

Chronic Inflammatory Response Syndrome (Shoemaker Protocol) Overviewⁱ

RJ Oenbrink DO

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Overview

25% of the population at large is genetically susceptible to Chronic Inflammatory Response Syndrome ([CIRS](#))ⁱⁱ. As described by Ritchie Shoemaker, MD, the individual who elucidated the complex pathophysiology of CIRS; “Genes load the gun, exposure pulls the trigger”. These folks will have the worse effects after exposure to toxic environments, yet given sufficient exposure intensity and duration, anybody can suffer ill-effects.

Essentially, anything that causes an inflammatory cytokine storm in a genetically susceptible individual can set the syndrome into motion; CIRS is a host response, not a dose response but those who have a subsequent exposure get "sicker quicker" 2' to having a "primed immune system" after an initial exposure.

There is a way to treat CIRS.

The protocol is extremely complex with a steep learning curve.

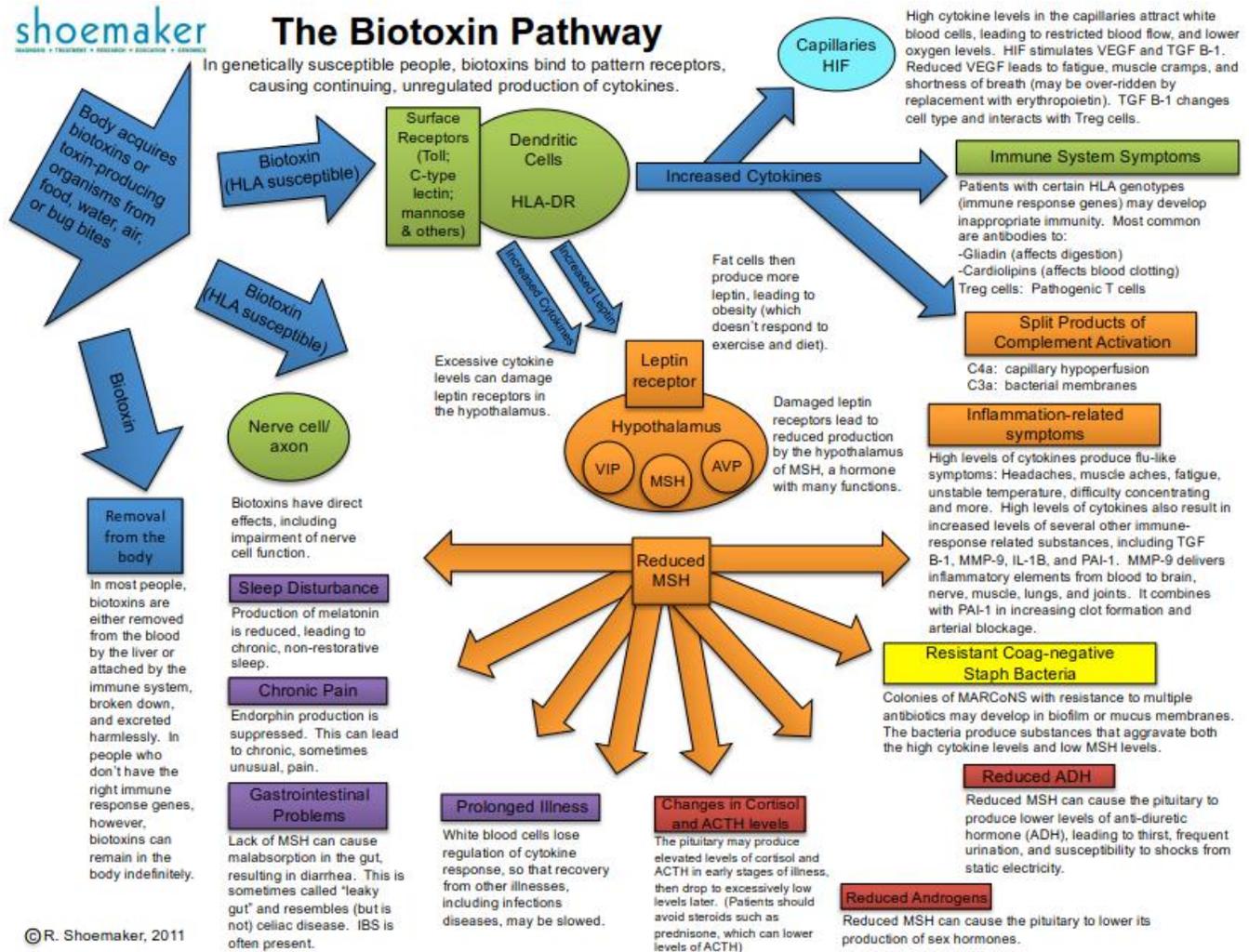
CIRS manifests itself in numerous organ systems, leads to significant suffering and premature death. Ed McMahon of the Johnny Carson show succumbed to this illness after improper remediation from a broken water pipe in his home.ⁱⁱⁱ

