Chronic Inflammatory Response Syndrome (CIRS)

by

Aaron Newman DC, MSN-FNP-C, PMHNP-BC, RN

135 South State College Blvd., Ste 200,

Brea, CA 92821

www.mindsparkhealth.com

info@mindsparkhealth.com

(714) 695-5837

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Abstract

Chronic Inflammatory Response Syndrome (CIRS) is a complex chronic illness characterized by specific signs and symptoms, along with abnormalities in laboratory findings, imaging, and transcriptomics. Originating from Dr. Ritchie Shoemaker's groundbreaking work in the 1990s, CIRS is linked to biotoxin exposure and encompasses a wide range of multisystem manifestations. This paper provides an in-depth exploration of the diagnostic criteria, encompassing exposure history, symptomatology, and laboratory tests including Visual Contrast Sensitivity (VCS) and genetic testing for HLA haplotypes. Additionally, it outlines the Shoemaker Protocol, a comprehensive treatment approach aimed at addressing the underlying mechanisms and alleviating symptoms associated with CIRS. Emphasizing the significance of early detection and intervention, this paper underscores the importance of timely diagnosis and personalized management strategies in addressing this debilitating condition.

Introduction: Background to CIRS

Chronic Inflammatory Response Syndrome (CIRS) is a growing concern in modern medicine, affecting millions of people worldwide. CIRS is a multisystem, multi-symptom illness from exposure to environmental biotoxins and subsequent chronic inflammation throughout the body. This illness causes the body's immune system to become dysregulated, leading to inflammation that can damage tissues and organs. CIRS itself is modeled after systemic inflammatory response syndrome (SIRS) where heightened activity of TH1, TH2, TH17 immunity, coagulation factors, and complement proteins are expressed in response to an overwhelming stimulus. Normally, the innate immune system will communicate with the adaptive immune system for antigen presentation and clearance of the offending biotoxin, but in those who are genetically susceptible with certain HLA-DR DQ genotypes, this process becomes impaired and chronic inflammation ensues. This paper aims to review the diagnostic criteria, laboratory markers, and the Shoemaker Protocol as an evidence-based approach to managing CIRS.

What is a Biotoxin?

Biotoxins are a diverse group of substances produced by living organisms that can ignite the innate immune system. They tend to be very small and fat soluble, and burrow among cell membranes and the cytoplasm of the cell. They bind to cell surface receptors releasing inflammatory molecules as part of the innate immune response. These inflammatory molecules are non-specific and cannot remove biotoxins. In patients with CIRS, the adaptive immune system is impaired leading to an inability to create antibodies to clear the biotoxins. This results in persistent expression of the innate immune system and ongoing inflammation. Biotoxin sources may be from, but not limited to toxigenic fungi, inflammagens, endotoxins, actinobacteria, spirochetes, viruses, and cyanobacteria. Certain biotoxins are ionophores, which are small molecules that can move from cell to cell via cell membranes. Upon exposure to these biotoxins, often through inhalation or ingestion, a triggering cascade of inflammatory events will inevitably lead to a wide range of symptoms that represent CIRS.

Historical Context

The origin of CIRS began from the investigational work of one physician named Dr. Ritchie Shoemaker who noticed very unusual fish kills and human illness in Pocomoke, Maryland back in the 1990's. His interest in the wetlands and investigative science led him to a dinoflagellate known as Pfiesteria, as the cause of this illness; CIRS. At the time, it was Pfiesteria and ciguatera; two dinoflagellate illnesses, that were causative in this inflammatory illness. Soon after, cyanobacteria were discussed, and it was found that patients exposed to water damaged buildings demonstrated the same symptom presentation as well. This made for an early case definition of CIRS involving the potential for exposure, presence of multi-system, multi-symptom illness and the absence of confounding exposure or diagnosis.

A treatment protocol was being developed in the 1990's as well. A breakthrough came when Dr. Shoemaker treated a patient that had secretory diarrhea and a host of other symptoms resembling CIRS. He prescribed Cholestyramine (CSM), a bile acid sequestering agent, which allows for elimination of biotoxins from the stool. This treatment led to resolution of gastrointestinal symptoms and other chronic, systemic symptoms as well. This spawned the development of using CSM in patients with CIRS and eventually gave rise to the clinical protocol involving other steps in treating this illness.

