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FOR HEALTH & HEALING

TREATMENT OF CHRONIC INFLAMMATORY RESPONSE SYNDROME

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INTRODUCTION:

CIRS is a multi-system, multi-symptom progressive illness that occurs secondary to poor antigen presentation, resulting in an escalating inflammatory cascade triggered by biotoxin exposure, especially in HLA susceptible individuals (22 percent). Essentially, **the host response becomes the illness.**

The specifics of biotoxin illness were first recognized by Dr. Ritchie Shoemaker, who in 1997 illustrated the connection between a multitude of patient symptoms being linked to exposure to a biotoxin producing, fish killing, dinoflagellate called *Pfiesteria* by direct water contact and/or aerosol.

The causes have now been seen to include other single-celled organisms or fragments of them that act to trigger an unchecked innate immune response, such as, ciguatoxin A from reef dwelling fish contaminated by the marine microalgae *Gambierdiscus toxicus:* Microcystis, lyngbya, cylindrospermopsis, anabaenopsis found in freshwater ponds, lakes and lagoons; Lyme related tick bites **(CIRS-PLS)**; recluse spider bites, and from apicomplexans like babesia ssp**.** However, the most common cause is thought to come from, filamentous fungi, mycotoxins, bacteria (GNB and actinobacteria) along with mannans, beta glucans, hemolysins, proteinases, spirocyclic drimanes, and VOC's occurring in **water damaged buildings (CIRS-WDB)** and most recently may include viruses, such as coronavirus resulting in a post-covid syndrome**.**

The 2008 US Government Accountability Office **case definition of CIRS** includes the following:

a. Potential for exposure to a biotoxin.

b. Presence of a multisystem, multisymptom illness like those seen in peer reviewed literature.

c. Presence of laboratory test results like those seen in published literature.

d. Documentation of response to therapy.

However, the 2019 case definition in the Townsend Letter has been expanded to not only include the **abnormal proteomics**, regulation of immune functions and hormone feedback loops with loss of its neuropeptide regulation. But now includes abnormal "**transcriptomics"**, where changes in activity of ribosomal and nuclear encoded mitochondrial genes are seen.

In summary, cases with **CIRS-WDB** will have a multi-system, multi-symptom illness; presence of multiple reliable objective laboratory biomarkers, which taken as a group but not individually, will aid in the diagnosis and in the monitoring of therapy. Markers include genetic haplotypes, innate immune inflammatory elements, deficiency in neuroregulatory peptides or their receptors, dysregulation of pituitary and end organ factors, as well as clearly defined abnormalities in transcriptomics.

Once a diagnosis is made, the evidenced based **12 Step Shoemaker Protocol** followed sequentially, has been objectively shown to return the patient back to health.

DIAGNOSIS:

First a thorough history and physical with determination of **exposure** is completed.

The most common cause to date of CIRS is due to chronic exposure to a WDB.

If clues of such exposure are seen, then **ERMI** (Environmental Relative Moldiness Index) and/or the more specific **HERTSM1 2** (Health Effects Roster of Type Specific (formers) of Mycotoxin and Inflammagens-2) testing of collected dust are recommended. Air sampling is of limited benefit. It has been shown that it only takes 48 hours of dampness to create microbes with their resultant health effects. An ERMI greater than 2 and HERTSMI-2 score greater than 11 can result in the perpetuation of a chronic inflammatory response.

Some indicators of water damage could include history of leaky HVAC system, water stains, condensation around vents, plumbing issues, rotten wood around windowsills, baseboard gaps, and visible mold.

Evaluation for Lyme disease history or risk, such as a known previous tick bite, hiking in tall grass, history of bullseye type rash (erythema chronicum migrans), or travel to an endemic area should be determined. In addition, a history of a possible recluse spider bite, a gastrointestinal illness after eating reef dwelling fish or some type of illness following swimming/surfing in a body of water can be helpful clues in the identification of exposure.

