is to get TGF beta-1 <2380
- Losartan – a blood pressure medication – can prevent TH17 conversion of T reg cells thus correcting TGFB1.
- Losartan dose = 12.5mg BID
    - Peds dosing is 0.6-0.7 mg/kg/day BID
- Use of VIP can also lower TGF beta-1
    - Use VIP if blood pressure is low

Step 12: Replace Low VIP

- Requirements before beginning VIP:
    - Normal VCS
    - Eradication of MARCoNS
    - ERMI of less than or equal to 2 or HERTSMI-2 less than or equal to 10
    - Normal lipase
- Initial dose should be given in the office
    - 50mcg in single nostril
    - Observe changes in patient; look for rash, SOB, improved cognitive function
    - Check blood pressure and pulse every five minutes x3
- 15 minutes after VIP is administered, re-draw the following labs:
    - TGF beta-1
    - If there is a two-fold increase in above markers, hidden exposure may be ongoing.
- VIP at-home dosing is 50mcg QID
- Check lipase levels monthly
    - If elevated, VIP must be discontinued.
- If symptom improvement is limited, increase dose to 8x per day
- If VCS and labs are stable combined with symptom improvement, taper VIP to 2x/day for 30 days before discontinuing use.

Re-Exposure Checklist

Due to the immediate upregulation of immunological markers, CIRS patients that are re-exposed to biotoxins become “sicker quicker”.

The Sequential Activation of Innate Immune Elements (SAIIE) protocol can be implemented to prove that a certain building is unsafe. Use the below protocol to determine if a building is safe for occupancy.

Step 1:

Draw the following labs:

- C4a
- TGF beta-1
- VEGF
- MMP9
- Leptin
- CD4+
- CD25+

Step 2:

- Stop all treatment medications/supplements

Step 3:

- Stay away from the suspected building for 3 days

Step 4:

- Document symptoms
- Perform VCS test
- Redraw above labs

Step 5:

- Return to suspect building for 8 hours – no medication.
- Record symptoms.
- Redo labs

Step 6:

- Return to building on second day for another 8 hours
- Record symptoms
- Redo labs

Step 7:

- Return to building on the third day for another 8 hours
- Record symptoms
- Redo labs

Step 8:

- Restart medications
- Record symptoms
- Redo VCS

Scoring:

- Compare the C4a on day 1 to the baseline
- Compare Leptin on day 2 to the baseline
- Compare MMP9 as an average of day 2 and 3 to the baseline
- Compare VEGF to baseline; rise on day 1, fall by day 3
- Compare symptoms from day 3 to baseline.
- Add the values

SAIIE Scores

- - 5 for 100%; 4 for 80%, 3 for 70%, 2 for 60%, and 1 for 50%
- - Controls mean is 6.3
- - Cases mean is 17.9
- - TGF beta-1 rapidly changes