Etiology & Pathogenesis

CIRS is acquired from exposure to biotoxins that will activate the innate immune system in genetically susceptible patients. Normally, the innate and adaptive immune system work in harmony, involving antigen presentation, antibody formation and clearance of antigen. This removal allows for innate-immune inflammation to seize and symptoms to abate. In patients with certain HLA-DR DQ genotypes, the inflammation continues. Cytokines attach and damage leptin receptors in the hypothalamus making it difficult for Leptin to bind. As a result, a regulatory neuropeptide, Melanocyte stimulating hormone (MSH), becomes suppressed.

The consequences of low MSH:

- Sleep Disturbances
- Chronic Pain

- Gastrointestinal Problems
- Prolonged Illness
- Changes in Cortisol and ACTH
- Reduced Androgens
- Reduced ADH
- Inflammation
- Colonization of MARCoNS

The Biotoxin illness pathway below: A detailed description of the progressive nature of CIRS

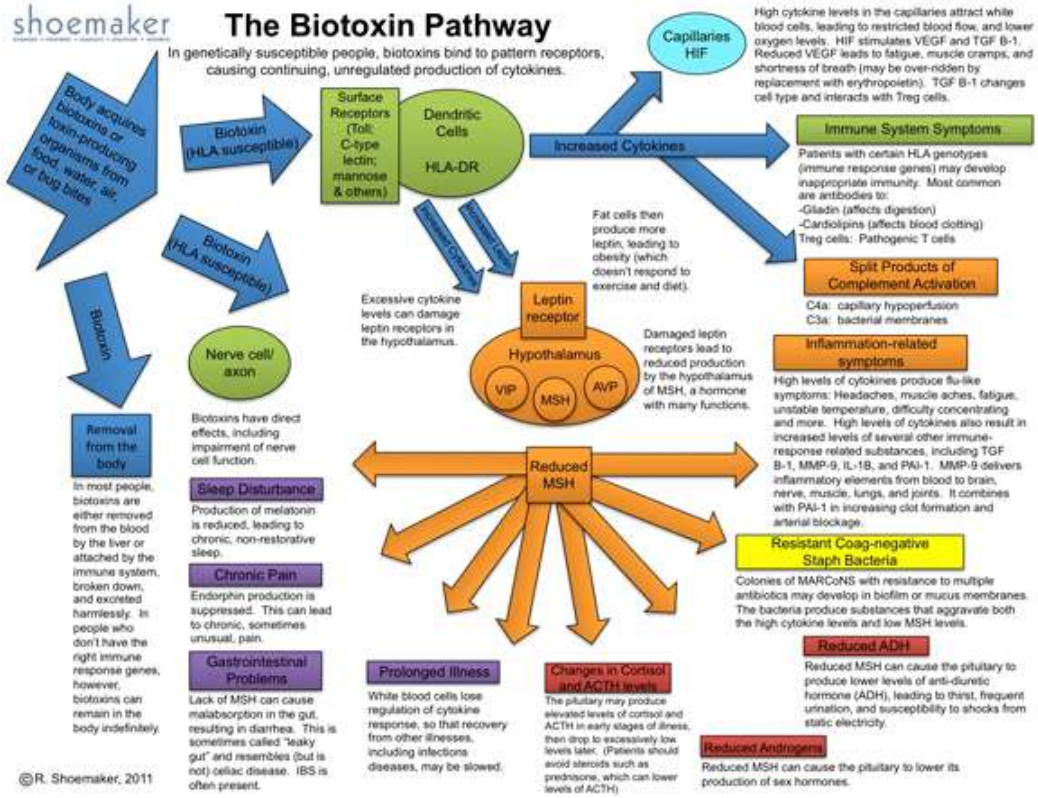

Figure: The biotoxin illness pathway illustrates the progressive nature of CIRS (see Surviving Mold Biotoxin Pathway).

Common Biotoxins found in water damaged buildings:

Beta-glucans	Hyphal fragments	Mycotoxins	Particulates (small, fine & ultra)
Mannans	Cell wall fragments	Mycolactones	Conidia
Spirocyclic drimanes	Bioaerosols	Hemolysins	Protozoa
Lipopolysaccharides (LPS)	Endotoxins	Proteinases	
Actinobacteria	Microbial VOC's	Gram (+) & (-) bacteria	

Figure 1: Table of Biotoxins

Biotoxins ignite an attack on cellular metabolic elements and impact ribosomal and mitochondrial function in cells. Patients with CIRS do not recover unless toxins are cleared and exposure to toxin-producing organisms are removed. The most common reason for CIRS is exposure to a water damaged building (CIRS-WDB) where water intrusion yields a toxic combination of microbial growth, fragments of microbes, and subsequent chemicals that may be harmful to the human body. The World Health Organization (WHO) estimates that 50% of all buildings are water-damaged, which is a frightening statistic knowing that 24% of all people are genetically susceptible to CIRS.