There are 13 defined symptom clusters, which include 37 separate symptomatic complaints:

1. Fatigue
2. Weakness, decreased assimilation of new knowledge, aches, headaches, light sensitivity
3. Memory, decreased word finding
4. Concentration
5. Joint pain, morning stiffness, cramps
6. Unusual skin sensations, tingling, unusual pain, tremors
7. Shortness of breath, sinus congestion
8. Cough, excessive thirst, confusion
9. Appetite swings, body temperature regulation issues, urinary frequency
10. Red eyes, blurred vision, night sweats, mood swings, icepick pains
11. Abdominal pain, diarrhea, numbness
12. Tearing, disorientation, metallic taste
13. Static shocks, vertigo

Physical Exam along with Visual Contrast Sensitivity (VCS) testing is then done. A **VCS** test measures the **capillary hypoperfusion** that occurs in response to the biomarker changes found in CIRS. It remains to be the most accurate assessment for functional vision. It represents the neurological basis of vision and optic nerve function. Contrast assesses the eye's ability to see the difference in a door frame from its background or to see an edge. When tested it controls for near, far, peripheral and night vision. **Ninety two percent** of CIRS patients demonstrate VCS deficits. We can see VCS deficits improving with proper treatment and then returning within just 36 hours of re-exposure.

This test is best performed in office but can also be performed online only from www. survivingmold.com without substitutes. Other online programs have been found to be inaccurate. A positive test represents the inability to see 7 in column C and 6 in column D.

There is a **98.5 %** accuracy in a CIRS diagnosis if that patient fails the VCS test and exhibits symptoms in 8 of 13 clusters for adults, and 6 of 13 for children.

A **physical exam** is very important in the process of diagnosis. Paying particular attention to vital signs is important: the blood pressure and pulse (supine, sitting and standing with 1 minute between each reading) can give information regarding the possibility of postural orthostatic tachycardia syndrome (POTS), or if carrying out certain steps in the protocol is advised. Breathing patterns and pulse character are important to rule out any elevation in PASP, heart failure or stroke related breathing patterns (Cheyne-Stokes respirations) in patients with symptoms such as, fatigue, shortness of breath, dyspnea on exertion and cognitive deficits that can be seen in those suffering from CIRS.

Some signs suggestive of the diagnosis are a resting tremor, abnormal skin turgor, rashes (mold facies), venous stasis changes, enlarged nasal turbinates or polyps, scleral injection, acne and gingivitis type changes. Palpation for thyromegaly, cervical lymphadenopathy, cranial nerve abnormalities (CN VII) and jugular venous distention; as seen in right ventricular hypertrophy, should be assessed for.

Lungs, heart, and abdomen should be evaluated, and the extremities should be analyzed for abnormalities. Proximal and distal arm strength is recommended to be tested looking for fatiguing of the anti-gravity muscles. In addition, dermatographia should be assessed for and is a sign of the associated elevation of c4a in this condition. Of special note, is measurement of the wingspan compared to height as seen elevated in those with the CIRS vulnerable HLA 11-3-52 B and rising TGF beta 1.

This **genetic vulnerability** needs to be determined looking at the expression of the **human leukocyte antigens (HLA)** on chromosome 6. There are certain haplotypes that predispose people to having an inability to remove certain biotoxins leading to CIRS. HLA DR by PCR can be done thru Quest or Lab Corp and includes 5 different elements: DRB1, DQ, and one from the group of DRB3, DRB4 or DRB5. It has been noted that about 25 percent of the population carry an HLA vulnerability with only a small percent of CIRS cases being without it.

The HLA haplotypes that correlate with being multi-susceptible (unable to clear any/all toxins from the system) are 4-3-53, 11/12-3-52B, and 14-5-52B. The ones that are associated with an inability to recognize and clear mold toxins specifically are 7-2/3-53, 13-6-52 (A, B, C), 17-2-52A, and 18-4-52A. The types associated with an inability to clear Lyme toxins are 15-6-51 and 16-5-51 with the HLA haplotype 4-7/8-53 creating a vulnerability to CIRS secondary to dinoflagellates. In addition, the HLA haplotypes 11-7-52B relates to difficulty clearing MARCoNS and the type 1-5 with persistently low MSH.

PROTEONOMICS/LABORATORY TESTING:

We need laboratory confirmation to support the differential diagnosis of the patient's symptoms, direct individualized targeted therapies, access response to treatment and to direct further research to identify novel approaches to other similar inflammatory illnesses.

