Chronic Inflammatory Response Syndrome (CIRS)
The Shoemaker Protocol

October 2017

CIRS is an acute and chronic, systemic inflammatory response syndrome acquired following exposure to the interior environment of a water-damaged building with resident toxigenic organisms, including, but not limited to fungi, bacteria, actinomycetes and mycobacteria as well as inflammagens such as endotoxins, beta glucans, hemolysins, proteinases, mannans, c-type lectins and possibly spirocyclic drimanes, plus volatile organic compounds[1].

The resulting mold illness is a multi-system, multi-symptom immunological illness. The immunological changes result in predictable and measurable lab markers that in addition to client symptom pattern support diagnosis and chart treatment progress. The exact trigger could be any of the items listed above, but it is the immune response that is the key to the illness, because not everyone who is exposed to mold or other biotoxins becomes chronically ill.

For some, the symptoms that ensue are systemic and include neurological deficits, musculoskeletal pain and weakness, respiratory and gastro-intestinal symptoms to name but a few. Many people experience exposure to mold, but how some people succumb and experience such devastating symptoms is largely down to existing functional capacity/level of homeostasis (such as imbalance in complement immune activity, detoxification capacity etc), genetics at the time of exposure and the type, level and length of that exposure (although it is important to note that CIRS mold illness is immunological and is not dose dependent or toxicological). CIRS patients are unable to adequately tag and clear biotoxins so the immune system remains up-regulated and therefore imbalanced, which has a knock on effect to many other body-wide systems. The Shoemaker protocol is unique in that it accounts for all of these things, and also self-audits to ensure no possible additions to the protocol are missed (see Appendix 7 for this author's additional research suggestions). Its inclusive approach has been beneficial to many chronically ill patients who finally have not just an explanation and diagnosis for their symptoms, but also a proven route to recovery and understanding of how to remain optimally healthy.

CIRS testing is the key to the Shoemaker protocol. By testing the immune system, reproducible results can be measured upon exposure to toxigenic organisms, and a chronicity can be defined. The effect that biotoxins have when they initially trigger the immune system is how CIRS came about through the detailed work of Dr Shoemaker, and

[1] Surviving Mold, R.C Shoemaker MD. Otter Bay Books, Baltimore, MD, USA

further development of both the testing and protocol by Dr Shoemaker has evolved to complete the picture to date.

Dr Richie Shoemaker developed his CIRS protocol after working in the Pokemoke area of Maryland. He was the first to make the connection between Pfiesteria to symptoms in humans, and beyond that to make associations with the immune response to pathogens such as moulds, bacteria and mycotoxins. Having made those associations he devised a protocol which is supported by testing that gives a clinical diagnosis.

There are limitations to testing for the biotoxins in the blood as they are ionophoric so not easily detectible, they can be secreted by the liver into bile and then reabsorbed (unless they are tagged with appropriate HLA support), and they can trigger seemingly non-related issues thus making the decision of what to test for even more challenging (e.g. attachment to enzymes related to insulin receptor function thereby mediating blood glucose). By focusing more on the effects of the biotoxin on the immune system, the evidence base is growing and gaining increased traction.

The protocol initially allows for a CIRS diagnosis that comes as a result of testing and a very detailed health history and timeline along with symptom understanding, all of which come from seeing an expert in the field. This is key as most patients will not have had a root cause diagnosis to date. This differential diagnosis is an important first step. After the diagnosis comes a clear treatment path.

The Symptom Cluster Analysis offers 37 distinct symptoms, grouped into 13 clusters (see appendix 5). If 8 are positive then CIRS can be considered. The symptom questionnaire is filled in together with the client so that the practitioner can fully understand the current symptoms and symptom history.

Health history is important from both a medical and functional perspective- from a medical point of view information will the gained regarding any previous diagnoses, medications, surgeries etc. From a functional perspective, the health timeline will tease out information about foundational health, triggers and mediators, as well as other factors such as behavioural history, family history and lifestyle. A physical exam is also appropriate, and Dr Shoemaker recommends a nine system exam from head to toe.