Other known triggers for CIRS include Ciguatera fish poisoning from fish contaminated with ciguatoxin, Pfiesteria, a dinoflagellate, a recluse spider bite, inhalation or contact of Cyanobacteria (cyanotoxins) through infected pond water or lakes, exposure to a tick bite, or a traumatic brain injury.

Clinical Presentation

CIRS presents as a typical set of symptoms among 8 main categories in 13 clusters; general, musculoskeletal, eye, respiratory, gastrointestinal, cognitive, hypothalamic, and neurologic. This "cluster analysis" provides means to organize symptoms and assist in diagnostics. If an adult has eight or more clusters of symptoms positive, there is a 95% probability of having CIRS and if combined with a failed visual contrast sensitivity (VCS) test, it increases to 98.5%.

Treating the individual symptoms will not resolve CIRS, the underlying condition. Being symptomatic is highly dependent on genetic susceptibility as this will determine biotoxin clearance through both antigen presentation and antibody formation.

The HLA-DR DQ genotypes with CIRS:

24% of the population will have HLA-DR DQ genotypes found on chromosome 6 that make them susceptible to CIRS. This 24% then makes up 95% of the CIRS population.

	DRB1	DQ	DRB3	DRB4	DRB5
Multisusceptible	4	3		53	
	11/12	3	52B		
	14	5	52B		
Mold	7	2/3		53	
	13	6	52A, B, C		
	17	2	52A		
	*18	4	52A		
Borrelia, post Lyme Syndrome	15	6			51
	16	5			51
Dinoflagellates	4	7/8		53	
Multi Antibiotic Resistant Staph epidermidis (MARCoNS)	11	7	52B		
Low MSH	1	5			
No recognized significance	8	3,4,6			
Low-risk Mold	7	9		53	
	12	7	52B		
	9	3/9		53	

The 37 symptoms are clustered into 13 categories. Patients diagnosed with CIRS will have at least 8 of 13 categories positive, although children can have 6 and still be diagnosed with CIRS.

Symptom Clusters are as follows:

*Fatigue	*Difficulty concentrating	*Shortness of breath *Sinus congestion	*Red Eyes *Blurred Vision *Sweats *Mood Swings *Ice Pick Pain	*Static shocks *Vertigo
*Weakness, *Decreased assimilation of new knowledge, *Aches	*Joint pain *AM stiffness *Cramps	*Cough *Excessive thirst *Confusion	*Abdominal pain *Diarrhea *Numbness	

*Headache *Light sensitivity				
*Memory impairment *Decreased word finding	*Tingling *Tremor *Unusual pain *Unusual skin sensitivity	*Appetite swings *Difficulty regulating body temperature *Increased urinary frequency	*Tearing of the eyes *Disorientation *Metallic taste	

Figure 2. Table of symptom clusters

Diagnostic Criteria

In 2008, the United States Government Accountability office (GAO) developed a working definition for CIRS-WDB:

1. Potential for exposure to a damp indoor environment
2. Multi-system and multi-symptom illness present with symptoms like those seen in peer-reviewed literature
3. Specific laboratory results like those seen in peer-reviewed literature
4. Response of improvement with treatment protocol

A CIRS diagnosis should include a thorough history, conducting a physical examination, developing a differential diagnosis list, and using laboratory testing to differentiate CIRS from other common misdiagnoses that present with systemic symptoms. Patients with CIRS are often ignored as providers feel “it’s in their head” and are subsequently diagnosed with psychiatric illness. Objective biomarkers become critical for the correct diagnostic impression here.

Common Misdiagnoses:

- Fibromyalgia
- Chronic Fatigue Syndrome
- Multiple Sclerosis
- Depression
- Stress
- Allergy
- Post Traumatic Stress Disorder

- Somatization
- Irritable Bowel Disorder (IBS)
- Attention Deficit Disorder (ADD)

Visual Contrast Sensitivity (VCS)

Visual Contrast Sensitivity (VCS) is conducted to aid in the diagnostic process. VCS is a measure of visual contrast and is an important functional diagnostic test to help identify CIRS, along with cluster symptoms. Contrast is the ability to see an edge and is one of the seven functions of the optic nerve. Exposure to biotoxins may lead to contrast abnormalities that are improved upon the appropriate treatment. A failed VCS in combination with a positive symptom cluster is 98.5% sensitive for a CIRS diagnosis. A VCS can also track patient improvement as the patient is undergoing care.