General Labs:

Complete blood count with differential (CBC), complete metabolic panel (CMP) including a

GGT level, homocysteine level (HC), sedimentation rate, thyroid profile, lipid panel, 25 (OH) D3, HbA1c, Fe, TIBC, ferritin level, male hormone panel, or female mid-luteal hormone panel (progesterone, DHEA-S, estradiol, estrone, testosterone and androstenedione).

Specific Labs:

HLA DR, MSH (follow instructions), leptin, TGF beta 1, MMP9 (spin immediately), VEGF, C3a and C4a (National Jewish Lab/Quest), ADH/Osmolarity, ACTH/cortisol, VW profile, anticardiolipin, antigliadin, lipase, CD4+ and CD25+.

The **biotoxin pathway** is a schematic of the pathophysiology of CIRS and illustrates the effects of these biomarker changes that occur when a person with certain HLA DR vulnerable states (25 percent of the population) is exposed to a biotoxin. It is the basis behind the above laboratory tests applied. It can be found on the surviving mold website (www.survivingmold.com).

Nasal Swab for MARCoNS:

We need to perform nasal swab testing for multiple antibiotic resistant coagulase negative staph (MARCoNS) bacteria and biofilm. It is a secondary source of brain inflammation that "silently" resides deep in the nasal passages of many CIRS patients and exacerbates their low MSH state. It has been likened to producing "slime" that evades the immune system and further perpetuate the low MSH state by secreting **exotoxins A and B** cleaving the MSH molecule. In addition, it increases inflammation by secreting hemolysins and changes genomic expression. It not only releases these exotoxins and **hemolysins**, but it further releases small neurotoxins, such as, **polycyclic ether toxins,** through the olfactory bulb worsening the effect on the central nervous system and brain. Effective treatment (VIP nasal spray) and recovery generally cannot occur without its eradication.

NeuroQuant (NQ) MRI:

A brain MRI with NeuroQuant is another tool that assists in diagnosis and monitoring of therapy. This is a computer-based program that has been used in the traumatic brain injury (TBI) field since 2007. It extrapolates data from an MRI of the brain and illustrates any volumetric changes in eleven brain areas. It now validates cognitive impairment, the fingerprint of the source of CIRS, response to therapy and assists in the clarification of newer therapies such as transcriptomics.

Of current importance is that the **NQ data must be associated by age** paying particular attention to the presence or absence of gray matter nuclear atrophy, initial enlargement, and eventual atrophy of the forebrain parenchyma (FP) and cortical gray (CG), and enlargement of the superior lateral ventricle (SLV).

Known fingerprints are that a small putamen and large right thalamus can be tracked by GENIE in PLS and interstitial edema of FP, CG and a small caudate is seen CIRS-WDB. The fact that NQ can show the reversal or diminution of these changes with treatment; illustrating the neuroplasticity and capacity of the brain to heal.

Now however, transcriptomic testing is leading the way and hypometabolism effects must be considered in the process. Without correction of ribosomal gene abnormalities and eradication of MARCoNS there is limited benefit and atrophy increases. The focus of treatment is now on the hippocampus, amygdala, caudate, putamen, pallidum, and thalamus. The use of the NQ calculator on www.survivingmold.com can abate any confusion.

Echocardiogram, Cardiopulmonary Exercise Testing, VO2 max, PFT:

A metabolic complication of CIRS is pulmonary hypertension (PAH). It can be calculated directly through heart catherization or is more commonly calculated indirectly by an echocardiogram. However, many times the focus of an echocardiogram is to evaluate left ventricular function instead of the velocity of flow moving backwards across the tricuspid valve. Unless the **"tricuspid jet**" is evaluated the calculation is difficult to obtain. We can calculate the **pulmonary artery pressure (PASP)** by squaring the jet and multiplying it by 4 and adding that result to the right atrial pressure. Jet velocity **greater than 2.5 mm per second** is of concern and any resting **PASP greater than 30 mm Hg** is consistent with PAH. If a stress echocardiogram is obtained any change in **PASP over 8mm Hg** is considered abnormal with exercise and the indication for treatment with VIP is validated.