Many of these items might already be commonplace in a functional medicine practice, but it is the level of detail that marks a CIRS appointment. That detail includes the symptom cluster analysis is key, along with an environmental history. The kinds of questions asked in this section include exposure to (a) water damaged building(s), mold, environmental chemicals/pesticides (A fuller list of questions can be reviewed in the IEP Consensus Statement, Appendix C)[2]. Accounting for possible Lyme + co-infections or dinoflagellate

[2] Indoor Environmental Professionals Panel of Surviving Mold, Consensus Statement, 2016

exposure is also important as this will affect sections of the protocol such as removal from exposure.

It is then recommended that a Visual Contrast Sensitivity (VCS) is undertaken. VCS testing is used initially to understand a baseline response to this test for clients. It is reproducible, reliable and non-invasive and has been used for over forty years by the US military in studies relating to toxicants. Dr Shoemaker values the VCS, in particular, beyond day four of biotoxin-associated/cytokine exposure. The test can be repeated to evaluate progress on the protocol and alert to re-exposure, and should be checked one month after treatment commences and then at each step of the protocol. VCS is a neurotoxicity marker, but also points to retinal area capillary hypo-perfusion, so it is important that a normal VCS is ultimately achieved.

The following is a list of laboratory tests that can be used to support a CIRS diagnosis

Blood markers:

Melanocyte Stimulating Hormone (MSH)*
Vasoactive Intestinal Peptide (VIP)*
Vascular Endothelial Growth Factor (VEGF)*
Anti-diuretic hormone (ADH)*/Osmolality*
Adrenocorticotropic hormone (ACTH)/Cortisol
Transforming Growth Factor (TGF)-Beta 1*
Complement component 4 (C4a)*/C3a
Matrix Metalloproteinase 9 (MMP-9)*
Leptin*
Plasminogen activator inhibitor 1 (PAI-1)
Antibodies such as anti-gliadin* (stool or Cyrex and tTg) and Anti-cardiolipin
Von Willebrand panel and wider coagulase study looking at PT, PTT, PT/INR

(Four of the 12 asterisked markers, plus VCS and multiple anti-biotic resistant coagulase-negative staph (MARCoNS) can indicate the presence of CIRS)

Consideration of pulmonary function testing; arterial pressure measurement and VO2 max testing can also be undertaken at this stage.

Neuroquant MRI testing can also be considered at this stage. FDA cleared in 2007, Neuroquant is again reproducibly reliable with control data sets available. Changes in the brain can be tracked, such as volume or oedema and this information can be matched with genomic information to further understand the clinical picture. Typically a volumetric study of 11 (or up to 15) key brain regions can be assessed, with caudate atrophy commonly

being seen in CIRS. The twelve point scoring system identifies that the higher the score the worse the VIP response. In CIRS this typically involves caudate nucleus atrophy.

Genetic testing can also be considered at this stage. HLA inheritance (antigen presentation and disorder immune response) has been linked with susceptibility to CIRS. HLA type involves preformed proteins that are primed for action. Complement system pattern receptors pick up this information, activation is triggered (e.g. C4a) and in the average person this is dealt with effectively as HLA reflects ability to respond to pathogen associated molecular patterns (PAMPS). Presence of at least one of the fourteen HLA genotypes identified (DRB 1,3,4,5 and DQ HLA types) can influence symptoms and further inflammatory activation mechanisms and responses in the body. Dr Shoemaker's Rosetta stone can be utilised to understand HLA type and susceptibilities further. Twenty five percent of the population are genetically predisposed to develop CIRS when faced with biotoxin exposure, with 2% susceptible for more an even more severe CIRS response.

The testing outlined above can be employed at appropriate stages of the protocol to reassess progress, but at the very least at the outset and when moving on between steps. If any abnormal lab results are found then these must be tracked through the treatment course.