Further testing is done to evaluate genetic susceptibility and the innate immune system through proteomics. Along with genetic susceptibility, many other analytes are tested to evaluate the innate immune system and CIRS in more detail. With poor antigen presentation to the adaptive immune system, the innate immune system is chronically activated and biotoxins are unable to be cleared. It is common to find TGFβ-1, MMP-9 and C4a elevated, which are the hallmarks of innate immune expression.

The following key analytes are tested for in CIRS:

TGFβ-1	MSH	C4a	MMP-9
AGA & ACLA	ADH & Osmolality	Leptin	ACTH & Cortisol
VIP	HLA haplotypes	vWF	VEGF

Figure 3. Table of analytes tested for CIRS

MSQPCR Testing: ERMI and HERTSMI-2

An environmental assessment is carried out with a Mold-Specific Quantitative Polymerase Chain Reaction (MSQPCR) test. This is a DNA-based test to detect and quantify species of fungi found in water-damaged buildings. Either an Environmental Readiness Mold Index (ERMI) can

be utilized, or the Health Effects Roster of Type-Specific Formers of Mycotoxins and Inflammagens (HERTSMI-2) can be used; both requiring dust samples with a Swiffer cloth. These tests allow for a reliable diagnostic impression of fungal DNA in spore equivalents/mg of dust. Unfortunately, this testing will not identify endotoxins, bacteria, volatile organic compounds, or actinomycetes, which are all commonly found in water-damaged buildings as well. An ERMI will evaluate 36 strains of fungi, where the HERTSMI-2 identifies 5, but is more specific, sensitive, and economical.

The HERTSMI-2 Testing:

This is suggested instead of an ERMI as it is more sensitive and specific and cost-effective for the patient. It can also be derived from an ERMI as well. Either Envirobiomics or Mycometrics can send test kits. The HERTSMI-2 scoring is based on the results of 738 consecutive ERMI test results with 592 that were over 2 and 146 under 2.

Helps identify "the big 5" mold species in spore E/mg

- Aspergillus Penicillioides
- Aspergillus Versicolor
- Chaetomium Globosum
- Stachybotrys Chartarum
- Wallemia Sebi

Laboratory Markers

Transforming Growth Factor beta-1 (TGFβ-1)
Normal Range <2380 pg/mL

TGFβ-1 is a pleiotropic molecule that modulates inflammation with both inflammatory and anti-inflammatory functions. The evidence is clear that an elevation of TGFβ-1 is consistent with fibrosis and remodeling of different tissues, among other chronic and autoimmune conditions. TGFβ-1 may change regulatory T cell expression based on retinoic acid receptor (ROR) activity.

Complement C4a

Normal Range 0-2830 ng/mL

C4a is a protein of the complement system and activated through two pathways; the classical and mannose-binding lectin pathway. It is an important marker in evaluating re-exposure to water-damage buildings as it rises within the first 12 hours of exposure to biotoxins. This complement protein functions to increase vascular permeability, smooth muscle contraction, and activation of different leukocytes including basophils and monocytes, all in response to a biotoxin.

Matrix Metalloproteinase-9 (MMP-9)

Normal Range 85-332 ng/mL

MMP-9 is a cytokine that is derived from the MMP-9 gene and MMP-14 after stimulation of pro-inflammatory cytokines. It is involved with the breakdown of the extracellular matrix in blood vessel walls, which leads to inflammatory compounds exiting blood vessels and moving into organs and tissue such as the brain, joints, and nerves. Regarding CIRS, when MMP-9 is expressed, it continues inflammation, cytokine activity and tissue remodeling.

Leptin

Normal Range Male 0.5-13.8 ng/mL; Female 1.1-27.5 ng/mL

Leptin is known as the satiety hormone and plays a major role in the inability to lose weight with CIRS. Inflammation targets the leptin receptor in the hypothalamus, which then influences MSH. High levels of leptin and leptin resistance will lead to weight gain in the body, despite physical activity and a healthy diet. This is due to leptin having a pro-inflammatory effect on the immune system, stimulating appetite, and slowing metabolism. As Leptin receptors become damaged in the hypothalamus, MSH is reduced and sleep disturbances, suppressed endorphins, and cortisol elevations all ensue.