CIRS is usually triggered by “toxic black mold” species, Lyme disease, Pfiesteria, blue green algae (cyanophyta), red tide blooms, ciguatera and other exposures including certain vaccines (which we know all troops are given pre-deployment to theater); anything that increases inflammatory cytokines.

For the immune system to function properly, there must be an "on" switch and an "off" switch.

A population of T-lymphocytes known as the CD4+CD25+^{iv} group (detected by flow cytometry) normally works as the "off" switch, which should engage upon threat resolution/neutralization.

The Biotoxin Pathway



High Risk HLA Haplotypes

Unfortunately, the CD4+CD25+₋ "off switch" doesn't always engage, especially in those with susceptible genotypes/haplotypes (based on the Human Leukocyte Antigens (HLA) DR1, DQ, DR3, DR4, DR5. Dr. Shoemaker has created a "Rosetta stone" document^v to assist with interpreting the complex genetic results of the HLA testing. When HLA-susceptible individuals are triggered, the off switch won't properly engage and autoimmunity develops--similar, but different to Systemic Lupus Erythromatosis (SLE), Rheumatoid Arthritis, etc.

Unfortunately for the CIRS-afflicted, their immune system begins to attack their own cells--all over the body. Joint damage, nerve damage, heart & lung damage, brain damage, vascular damage, impaired mitochondrial oxygen supply due to deficits in regional micro-circulation at the capillary level ensues.

VCS Testing

The US military developed a "visual contrast sensitivity (VCS)" test that evaluates function of the rod cells in the retina^{vi}. This capillary-level dysfunction which is part of CIRS can be quickly and easily checked and monitored with this simple vision test. Those afflicted with

CIRS have inflammation & impaired circulation at the capillary level, inadequate mitochondrial oxygenation at that level (diffusely, all over the body) and an abnormal VCS^{vii} as determined by Ritchie Shoemaker, MD. This test can not only be used in part diagnostically for CIRS, but also as a prognosticator while CIRS is being managed to quantitate improvement after therapeutic endeavors.

There are very reproducible markers for those who have the syndrome. These markers are more than reproducible in their presence and level for those with the syndrome. Thanks to the extensive efforts of Dr. Shoemaker, even the timing and sequence of the Sequential Activation of Innate Immune Elements (SAIIE)^{viii} has been discerned.

Lab markers include elevations of C3a or C4a (complement system)^{ix}, reduced α -melanocyte stimulating hormone (MSH), dysregulation of anti-diuretic hormone (ADH) & serum osmolality & AdrenoCorticoTropic Hormone (ACTH)/cortisol activity, elevations in Transforming Growth Factor β -1(TGF β -1), Matrix Metalloproteinase 9 (MMP9), Leptin and other markers with concurrent reductions in the MSH as mentioned, Vascular Endothelial Growth Factor (VEGF) and others.

Approach to the patient

The protocol developed by Dr. Shoemaker takes on a very methodical, stepwise approach to treating CIRS.

The absolute most important step is absolute avoidance of exposure in the future. The afflicted become “sicker quicker” due to the fact that their immune system has already been “primed”. This makes evolutionary sense; when triggered with a threat to our lives, our immune system, our “storm troopers” against infection, need to be “ready to go in an instant” with hefty armament to take out specific attackers, be they Strept, Staph, specific viruses that we’ve been exposed to in our past, etc.

It’s important to remember too, that if the patient suddenly seems to relapse and worsen, the only logical approach is to assume re-exposure (we don’t know what/when/where until we look) and go back to the basics at the initial step and resume the sequential treatment.

VCS testing is very specific for CIRS, it can serve as an early warning system for exposure.

Once exposure has been removed (often THE MOST DIFFICULT STEP), the toxins need to be removed and may require monitoring. This cannot be over-emphasized.

Briefly; the steps will be listed below (more detail to follow).