The protocol is in essence a two-fold process. The first involves answering the question of what are we doing for the client in terms of supporting their physiology internally and secondly, what are we recommending for them externally? The treatment pyramid designed by Dr Shoemaker clearly outlines the twelve protocol steps and the order they should be addressed in, which combines both of the underlying processes. There are 15 steps in total and an additional three bookend the twelve that are focused on below; these are firstly the differential diagnosis and Environmental Relative Moldiness Index (ERMI) testing and lastly, a final check for confirmation of stability once the protocol ends.

Step one of the pyramid begins externally. Exposure has to be considered and where current exposure is an issue, either removal from that exposure by moving (job or home), or remediation has to be considered if the source is related to water damaged building exposure, or determining any other trigger such as borrelia spirochete or dinoflagellate food poisoning.

In order to ascertain water damaged building exposure an ERMI test can be undertaken by the client in the place of probable exposure, usually home or work. To educate the patient the *Inside Indoor Air Quality* handout authored by Dr Ritchie Shoemaker and Dr King-Teh Lin can be shared with them. ERMI should also be used to ensure that remediation has been successful and a repeat test can be undertaken one to six weeks after any remediation. An ERMI score is based on the average spore and species from calculations of the main living area of 1000 US homes. In the UK a total spore count and PCR-DNA sampling can also be undertaken, which can add to the picture and help compensate for

any draw backs from ERMI alone due to the differences in the base point of US houses vs. house construction in the UK, as there are some key differences in construction and construction environment. Ensuring that the client has the support of a qualified and experienced environmental consultant is crucial at this stage.

The ERMI considers thirty six species of mold and these are further broken down into 26 groups associated with water damaged buildings, (group 1) and 10 not associated with water damaged buildings (group 2). The mold index is the difference between groups 1 and 2. A concentration of all 36 is also measured. Shoemaker notes that an ERMI of 14 is in the top 25% of homes for relative mould burden and an ERMI of 6 would be in the lowest 25% of homes. Each value is plus or minus 3 (see appendix 1 for an ERMI sample report).

In evaluating ERMI, Dr Shoemaker noted that ERMI results correlated with lab test results and symptoms. An elevated ERMI correlates with neurological symptoms and brain metabolites, with some key markers being particularly prominent, such as elevated levels of lactate and changes in ratios of glutamate to glutamine. Extrapolating that to his protocol, Dr Shoemaker notes that the ERMI score can't be higher than 2 if your MSH is less than 35 and your C4a is less than 20,000. The cut-off ERMI falls to -1 if the MSH is less than 35 and the C4a is over 20,000.

When considering whether a building is now safe after remediation and the Shoemaker Protocol has been successful regarding the client's health, the ERMI information from repeat testing also feeds into a HERTSMI-2 score to add to the picture for the client as to whether there is any current risk of exposure in their home/work space. A score of less than 11 would indicate a statistically safe space, 11-15 would be borderline and a score of more than 15 could be dangerous (HERTSMI-2 can be viewed in Appendix 2), but again, the client's own immunological response is also key.

Step two is where the internal work has to begin in the digestive tract to bind and remove biotoxins. This is especially important as it is essential that bile is removed expediently from the body, as this bile can contain biotoxins. Cholestyramine (CSM) is typically considered for this, or Welchol if cholestyramine is not well tolerated, although Welchol does not bind quite so efficiently and so may need to be prescribed for longer. A combination of the two can also be considered. Welchol can be dosed at 2 tablets TID. If dosing in combination CSM can be taken the morning and at bedtime and Welchol can be taken at lunch and dinner time. CSM can trigger constipation, bloating and reflux symptoms so symptoms need to be monitored. Where the client has existing constipation then Welchol can be considered initially rather then CSM and Magnesium citrate powder can also be considered. Where gut work is being done, off-protocol support for the liver could also be considered for phase II detoxification in particular. CSM is dosed at 1 scoop (4gm) 4 QID for four weeks, and the cholestyramine protocol can be viewed in appendix 3. Where the patient may have a diagnosis of Candida or there are any other relevant

sensitivities compounded CSM from Hopkinton Drug, which contains Stevia can be considered. It should be noted that any drugs used in the protocol should be checked for interactions with any of the clients existing medications and administration adjusted accordingly, this includes any supplements as, for example, CSM can impact on absorption of fat soluble vitamins.