Vascular Endothelial Growth Factor (VEGF)

Normal Range 31-86 pg/mL

Vascular endothelial growth factor stimulates growth of new blood vessels and responds to hypoxic situations within the body. In CIRS, 1/3 of all patients will have low VEGF, 1/3 will be normal and 1/3 will be high. Hypoxia-inducible factor (HIF) will stimulate the production of VEGF, and EPO. With inflammatory states, VEGF is reduced and poor oxygenation to tissues will occur, resulting in fatigue and exercise intolerance.

Anti-Gliadin Antibody (AGA)

Normal Range 0-19

Gliadin is a protein found in wheat, rye, and barley. Antibodies are commonly found to gliadin in those with CIRS, especially children. Gliadin activates zonulin signaling, which creates inflammation, but also permeability of the gut through tight junction breakdown. This leads to systemic symptoms with inflammation and possible autoimmunity through loss of oral tolerance. If anti-gliadin antibody is found, further testing for Celiac Disease through transglutaminase antibodies should be carried out. A gluten-free diet is necessary for 3 months with confirmatory testing that antibodies are negative. If so, gluten can be reintroduced if desired.

Alpha Melanocyte Stimulating Hormone (MSH)

Normal Range 35-81 pg/mL

MSH is a hormone expressed in the hypothalamus and is often deficient in CIRS. This neuropeptide has modulating properties to other hormones and plays a role in weight, circadian rhythms, and energy. Serum levels are generally low in CIRS from cytokine activity and hypothalamic inflammation. Low MSH leads to chronic pain from decreased endorphin production and will also influence the integrity of tight junctions in the gut. Most people with low MSH will have MARCoNS; multiple-antibiotic-resistant coagulase-negative staphylococci. MARCoNS will perpetuate CIRS by releasing exotoxins. These exotoxins split MSH molecules causing reduction in MSH and furthering the inflammatory cascade.

Anti Diuretic Hormone (ADH)/Osmolality

Normal Range ADH 1.0-13.3 pg/mL; Osmolality 280-300 mOsm/kg

Antidiuretic hormone also known as Vasopressin, controls fluid dynamics and osmolality of the blood. It is produced by the Hypothalamus and released by the pituitary gland. It reduces the elimination of free water, and if low, patients generally have symptoms of polyuria and nocturia. Low ADH levels may occur from inflammation with CIRS and hypothalamic dysregulation of MSH. Osmolality is a representation of how concentrated the blood is with sodium and other electrolytes and will inevitably shift because of intravascular dehydration. Patients with low ADH often have excessive urination, dehydration, thirst, and a higher susceptibility of migraine headaches, too.

ACTH and Cortisol

Normal Range ACTH 8-37 pg/mL; Cortisol a.m. 4.3-22.4 µg/dL

Both ACTH and cortisol are involved in the stress response as ACTH is secreted by the pituitary gland to stimulate the adrenals in producing cortisol and catecholamines. Cortisol is a steroid hormone involved in the formation of blood sugar, immune function, and is affected by chronic inflammation from CIRS. When patients have dysregulation of this system, it is rarely due to adrenal insufficiency or Cushing's, and more commonly from disruption in melanocortin physiology. Patients may present with sleep abnormalities, anxiety, blood sugar imbalances and daytime fatigue, as the ACTH/Cortisol feedback is impaired. In the early stages of CIRS, ACTH and Cortisol levels are often elevated and then eventually fall with progression of disease state.

Vasoactive Intestinal Peptide (VIP)

Normal Range 23-63 pg/mL

VIP has neuromodulation and immune modulation benefits and is an important addition in CIRS recovery, and the last step of the Shoemaker protocol. VIP is a neuropeptide found in the gut, but has influence in the lung and other tissues by regulating inflammation throughout the body.

VIP also plays a role in managing high pulmonary artery systolic pressure through neuroregulatory mechanisms and increasing exercise tolerance. Specifically, this improvement may stem from VIP influencing ribosomal and mitochondrial gene expression. With treatment, VIP is administered by nasal spray up to four times a day and may assist in the rehabilitation of gray matter nuclear atrophy by correcting neuroinflammation. VIP can also correct vitamin D levels, T regulatory cells, androgens, aromatase, MMP-9, VEGF, C4a, TGFβ-1 and VIP levels.

Further Testing

Additional testing includes von Willebrand's panel and further screening for anti-cardiolipin antibodies (ACLA). These antibodies occur in 33% of children with CIRS. Androgens such as DHEA and Testosterone are often low in patients due to MSH suppression, inflammation, and increased aromatase activity. Screening for DHEA, Testosterone, LH, FSH and Estrogen should be carried out.