VO2 max is often low in the CIRS patient population because of metabolic changes that occur due to tissue hypoxia (**capillary hypoperfusion**), glycogen storage depletion and mitochondrial gene issues. An important test to evaluate this process is through **cardiopulmonary exercise testing.** It measures oxygen use and carbon dioxide production during exercise. Determining the milliliters of oxygen consumed per kilogram per minute (VO2 max) is very important to delineate **anaerobic threshold** (AT). If this is exceeded, oxygen is not available to the mitochondria and the production of the full 38 ATPs from a molecule of glucose does not occur. This resultant depletion of glucose and glycogen stores leads to the necessity of beta oxidation for fuel. However, in the presence of low MSH and leptin resistance in those afflicted with CIRS, this cannot occur, and post-exertional malaise or the "push/crash" phenomenon ensues. A restrictive pattern consistent with interstitial lung disease can be seen on pulmonary function tests (**PFT)** especially if the elevated transforming growth factor beta 1 (TGF beta 1) level is not corrected.

TRANSCRIPTOMICS:

Pax Genomics: GENIE (Gene Expression: Inflammation Explained)

We now know that genes that help ribosomes make proteins and the genes that make mitochondrial enzymes function to produce most of our energy. It has been shown that they are greatly impacted by CIRS. Ribotoxins exposure released from biotoxins will lead to hypometabolism. The future of the assessment and treatment response of CIRS patients lies in following the differential in activation of these genes and much is yet to be learned.

TREATMENT:

The Shoemaker Protocol

The effectiveness in returning patients back to health lies in following the sequential steps in the protocol. Some additions of integrative medicine can be added. However, the only evidence-based therapy to date is following this protocol, with each step followed sequentially, for the patient to regain vitality.

1. Remove from exposure
2. Remove biotoxin with cholestyramine/ welchol.
3. Eradicate MARCoNS.
4. Correct antigliadin antibody
5. Normalize abnormal androgens
6. Correct ADH/osmolality
7. Correct elevated MMP-9
8. Correct low VEGF
9. Correct elevated C3a
10. Correct elevated C4a
11. Reduce elevated TGF-beta 1
12. Correct with VIP

Step 1: Remove from Exposure

This can be the most difficult step in the process. Evaluating the type of biotoxin is of upmost importance in the process. Ongoing exposure will only impede wellness.
The history, proteomics, and transcriptomics can all aid in this process. If untreated Lyme is a possibility, then antibiotics may be necessary and if water intrusion is expected, as seen in 50 percent of homes in the US, having an ERMI less than 2 or HERTMI less than 11 is required. In addition, if a musty order is present, then actinomyces and endotoxin must be included in the evaluation of the settled dust in the building or home.
Proper "medical" remediation is needed before re-occupancy. If the C4a count is above 20,000 this indicates a re-exposure and increased sensitivity or a "sicker quicker" phenomenon through the MASP-2 enzyme. At this point, the WDB must have an ERMI under 1. In addition, if the MSH is less than 35 we may also want a more limited ERMI measurement of less than 1. Anything porous must go. Whereas non-porous materials can possibly be cleaned along with clothing.

Step 2: Remove Biotoxin with Cholestyramine (CSM)/Welchol

Goal: Pass VCS

Dose: CSM 4 grams QID on empty stomach or Welchol 625mg 2 tabs TID with food for 30 days. NO food, medication or supplements--30 minutes prior or 60 minutes after dosing CSM and drinking 4-6 ounces of water after each dose is recommended.

Pediatric Dose: 60 mg/kg TID or if 60-120 lbs then 4 grams TID for 30 days and PRN.

Cholestyramine is known to be the most effective binder to remove the negatively charged biotoxin by an organic **anion transport system**. It has a positive quaternary structure that can bind the biotoxin and prevent its recirculation in the entero-hepatic circulation. It's positively charged ammonium side chain allows the negatively charged ionophore (one end lipophilic and one hydrophilic) to be impeded from traveling around creating tissue damage by binding to it allowing it to be eliminated in stool.

Based on these principles, **neither zeolite nor charcoal** can effectively bind to biotoxins and are of limited benefit. However, if the gastrointestinal side effects of CSM are too much, less effective but helpful treatments are Welchol tablets with addition of okra, beets with fiber being possible additional integrative options. In addition, adding magnesium citrate 300 mg per dose or Miralax may help with possible constipation. If acid reflux is experienced, an acid blocking medication can be added.