Cholestyramine (Questran) and/or Coleselevam (Welchol) bind the toxins, C3a rises with the presence of pathogenic membranes (think Lyme/Borellia), C4a rises with other non-membrane biotoxins (mold, ciguatoxin, dinoflagellates, etc.).

Patients need to be educated about the risks posed by VOC’s.

MARCoNS needs to be looked for and cleared. The API Staph testing takes time—biofilm (non-planktonic) staph takes time to culture, it’s best to obtain this culture at the patient’s initial visit.

Gliadin/Gluten sensitivity needs to be looked for—especially in younger patients, initially with an AGA, if positive, a 3-month trial of a strict gluten-free diet may improve their condition. If they relapse on re-introduction, TTG testing and further avoidance may be necessary.

Androgen/aromatase function, if impaired often responds to “upstream” DHEA supplementation.

The “middle steps” of the protocol involve MMP9, ADH/Osmolality and ACTH/Cortisol may also be affected—we need to look, Leptin levels will influence our approach to correcting these as well as C4a.

Monitoring all of these parameters during treatment may be indicated based on the overall patient condition and as indicated by the VCS “early warning system”; back to square one if the patient worsens.

The pinnacle of treatment involves correction of high TGF β -1 and low VIP by replacing VIP with a nasal spray.

The [diagram](#) shows that many folks will improve before this step is reached.

C3a & Lyme

C3a tends to increase^x in the presence of foreign membranes^{xi}. *Borellia burgdorferi*, the causative agent of Lyme disease causes greater increases in C3a, which can thus be used as a marker for the inciting event of a patient's CIRS episode. It's an extra-cellular pathogen that can “hide” intracellularly^{xii}. It has a slow doubling time, thus necessitating prolonged treatment with antibiotics. This also leads to the confusion of when to stop antibiotics on a patient who is obviously still sick and not fully recovered from their tick-borne illness; lack of recognition of the transition from acute infection to chronic inflammation due to a malfunctioning immune system in HLA-genetically susceptible patients is an easily understandable source of confusion!

C4a

C4a on the other hand is a marker for biotoxins in general, much less specific than the C3a-bacterial membrane link. C4a levels can even rise in the presence of Volatile Organic Compounds (VOC's)^{xiii} which are present in Water-Damaged Buildings (WDB).

Erythropoietin lowers C4a & TGF β -1, it works well in CIRS/Mycotoxic patients

This use is off-label and should involve documentation of informed consent

Baseline labs would include TGF β -1, C4a, D-Dimer & CBC. If Hemoglobin >16.5 it's gone to high, the FDA doesn't want it above 10 grams/dl. It's a good idea to record the lot number of the Erythropoietin product used.

Erythropoietin is used at 8,000 units twice per week for 5 doses or until Hb >10

Beware of thrombosis complications!

VOC Dangers

Once CIRS is established, things as seemingly innocuous as “volatile organic compounds^{xiv}” (VOC's; frequently *but not always* produced by pathogenic species and conditions) can trigger flares of the CIRS process with diagnostic worsening of the VCS & blood markers.

An important concept to note is that VOC's can be subliminal—below the ability of the senses (olfaction) to detect, yet still cause the inflammatory cascade/amplification common with CIRS. A patient living near a power plant burning coal, producing various sulfoxides can be triggered by subtle changes in meteorological conditions, being exposed to plasticizers common in new cars, buildings, carpeting etc. that has not yet finished outgassing their VOC's. These VOC's are very small molecular weight entities that are not triggering a classic antibody-mediated immune reaction (including IgE/allergic), but are engaging the complement cascade with its inherent

amplification (read-severely symptomatic on an immediate basis without any prior warning) by subliminal exposure.

“You can’t smell it, discern its presence, know that it’s in your immediate vicinity—but it can trigger a severe asthma attack that can kill you in short order and it’s ALWAYS a risk for you and you alone!” The ultimate Ninja.

And we in “modern medicine” who have studied so long and hard don’t understand this. We think of these neurotic people as crazy. “Crocks get sick too” is an adage to stick to. Physicians tend to react to ignorance with arrogance; “I’m a physician, if I don’t know it, it can’t be important!” These poor folks are suffering, have been kicked around and need to be treated with compassionate understanding.