Neuroquant MRI (NQ):

Neuroquant (NQ) is an FDA-cleared, automated software that analyzes brain MRI scans to quantify and compare brain structure volumes. It is an addition to a standard MRI scan and takes 10 minutes to process. It is efficient, affordable and a reliable diagnostic measure to differentiate CIRS-WDB from CIRS-PLS, and may assist with identification of TBI, and post-traumatic stress disorder (PTSD). CIRS-WDB patients show a specific NQ pattern of an increased forebrain parenchyma, cortical gray, and a decreased caudate. Patients with CIRS-PLS show a small putamen and large right thalamus.

Transcriptomics:

PAXgene testing allows for direct measure of genetic expression related to immune function and inflammation by measuring messenger RNA. This testing can further assist in CIRS diagnostics and prognostics for the clinician and patient. It adds another layer of objectivity and a unique transcriptomic fingerprint as a diagnostic aid for CIRS and other complex immunological illnesses.

VO2 max testing:

Patients with CIRS often complain about being tired and suffer from "post-exertional malaise," like chronic fatigue syndrome. Their VO2 max testing is below 25ml/kg/minute when it should be around 50. Oxygen delivery is impaired in addition to capillary hypoperfusion and mitochondrial gene abnormalities. Patients with CIRS are often tired and have trouble walking around the block or going up stairs. Their anaerobic threshold is altered and ATP production is inefficient.

Pertinent negative testing:

These are biomarkers that are generally absent in a CIRS patient when they may show in other diagnoses. Many standard objective markers are normal in CIRS; sedimentation rate, C-reactive protein, CBC with differential, immunoglobulins, metabolic panel, ANA, viral studies, thyroid testing, EKG, Pulse oximetry, and Chest X-ray, among others. These markers should not be overlooked as they will help with correct diagnosis.

The Shoemaker Protocol

Step 1: Eliminate Exposure

PCR testing with ERMI or HERTSMI-2
Goal: ERMI <2 and/or HERTSMI-2 <11

The initial step is to remove oneself from exposure to a biotoxin and/or water damaged building. It is estimated that 24% of people are susceptible to biotoxin illness based on human leukocyte antigens, and close to 50% of all buildings are water damaged. Sources of water damage may include poor ventilation, crawl spaces, poor sealant on windows, leaky roofs, pinhole leaks, and HVAC system, among others. To evaluate the building or the residence, an MSQPCR test is done; either an ERMI or HERTSMI-2. The HERTSMI-2 evaluates 5 species of mold, where the ERMI does 36. If positive, the next step is detection of the source in the building and then mold remediation. It is recommended to work with an indoor environmental professional (IEP) and one that is knowledgeable in CIRS. The person affected will reduce exposure and go through remediation phases to improve overall health. On occasion, the patient will temporarily vacate the

property and only return once remediation and repeat testing have been completed. An ERMI score of <2 or HERTSMI-2 of <11 is generally acceptable. If MSH is <35 and C4a >20,000, the ERMI must be -1 or less.

Step 2: Removal with a Binder

Cholestyramine 4 grams QID or Welchol 625mg two pills TID with food

Goal: to reduce biotoxins and pass VCS

Cholestyramine (CSM), a bile acid–sequestering agent, is a non-absorbable resin that is prescribed to bind biotoxins. Instead of recycling them through the entero-hepatic loop, CSM will remove them through the stool. CSM has a positive net charge as quaternary ammonium salt that binds to negatively charged biotoxins. CSM must be taken between meals and away from medications and supplements. A general rule of thumb is 30 minutes before a meal or 1 hour after eating. A small starting dose may be worked up to 4 grams 4 times daily for continuous removal of biotoxins. Pediatric dosing is 60mg/kg/dose TID. Side effects of this medication may include constipation, acid reflux, and/or heartburn, where patients can take magnesium, vitamin C, fiber, or MiraLAX to improve motility and reduce constipation. Some patients may select Welchol, which is a CSM substitute and taken with food. Although there are generally fewer side effects, it is less effective with only 25% of the binding sites compared to CSM. Some patients may benefit from taking Welchol and CSM together. Other natural binders like clays, zeolite and pectin's should not be used as there is a lack of evidence with binding toxins. It is recommended to continue CSM until symptoms improve and one is out of exposure with a passing VCS test. Preloading with 2.4g EPA and 1.8g DHA for 7 days will help patients tolerate the medication.