Of special note, is that Welchol is only a quarter as effective in binding the biotoxin and removing it out of the enterohepatic circulation than CSM. However, some have found it easier to comply with the four times a day dosing on an empty stomach by combining the two drugs: Welchol with meals BID and CSM on empty stomach BID with success.

Some patients have exacerbation of symptoms. This has especially been seen in CIRS-PLS and those with elevated MMP-9 levels. Pre-treating with 5 days of 2.4 grams of EPA/1.8 grams DHA may be beneficial along with a low amylose diet.

Step 3: Remove MARCoNS

Goal: Must have negative nasal swab in order to retard differential gene activation and for VIP response.

Dose: 2 sprays of 0.5 percent EDTA nasal spray TID for at least 30 days.

MARCoNS, multiple antibiotic resistant coagulase negative staphylococci exacerbate the high cytokine and low MSH effect. This drives the differential gene response and patients cannot improve without its eradication because it results in the perpetuation of the multitude of symptoms for the patient when MSH is low. It is a regulatory neuropeptide. It regulates inflammation, immunity, hormones, the limbic system, circadian rhythms, pain, the gut tight junctions and weight.

EDTA is needed to break through the biofilm for antibiotic penetration with MARCoNS. An Anti-fungal can perpetuate the issue and is never recommended. Children under 15 years of age do not usually have colonization of MARCoNS. If still positive after proper treatment we must consider pet transference or continued exposure to biotoxin. A negative test is needed to proceed to the final VIP step. However, transcriptomic testing (GENIE) of Ikaros and VIP receptor gene expression has been helpful in determining if a patient can proceed.

Step 4: Correct Anti-gliadin antibodies

Goal: To tolerate gluten without rise of antibodies and inflammation.

Antigliadin antibodies are produced in response to gliadin. This is a peptide including 18 amino acids strung together in a specific sequence from wheat, barley, and rye. If there is rise in the antibodies and gluten is eaten, the patient will have perpetual inflammation in response. This is common in children with biotoxin exposure. It is best to eliminate gluten for 3 months and then re-attempt reintroduction. However, The HLA haplotype unable to recognize and clear mycotoxins, 17/2/52A, is associated with celiac and long-term removal may be necessary.

Step 5: Normalize abnormal androgens

Goal: Optimal androgens and attenuate aromatase.

Dose: DHEA 25mg TID in men and 5mg QD to TID in women with levels of estrogens and DHEA-S followed.

Almost half of CIRS patients have upregulate aromatase leading to estrogen dominance or increased estrogens with declining testosterone levels. Replacing testosterone exogenously before correction of biomarkers may exacerbate symptoms. Aromatase inhibitor medication is also not recommended. Eventually, VIP treatment can improve this.

Step 6: Correct ADH/Osmolality

Goal: ADH 1-13.3 pg/ml with Osm 280-300 mOsm and resolution of associated symptoms.

Dose: DDVAP 0.1 mg 1 tab QHS QOD for 10 days (5 doses).

Antidiuretic Hormone (ADH) is produced in the hypothalamus and released by the pituitary gland in response to the concentration of all chemical particles found in the fluid part of the blood. If this is dysregulated, dehydration, static shocks, headaches, orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS) and frequent urination can occur. If the osmolality in blood is high with ADH less than 0.8, DDVAP is recommended at the above dose. Side effects can be fluid retention, nausea, fatigue, drowsiness, new onset seizures, loss of consciousness and weight gain. It is recommended to limit fluid intake to 1 L/day while taking the medication. Labs to evaluate for hyponatremia need to be re-checked after 5-10 days. If von Willebrand Syndrome is present, then PRN dosing for epistaxis may be needed.

Step 7: Correct elevated MMP-9

Goal: 85-332 ng/ml. Decrease elevation and increase PPAR.

Dose: Actos-45mg QD for 30 days (risk of bladder cancer if used long term) if leptin greater than 7, EPA 2.4 grams/DHA1.8 grams divided BID.