The absolute initial and most important step in dealing with biotoxin illness/CIRS is identification and isolation from the source of the toxin exposure! Unfortunately, this is also generally the most expensive and difficult step. Somebody who has been ill, perhaps unable to work, has exhausted any financial reserves and now must choose between leaving their home, place of work, place of worship, place of education, etc. for an undetermined period while possibly extensive and expensive remediation is undertaken. Remember; one will NOT improve without this initial step. The final outcome (after great suffering) will be a premature and painful demise. This may seem dramatic, but cannot be overstated!

Medical schools frequently teach that the best clinicians are those who obtain the most thorough, detailed and focused history; “the patient will tell you what’s wrong if you listen to them properly”. The trick lies in teasing out the essential, valuable information!

ERMI

www.mycometrics.com provides testing via DNA amplification of environmental samples, creating what is known as the Environmental Relative Moldiness Index (ERMI). Thirty-six species, divided into 26 species/clusters associated with WDB (Group 1) and 10 common species/clusters not associated with WDB, called Group 2. The number calculated as the ERMI is actually the sum of the logs of the concentrations of the DNA of the different species. The "mold index" is the difference between Group 1 and Group 2^{xv}.

The "safe" level of ERMI will depend on other factors such as the patients C4a & α -MSH level as noted below;

ERMI	MSH	C4a
≤ 2	<35	<20,000
-1	<35	>20,000

A thorough and careful history^{xvi} may reveal clues to other exposure risks, ranging from dinoflagellates (aquatic and/or marine), Ciguatoxin (consumption of tropical reef predator fish), Lyme, Vaccine exposure etc. If a one-time vaccine triggered the cytokine storm that preceded CIRS onset, the patient should be counseled to avoid a repeat of that vaccine or other exposure.

Cholestyramine

Cholestyramine ([CSM^{xvii}](#)) is an anionic binding agent taken by mouth. It disrupts entero-hepatic circulation by absorbing bile, preventing its re-absorption in the ileum and hepatobiliary recycling. Toxins are excreted by the liver into the biliary system. It binds toxins, helping the body to excrete them via the fecal route. Side effects include severe constipation which can be improved with osmotic agents such as polyethylene glycol ([Miralax^{xviii}](#)), Sorbitol & Magnesium. It's taken as a 4 gram packet 30 minutes before meals and at bedtime (qid). Medications should not be taken for 2 hours after each dose as CSM can interfere with their absorption as well. CSM aids excretion of biotoxins from the body, thus reducing the overall toxic load that is triggering the immune systems complement system & cytokine activation pathways that the ineffective T-regulatory cells are unable to rein in and control. It will help to reduce C4a.

Not everybody will tolerate CSM as it can be difficult to take properly an alternative to CSM is Coleselevam ([Welchol](#)) 1,875 mg bid with meals which absorbs about 20% of what CSM is able to adsorb. Another option is to alternate CSM with Coleselevam

C3a can be reduced by high dose statins, such as Simvastatin at 80 mg/d^{xix, xx, xxi}. Prior to statin use, supplementation with ubiquinol/CoQ10^{xxii} is essential at a dose of at least 150 mg/d due to the effects of statins working against ubiquinol which is so important to mitochondrial respiration^{xxiii}.

Recall, as a practitioner, that medicine is an art. A patient who has had prior statin intolerance may refuse another round of such therapy as is their right.

MARCoNS

Low levels of α -MSH can reflect Multiply Antibiotic Resistant Coagulase Negative Staph ([MARCoNS](#)) living in biofilms within the sinus cavities. Unlike the free "planktonic" form of bacteria, MARCoNS lives safely ensconced in a thick mucopolysaccharide film that is not penetrated well by antibiotics. It's a slow-growing microbe that must be differentially cultured by API Staph technique that is not a simple routine test; <http://www.microbiologydx.com/> is the lab recommended by Dr. Shoemaker for this test.

MARCoNS is best treated with a proprietary "BEG" nasal spray containing Bactroban (Mupirocin)/EthyleneDiamineTetraAcetic acid (EDTA) and Gentamycin with or without Rifampin 300 mg 2 caps daily for 1 month. The biofilm alters the sensitivity of the API Staph to eradication due to its protective effects. This spray is available from [Hopkinton Drugs](#) in Hopkinton MA. EDTA breaks down the biofilm allowing the antibiotics access to the MARCoNS.

As MARCoNS is eliminated, the α -MSH will begin to rise back toward normal.

Lowering MMP9, TNF, PAI-1 & Leptin

Matrix Metalloproteinase-9, Tumor Necrosis Factor, IAP, Platelet Inhibitor Activator & Leptin all rise due to the CIRS process.