Step 3: MARCoNS Management

0.25% EDTA two sprays each nostril TID for 6 months and starting 1 month after binders

Goal: To eradicate MARCoNS and confirm absence on culture 2 weeks post-treatment

After beginning CSM, treatment of multiple antibiotic-resistant coagulase-negative staphylococci (MARCoNS) will be undertaken, if present. MARCoNS secrete exotoxins and are found in the deep nasopharynx. Antifungals are not used here, but rather 0.25% EDTA spray is the preferred treatment. 2 sprays each nostril TID for 6 months, and at least a month after binders. Some patients will require EDTA for the remainder of the protocol, however. MARCoNS is also found within other areas of the body including cavitations, and in the deep nasopharynx of dogs. Cats rarely carry MARCoNS. The protocol is followed by another nasal culture to ensure eradication, generally 2 weeks after the spray is completed. MARCoNS has been seen to cleave MSH, which is why MSH is often low on laboratory testing.

Step 4: Anti-Gliadin Antibodies

Eliminate gluten and retest anti-gliadin antibodies (AGA)
Goal: negative AGA or continual avoidance of gluten

Anti-gliadin antibodies are often found in CIRS and indicate gluten intolerance. If found, a gluten-free diet for 3 to 6 months will be undertaken and further testing of transglutaminase IgA and Celiac Disease will be carried out. Gliadin among other proteins that compose gluten may also lead to tight junction breakdown and gut permeability by expressing zonulin.

Step 5: Correction of Androgens

DHEA 25mg TID for 30 days and monitor Estradiol
Goal: Normalize Androgens

Androgens such as DHEA will have to be corrected along with other hormones like Testosterone. Testosterone replacement is not recommended and is even counterproductive since it does not address the underlying reason for the deficiency. In CIRS, aromatase converts testosterone to estrogen and secondly, inflammation suppresses the hypothalamic-pituitary-gonadal (HPG) axis. Since aromatase enzyme tends to be up-regulated in CIRS, a test dose of DHEA is done to evaluate changes with Testosterone and Estrogen. VIP may help here as it balances hormones and decreases the up-regulation of aromatase enzyme.

Step 6: Correction of ADH/Osmolality

Desmopressin 0.2mg every other night for five doses

ADH and osmolality will be corrected by Desmopressin at 0.2 mg every other night for 10 days. This is synthetic ADH and will help correct frequency of urination and nocturia. Patients often complain about excessive thirst and frequency of urination that is bothersome at night and even in the day. Careful monitoring of serum sodium, other electrolytes and daily weights are taken for 10 days. A longer protocol might be undertaken if correction does not happen initially.

Step 7: Correcting MMP-9

Use 2.4 grams of EPA and 1.8 grams of DHA and VIP if indicated

Matrix Metalloproteinase-9 (MMP-9) can be supported by high dose fish oil at 2.4 grams of EPA and 1.8 grams of DHA per day. Management also includes a low amylose diet to further decrease inflammation and pain. This is mainly done if Leptin levels are elevated. This dietary approach excludes gluten, rice, bananas, and all vegetables grown underground (except garlic and onions).

Step 8: Correcting VEGF

Use 2.4 grams of EPA and 1.2 grams of DHA and VIP if indicated

As with MMP-9, high dose fish oil at 2.4 grams of EPA and 1.8 grams of DHA will improve VEGF levels. VIP when indicated. Low VEGF is often seen in patients with CIRS and leads to poor oxygenation of tissues. Daily, graded exercise will help, but to the patient's tolerance. Correcting VEGF will improve energy, cognition, and exercise capacity.

Step 9: Correcting High C3a

Implementation of Statin and pre-medicate with 10 days of Coq10 at 150mg

C3a is a component of the complement system. High C3a is often found in Lyme Disease. C3a binds and induces breaks in bacterial membranes and is responsible for membrane leakage of

liposomes. C3a will modulate cytokines, activate dendritic cells, and regulate T cell signaling. Treatment to lower C3a consists of high-dose statin drugs like Zocor at 80 mg per day. The patient will be pre-treated with CoQ10 for 10 days at 150mg daily to reduce the side effects from a statin drug. Monitoring liver enzymes and creatine kinase (CK) are done for safety.

Step 10: Correcting High C4a

Use VIP to reduce high C4a

High C4a of the complement system is lowered either by erythropoietin or VIP. VIP is much safer though. VIP can only be used in the presence of a normal VCS test, a negative MARCoNS swab, normal lipase levels, an ERMI less than 2 or HERTSMI-2 less than 11, and the patient is out of exposure. VIP is done at 4 sprays daily alternating nostrils each spray.