Matrix metalloproteinase-9 (MMP-9) has been implicated in the pathogenesis of COPD (by destruction of lung elastin), in rheumatoid arthritis (RA), aortic stenosis (AS), cardiomyopathy, and abdominal aortic aneurysms (AAA) when found to be elevated. Its rise allows delivery of inflammatory particles of blood eventually into the brain, lung, muscle, peripheral nerves, and joints. Upregulating the PPAR gamma production by Actos, omega 3's, and a low amylose diet, will reduce the MMP expression. Chemical messengers will then be regulated reducing tumor necrosis factor (TNF alpha), leptin and plasminogen activator inhibitor-1 (PAI-1) while increasing the low VEGF seen in CIRS. Labs need to be repeated in 30 days. However, glucose levels with liver function testing needs to be followed if Rx for Actos is given and is currently not the preferred treatment.

Step 8: Correct low VEGF

Goal: 31-85 pg/ml. Goal is to normalize levels if not corrected with Step 7.

Dose: as above.

Vascular endothelial growth factor (VEGF) can often be high initially in biotoxin illness and then declines. It is a polypeptide that stimulates blood vessel growth and capillary perfusion. When low it can lead to hypometabolism and starvation of the cell. If still not improved after step 7, we can continue the above and add **anaerobic threshold exercises** for 45minute per day (15 minutes cardio, 15 minutes resistance training, 15 minutes core exercises), 7 days a week in a stepwise fashion. We can then increase intensity exponentially and train the muscle to extract oxygen more efficiently.

Step 9: Correct elevated C3a

Goal: 55-486 ng/ml

Dose: Lovastatin 80mg QD after pre-medication with Co Q 10 150-300mg QD for 10 days. Monitor if on Coumadin.

Complement C3a rises in response to a bacterial membrane and mainly rises within 12 hours of an infected tick bite. Its elevation leads to neutrophil activation and capillary hypoperfusion. Three weeks of antibiotic treatment is first indicated if Lyme disease is suspected per protocol. If no resolution, then CSM, after at least 5 days with high dose fish oil, can be entertained. The HMG co A reductase inhibitor will reduce T cell activation and lower TGF beta 1 and its detrimental effects. Following liver function is recommended.

Step 10: Correct elevated C4a

Goal: 0-2830 ng/ml

Dose: EPO 8000 IU SQ twice weekly for 5 doses after informed consent obtained.

Contraindicated in patients with high-risk for clotting disorder, throat/neck cancer and uncontrolled HTN. Monitoring of D-dimer, CBC and BP is recommended.

Dose: VIP if meets Criteria. 4 sprays intranasal at 50 mcg per spray QID for 30 days, followed by BID for 30 days, and then QD for 30 days. **SEE STEP 12.

Complement C4a rises within about 4 hours after being initially exposed to a mycotoxin through a "mannose-binding lectin pathway" and within about 12 hours in Lyme disease. With initial exposure to a toxin, it can rise to levels around the 10,000 range and can return to normal after treatment. However, if re-exposed, a patient can get sick within just 5-10 minutes of exposure. The C4a levels can then double or triple and can continue to elevate further with each new exposure. This "Sicker Quicker" phenomenon occurs from autoactivation of the MASP-2 enzyme that cleaves C4a for its removal from the body.

Step 11: Reduce elevated TGF-beta 1

Goal: Less than 2380 pg/ml

Dose: Losartan 25mg BID or VIP per protocol in Step 12.

Pediatric Dose: 0.6mg/kg/day divided BID or VIP per protocol in Step 12.

TGF beta 1 is a pleiotropic cytokine with both pro- and anti-inflammatory effects. It is an immune modulator of T cell activity and has important regulatory effects in the innate immune system through the **regulatory T cells**. It aids in proliferation, differentiation, motility, and apoptosis of cells. However, it is pro-inflammatory in that it can activate autoimmunity through the differentiation of **Th 17 helper T cells.** The difference between the responses is due to tissue receptors, such as the retinoic orphan receptor (**ROR**). Elevated levels have been linked to transformation in the lungs and fibrosis in tissues, nasal and vocal polyps, and as stated above, autoimmunity. Levels need to be repeated at 1 month and followed monthly until resolution. Blood pressure monitoring is recommended if a Rx for Losartan is given.

Step 12: Correct with VIP

Goal: Correction of biomarkers, NQ and differential gene activation. Fall in pulmonary artery pressure during and after exercise. Normal VO2 max and anaerobic threshold.

Dose: 50mcg/0.1 ml, 1 spray intra-nasally QID, alternating nostrils. Build up to 12 sprays QD. Progress to 250 mcg/0.1 ml QID, then 500 mcg/0.1 ml QID increasing to 12 sprays QD for 6 months.