These elevations are best dealt with in two ways.

First, an absolute necessity is a low-amylose diet. Amylose is a high-glycemic index sugar that can be quickly utilized. It's found in seeds and roots (except onion & garlic). This means the elimination of grains such as Wheat, Oats, Rice, Barley & Rye. Some seeds have an amylase inhibitor within them, including corn, sorghum, buckwheat, quinoa & amaranth; these are OK to eat.

Bananas are the only high-amylose fruit; these must be avoided too.

More information about low-amylose diets is available in a variety of sites such as [Surviving Mold](#), [Pinterest](#), [The-Labyrinth](#). There are numerous [low amylose recipes](#) on the web.

Second, medication or supplementation of omega-3 fatty acids is used. Welchol is a TZD-class drug used to treat diabetes; this is preferred for patients with a high baseline leptin level. If the leptin is <7, 2 grams of omega-3 fatty acids taken twice daily will help lower these CIRS mediators.

Gliadin Sensitivity

Since CIRS induces autoimmunity (the immune system reacting against “self”), gliadin sensitivity evolves in about half of children and third of adults. IgA & IgG anti-gliadin antibodies need to be ruled out. If present, the initial step will entail 3 months on a gluten-free diet followed by repeat testing. If testing remains positive for the antibodies, Tissue Transglutaminase Enzyme testing may be done; positive results generally require lifetime avoidance of wheat proteins. Useful resources for such patients include the [Gluten Intolerance Group of North America](#), [The Gluten Intolerance Group](#), [The Celiac Disease Foundation](#) among others. If GI symptoms return after the period of gluten abstinence, it may be worth life-long avoidance of gluten. This should be discussed with the patient.

Correcting Matrix Metalloproteinase 9 (MMP9)

MMP9 is produced by cleaving MMP14. This is a marker for spread of inflammation through soft tissues; MMP9 allows inflammatory mediators to migrate through tissues, spreading inflammation through the extracellular matrix that it has broken down. This level will be elevated in uncontrolled CIRS.

Lowering of MMP9 is accomplished via Ω -3 fatty acids such as Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) come mainly from fish, so they are sometimes called marine omega-3s. These should be taken in at least 4 grams/day. Alpha-linolenic acid (ALA) is another essential (unable to be produced by the human body) omega Ω -3 fatty acid^{xxiv}. Omega fatty acids work best when the Leptin is <7. If Leptin >7 however, Pioglitazone (Actos) at a thiazolidinedione that has a black-box warning (this is off-label use of this medication, a patient informed consent would be advisable, or at least documentation that it was reviewed in the chart) about being linked with congestive heart failure (CHF). Typically however, pioglitazone will be used for a much shorter duration than a diabetic would use it, which would likely reduce the risk of CHF^{xxv}

Correcting Anti-Diuretic Hormone (ADH) & Osmolality

ADH/Osmolality dysregulation can occur with CIRS. Normal physiologic response to dehydration (which is common in CIRS) would be an increase in ADH as osmolality increases; the two run in the same direction under normal circumstances. CIRS patients may break this pattern however. A careful history may elicit static electrical shocks (due to salt accumulation

on the skin), thirst, polyuria and “claw-like” cramping of the hands with severe muscle cramps in other areas as well.

CIRS patients are prone to dehydration. Normal physiologic response to dehydration begins with individual cells giving up some of their water to the extra-cellular space (both extravascular and intravascular). Orthostasis may develop with prolonged dehydration, this can be picked up historically or possibly documented with standing and supine pulse & BP measurement.

Vasopressin-Arginine (Desmopressin, DDAVP) may be necessary 0.1 mg per night, 0.2 mg every other day or at most 0.1 mg twice daily^{xxvi} can be helpful. If DDAVP is used, monitor daily weights and weekly electrolytes; low sodium (hyponatremia) is a risk factor.

DDAVP can also be used to correct acquired Von Willebrand Syndrome (VWS) which develops in some CIRS patients. If easy bruising/bleeding/heavy menses occurs, consideration should be given to running the VWS lab profile.

ACTH/Adrenal dysregulation also occurs with CIRS. Typically it will correct nicely once VIP and other abnormalities are corrected.

Correcting low Vascular Endothelial Growth Factor (VEGF)

Low VEGF can occur despite the lack of appropriate delivery of oxygen and nutrients at the capillary/cellular level. Typically, if cellular starvation is happening, VEGF will increase. Blocking VEGF is being used as a therapy against cancer. CIRS patients can develop this issue as a result of their disorder.