Step 11: Lowering TGFβ-1

Use of VIP or Losartan 25mg BID

TGFβ-1 is lowered by using Losartan, a blood pressure lowering medication. Careful consideration of blood pressure must be taken and if patients are already hypotensive, this step is skipped and the patient will proceed to VIP instead. Losartan is given at 12.5mg daily and worked up to 25mg twice daily if tolerated.

Step 12: Vasoactive Intestinal Peptide (VIP)

Use VIP 50µg QID supplementation. Dose may change when appropriate.

Vasoactive intestinal peptide (VIP) is a key neuro and immune-modulatory agent and the last step of the Shoemaker protocol. Most patients should be improved at this point by 75%, but VIP can still be used. Before starting VIP, patients must have an ERMI score under 2 or a HERTSMI-2 score under 11, a normal VCS test, a negative MARCoNS culture, a normal Lipase and GGTP, and be out of biotoxin exposure. VIP is first done as a test dose, and if TGFβ-1 rises by 33% then it indicates the patient is still in active exposure. Blood Labs will be monitored over

time, especially for lipase and GGTP, and routine examination of abdominal symptoms will be evaluated as well.

Key points of VIP administration:

- VIP maintenance can be 1 spray daily after initial protocol of 6-12 months
- Measure Lipase monthly and if elevated, evaluate further for pancreatitis
- The first dose of VIP is in-office after a baseline of TGFβ-1. Another draw is then done. TGFβ-1 should not rise and if so, then the patient is likely in exposure
- Dose titration may be needed to 12 sprays daily for full benefit
- Sensitive patients can do a 1:10 dilution at 5µg/spray

Exercise:

Exercise is suggested during the protocol to increase the anaerobic threshold. The patient will work up to 15 minutes of cardiovascular exercise, 15 minutes of resistance training and 15 minutes of core stability daily. The key is to be consistent and exercise to tolerance.

Re-exposure:

Being out of exposure is critical for patients with CIRS. With re-exposure, symptoms are magnified in onset and intensity known as the sicker, quicker phenomenon.

The following is the Sequential Activation of Innate Immune Elements (SAIIE) to determine if a building is safe.

Medications are stopped for 3 days with baseline VCS and labs (C4a, MMP-9, TGFβ-1, VEGF, and factor VIII). Exposure of 8 hours daily over 3 consecutive days without binders. Laboratory testing is performed that morning before exposure and the next 3 mornings following. VCS and symptoms are documented

- Day 1 findings: C4a, TGFβ-1, VEGF increases and Factor VIII decreases
- Day 2 findings: Leptin elevation, MMP-9 elevation, VCS abnormal and VEGF decreases, Factor VIII decreases as acute phase reactant
- Day 3 findings: MMP-9 increases, VCS abnormal, VEGF goes to nadir, Factor VIII normalizes, both vW antigen and ristocetin cofactor may drop

The patient will record their symptoms throughout the process. If there's worsening labs and VCS results along with symptom exacerbation, the building is then deemed unsafe for the patient and they will have to restart care.

Conclusion

Impact of Dr. Shoemaker's Work

Dr. Shoemaker's pioneering contributions have revolutionized the landscape of Chronic Inflammatory Response Syndrome (CIRS). His unwavering dedication and groundbreaking research have not only empowered healthcare providers to adeptly manage chronic diseases and CIRS, but have also provided hope and healing to countless individuals worldwide grappling with this debilitating condition.

Dr. Shoemaker's ongoing commitment to research, advocacy, and the advancement of CIRS treatment, notably through transcriptomics, underscores his enduring impact on the field. As we reflect on his legacy, it is evident that his tireless efforts have propelled the understanding and management of CIRS to new heights, promising continued advancements in the quest for improved patient outcomes and quality of life.

Future Directions in CIRS Research

Future directions in Chronic Inflammatory Response Syndrome (CIRS) research encompass several key areas. Transcriptomics offer insights into molecular mechanisms and potential therapeutic targets. Immunomodulatory therapies hold promise for symptom management. Understanding biotoxin exposure and environmental factors is crucial for prevention. Longitudinal studies and clinical trials are needed to evaluate treatments. Patient-

centered research and education initiatives are essential for improving care. By addressing these future directions in CIRS research, the medical community can advance scientific understanding, improve clinical outcomes, and ultimately, alleviate the burden of this complex and debilitating syndrome on affected individuals and communities.

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Based on the work of Ritchie Shoemaker, M.D.