Step three is to eradicate any present MARCoNS. MARCoNS can have many effects, such as inducing/perpetuating low MSH thereby affecting immune response and increasing risk of coagulation abnormalities. MARCoNS can also be linked with an exaggerated atrophy of grey matter in the brain. The deep nasal swab test is ideal for diagnosis, but dental MARCoNS may also have to be considered. Bactroban/EDTA/ Gentamicin (BEG) spray can then be used to treat nasal MARCoNS and a recommendation could be to treat after 30-60 days of cholestyramine for around 30 days. The dose would be 2 sprays to each nostril three times daily. Checking pets such as the family dog, or close family members may also be crucial for reducing risk of exposure/re-infection. Repeat nasal swab testing should be considered about 1-7 days after spray treatment process. If the patient feels worse upon starting MARCoNS treatment then this may be due to 'die-off' and the patient can be treated with Omega 3 fatty acids or Actos and a low amylose diet for five days. The BEG spray can then be recommenced with Omega 3 supplementation, stopping this at 5 days. Rifampin (300mg bid for 30 days, with caution if blood thinners are being used) can be considered for resistant cases.

The end of step three check would be to re-check MARoNS nasal swab and VCS if the client is improving. If MARCoNS is negative then the next step can be undertaken.

Step four is to eliminate gluten to lower anti-gliadin antibody levels (AGA). Antibodies to anti-gliadin are frequently seen where there are low MSH levels indicating an unregulated T cell response, and for this reason tissue Transglutaminase (tTg) is usually negative in these patients. A no amylose diet (see appendix 4) can be employed as this is also gluten free. Re-introduction of gluten can be considered if CIRS markers (including AGA) are normal after 3-6 months, but if the client is tTg positive then life-long removal appropriate of gluten would be essential, similarly if AGA become positive at any point in the future. Off protocol dietary advice regarding other cross-reactive foods which may mediate immune activity and mediating risk of nutritional deficiencies from significant dietary changes could also be sought in such cases. Monitoring of any existing malabsorption issues, or nutritional deficiencies related to villi damage from previous exposure to gluten may also be required. When testing antibodies a fuller picture of the extent of auto-immunity could be gained, plus a wider understanding of the results in the context of possible antigen presentation failure.

Step five relates to mediation of hormones and in particular androgen deficiency/ upregulation of aromatase. Where low VIP is seen aromatase tends to be elevated, which affects testosterone levels which in turn drop as oestrogen levels rise. Just treating with

testosterone is likely to be insufficient and perhaps drive oestrogen levels higher still. Sex hormone levels should be checked (including estradiol during DHEA supplementation) and if appropriate DHEA can be used to support testosterone levels (25mg TID for males and 25mg for females). Dr Shoemaker notes that normal ranges in males are 755-205 ng/mL for androstenedione and 350-1030 ng/mL for testosterone, along with 70-218 ng/mL for DHEA-S. Normal values for pre-menopausal women are 60-245, 10-55 and 48-247 respectively. Post menopausal ranges are 30-120, 7-40 and 48-247. VIP treatment can be considered at this point as it can regulate aromatase in some patients.