[Erythropoietin](#) is useful for resolving the low VEGF.

VIP supplementation will also resolve the problem and is generally considered safer.

Reducing elevated Transforming Growth Factor β-1 (TGF β-1)^{xxvii}

The sequence of steps in this presentation reflect the stepwise progression of treatment. Earlier steps on this pathway will correct many of the latter-system pathology issues. If the TGF β-1 remains elevated despite correction of prior issues, other steps can be added.

TGF β-1 elevations are problematic, indicating remodeling/autoimmunity, transforming cells. TGF β-1 down-regulates VEGF. TGF β-1 elevations cause ANCA levels to rise reflecting cellular immunity and producing adverse effects on the brain (tremors, MS, learning disabilities), lung (potentially lethal pulmonary hypertension) & immune systems (worsening autoimmunity and dysregulation).

Losartan 12.5-50 mg bid (beware of orthostasis/syncope) can help lower the elevations of TGF β-1. Exp3179 is an experimental compound, a metabolite of Losartan that has even stronger effects at lowering TGF β-1.

TGF β-1 needs to be collected properly in pre-chilled tubes that are immediately double-spun and refrigerated.

Intra-nasal Vasoactive Intestinal Peptide (VIP) is also a life-saver for correcting these elevations.

Replacing low Vasoactive Intestinal Peptide (VIP)

“Let’s not kill the golden goose by using it inappropriately”.

This is the biggest advance ever in the treatment of CIRS! It has many amazing properties.

1. FDA has designated VIP for treatment of Pulm Htn (other uses are off-label)
2. Down-regulates MASP-2 (C4 activator to C4a see # XII U 1)
3. Restores balance of Vitamin D3
4. Down-regulates aromatase which breaks down testosterone among other hormones
 - a. Raising testosterone and lowering estrogens
5. Up-regulates (increases low levels of) VEGF
 - a. If Actos or fish oil/omega-3 doesn’t work, VIP will correct the low VEGF
6. Restores diminished VO_{2max} ,
 - a. Reduced SOB
7. Immunoregulatory; this is a Neuro-Immune link
 - a. Improves cognitive problems
8. Drives up CD4 + CD25 + FoxP3
9. Reduced joint stiffness in ~10 minutes (causes endorphin release)
 - a. Main effect immediately is endorphin mediated...
10. Improved exercise tolerance
11. Global improvement in all modalities
12. Typically within 5 minutes of first dose patients can take a deeper breath
13. Joint symptoms @ baseline; tight clenched hands will typically open and relax on VIP
14. Immediate pain relief is a big deal and much appreciated
15. Cognitive issues respond more slowly
16. If there is a sudden increase in TGF β -1, there has probably been recent exposure to WDB with ongoing mycotoxin exposure.
17. VIP 50-mcg qid corrects paradoxical rise in PASP in exercise in days, not weeks, with durable effects with titration to bid and over time, discontinuation!
18. Warning Re; VIP may cause Lipase to increase a bit; measure baseline and monthly X 3 VO_{2max}
 - a. Draw blood at baseline (Lipase, TGF β -1), give VIP, repeat draw (VEGF, C4a, TGF β -1) in 15 minutes
19. (1) Warning Re; VIP may cause Lipase to increase a bit; measure baseline and monthly

VIP Trial Protocol

- A. Must be kept refrigerated.
- B. Baseline Lipase, VEGF, C4a, TGF β -1
- C. Give VIP, repeat draw in 15 minutes, if tolerated...
- D. Continue 2 puffs nasally 4 times daily
- E. Re-evaluate monthly
- F. In 6 months, dose can be reduced from qid to bid, slowly to qd then discontinued PROVIDING THAT THERE IS NO RE-EXPOSURE!

Final Check for Stability off medications (CIRS Resolution)

After working through the protocol, being able to stop at any time if full symptom resolution occurs, it may be safe to wean off and discontinue all medications with careful monitoring for relapse.

If there have been no re-exposures, the patient should do well and be able to tolerate monitored, sequential discontinuation of one medication/therapeutic step at a time.

If at any time, the patient's condition deteriorates however, it will be necessary to return to "Square One", the initial start of the Shoemaker CIRS Protocol.