Criteria for Administration: Documented negative MARCoNS nasal swab, proof of lack of continued exposure, negative VCS and monthly blood work (lipase/GGT). Baseline Stress echocardiogram can be followed.

Requires in office initiation of therapy and monitoring: 50mcg single nostril with observation of symptoms reaction and resolution. BP check every 5 minutes for 3. After the 15 minutes-redraw TGF beta 1 and C4a level. If 33 percent increase is seen, then possibility of ongoing mold exposure is probable.

Monthly monitoring: Lipase/GGT. Discontinue if new onset, abdominal pain, rash and hypertension. Patient can self-titrate based on the above.

Normal VIP levels are 23 to 63 pg/ml. However, VIP cannot be accurately measured.
It has 3 receptors and PACAP. It turns on Ikaros and Ikaros turns on production of VIP.
Its use has been seen to correct many of the abnormal proteomics, transcriptomics and brain changes seen on NQ. It has been shown to decrease aromatase activity, improve vitamin D physiology, regulate ADH/Osm levels, lower TGF beta 1, lower C4a, normalize low VEGF, lower MMP-9, elevate MSH, and improving circadian rhythms. It can also improve ribosomal and mitochondrial gene regulation, correct PASP during and after exercise, while improving fatigue and energy.
It can also improve one's tolerability of mild mold exposure. In addition, it is neuroprotective, decreases inflammation, and excitation of the nervous system. It is expressed in many brain regions; mainly in the cerebral cortex, hippocampus, amygdala, and hypothalamus.

However, if correction is not seen and elevation of biomarkers occurs then institution of the **re-exposure protocol** on consecutive days needs to be undertaken with informed consent.

Sequential Activation of Innate Immune Elements (SAIIE):

Baseline symptoms, VCS scores and labs are drawn.

C4a (Quest or National Jewish Lab), **TGF beta 1, MMP9, leptin, VEGF, CD4+, CD25+ and VWF** (not from LabCorp).

1. **AC-1 (after CSM 1):** CSM therapy for the first time is instituted (VCS is passed). Leave building and stay away for **3 days** off all medications (usually on a Friday).
2. End of day 3 (usually Monday morning)—again document symptoms, draw labs and complete VCS **(HOC-Home off CSM).**
3. Return to building and stay off medications for 8 hours.
4. Next morning-document symptoms, draw labs, VCS (**BOC-1**).
5. Return to building and stay off medications for 8 hours.
6. Next morning-document symptom, draw labs, VCS (**BOC-2).** Return to building and stay off medications for 8 hours.
8. Next morning-document symptom, draw labs, VCS **(BOC-3).**
9. **Clinic Review**
10. Restart all medications if needed.
11. **AC-2:** CSM therapy for the second time is instituted (VCS passed).
12. **Repeat lab, symptoms, and VCS— Repeat above as necessary.**

Clinic Review-If the VCS changes in 36 hours or the symptoms return in less than 10 minutes, VOCs are usually the culprit. Of note, is that for VCS to be considered significant we need a change in more than 1 block to be seen.

A Scoring System based on the time sequence of biomarker change is in place: C4a- rises within 4 hours on day 1, Leptin rises on day 2, MMP-9 rises in 60 hours, VEGF rises day 1 with hypoxia but as TGF beta 1 rises, it falls on Day 3.

Symptoms=baseline (5 points) (80 % return 4 points, 60 % return 3 points)
C4a day 1=baseline (5 points)
Leptin rise day 2 >day 1 (5 points)
MMP-9 (day 2 +3/2>day 1 (5 points)
VEGF up day 1 or fall by day 3 (2.5 points for each)

If the score is less than 8 it is safe to return; However, if equal to or greater 20, it is then recommended to remove oneself from exposure and retreat.

Further research is thankfully ongoing, and hope is now on the horizon. We continue to uncover overlapping conditions, such as, Pediatric Associated Neuropsychiatric Syndrome (PANS) and Postural Orthostatic Tachycardia Syndrome (POTS) that respond to the Shoemaker Protocol. Fortunately, by following this protocol carefully and in sequence, most patients can be confident that they will return to good health and wellness.

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