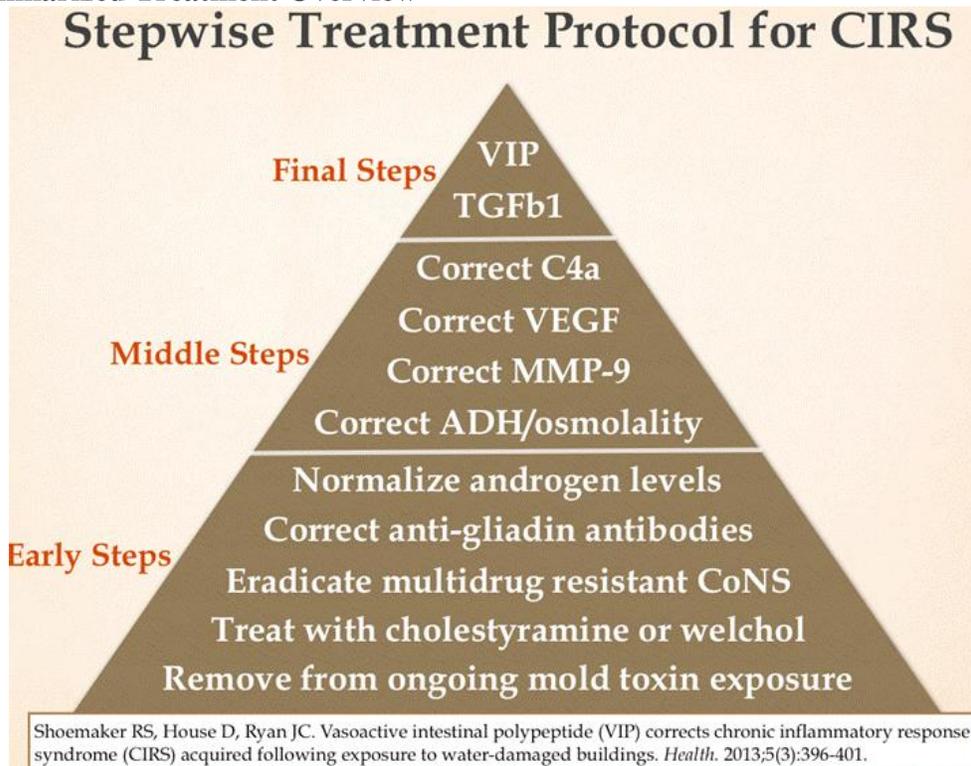
Return to "Square One" for any relapse

Remember that CIRS patients have a "host disease not a dose response" and that they "get sicker quicker"!

There are no shortcuts in treating CIRS. Absolute complete avoidance of triggers is mandatory. Although a fully recovered person may be able to tolerate a little bit of time (minutes to even hours, depending on severity) in a high-risk situation (Eg. WDB, near a fish kill, exposure to ciguatoxin), the patient who has been previously exposed has an immune system that has been primed for life. They will get "sicker quicker" for this reason and may respond more slowly after their first-ever treatment session. They may not recover as quickly to subsequent exposures as they did to their initial exposure.

This is the nature of CIRS.

Summarized Treatment Overview



- 1) Remove from exposure
- 2) Cholestyramine for 30 or more days
 - a. Reduces C3a/C4a elevations

- 3) Eradicate biofilm formers/MARCoNS
- 4) No gluten if AGA (+)
 - a. Do AGA initially
 - b. Tissue Trans Glutaminase if symptomatic at re-challenge after 30 days abstinent from Gliadin/Gluten IgA, IgG, IgM if Gluten (+)
 - i. Expect to find more of the IgG than IgM but measure all 3
- 5) Decrease MMP-9 elevation
 - a. Ω -3 fatty acids if Leptin <7
 - b. Actos if Leptin >7
- 6) Correct ADH/Osmolality;
 - a. Use DDAVP if abnormal
- 7) Elevated MMP9
 - a. If Leptin>7; Actos
 - b. Omega-3 Fatty Acids \geq 4 gm/d if Leptin <7
- 8) Increase Androgens;
 - a. Look at Testosterone/Estrogen ratio's to determine if Aromatase is up-regulated
 - b. Consider DHEA Sulfate to correct from "upstream"
 - i. Avoid Aromatase Inhibitors
- 9) Lower TGF β -1
 - a. Losartan
 - b. Consider Erythropoietin
 - c. Consider VIP therapy (generally safer than Erythropoietin)
- 10) Check VEGF
 - a. Consider Erythropoietin

References

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