Other hormones may also need to be considered off-protocol as they can be imbalanced by the immune markers in the testing process. MSH is a neuroregulatory polypeptide and decline can be seen in uncontrolled immune responses as alpha MSH reduces NF-KappaB to induce mast cell apoptosis[3] thereby lowering inflammation. MSH deficiency triggers dysregulation of key hormones; mediation of pituitary function affects sex hormones, but ACTH/cortisol and ADH can also be affected. Cortisol can initially rise, but then drop to low levels. Poor sleep is also seen with low MSH due to lack of beta endorphin production so melatonin levels are also low. Circadian rhythm imbalance may require consideration of VIP. Barrier permeability can also be affected by low MSH, which in the gut can contribute to excessive intestinal permeability, adding to dysregulation of the immune system, off-protocol consideration of this can be assessed. Importantly, a negative feedback loop begins as the lower MSH also contributes to an environment where MARCoNS can survive in biofilms, and in turn the elevated bacterial levels (plus associated lipopolysaccharide levels and resulting production of exotoxins A and B which cleave MSH) further suppress MSH levels.

Levels of MSH are initially lowered due to the inflammatory response which mediates leptin receptors in the hypothalamus, which in turn triggers the initial leptin resistance and inhibits production of MSH. MSH levels are classed by Dr Shoemaker as normal if they are around 35-81ng/mL and symptom improvements are reported at these levels too.

Leptin is another hormone frequently associated with CIRS. Leptin resistance sets up an inflammatory obesogenic cycle that is worsened as leptin encourages the body to hold on to fatty acids. Leptin levels can rise within 24-48 hours of exposure and this is a reflection of cytokines on leptin receptors. Leptin is actually an adipocytokine triggered in response to rising fatty acid levels and made by fat cells. Its function is to store fatty acids. Leptin levels frequently correlate with BMI and normal levels for men are 5-8ng/mL and women 8-18ng/mL. The no amylose diet can support leptin levels, as the diet is low carbohydrates and in lectins, which can exacerbate leptin resistance by binding to leptin receptors.

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[3] Kalden, D-H., Scholzen, T., Brzoska T., Luger TA. Mechanisms of the Antiinflammatory Effects of a-MSH: Role of Transcription Factor NF-kB and Adhesion Molecule Expression (1999) Annals of the New York Academy of Sciences

This concludes the first step of the treatment pyramid. The next section includes correcting ADH/osmolality, MMP-9, VEGF, C4a and C3a.

Step six is correction of ADH/osmolality. When MSH drops and ADH production also drops there is an associated loss of ability to respond to dehydration. When ADH is low more free water is excreted leading salt levels to increase thus increasing risk of static shocks, which are a common key sign of mould exposure and subsequent system dysregulation. Dr Shoemaker notes that abnormalities in ADH/osmolality are recorded as obsolete if ADH is <1.3 or >8pg/mL; or if osmolality is >295 or <275mOSM/kg. If simultaneous osmolality is 292-295 and ADH < 2.3 or if osmolality is 275-278 and ADH >4.0. ADH/osmolality can be treated with DDAVP (1 spray 5/week checking sodium, ADH and osmolality after 7 days- increases are possible up to 10x/week if required). ADH may self-correct with a normalised MMP-9.

With regards to ACTH/Cortisol often the higher the ACTH the higher the degree of severity of symptoms. Dr Shoemaker notes abnormalities are absolute if AM cortisol >19ug/mL or <8ug/mL, or if AM ACTH is >60 pg/mL or <10 pg/mL. Abnormalities are recorded as dysregulation if simultaneous cortisol is >15 and ACTH is >15, or if cortisol is <8 and ACTH <40.

Step seven is to mediate elevated MMP-9 levels. MMP-9 is a zinc dependent enzyme that delivers inflammatory elements into subintimal spaces out of the blood and ultimately to organs. As it also disrupts membranes it can increase permeability in areas such as endothelial lining cells in the intestines, the blood brain barrier and mitochondria, as well as contributing to vascular permeability. MMP-9 activates mast cells and stimulates production of VEG-F by endothelial cells. Therapies used to mediate MMP-9 include the low amylose diet and high dose Omega 3 fish oil supplementation (2.4g EPA and 1.8g DHA for 30 days). Pioglitazone at 45mg daily in one dose has also been used (But not for those with leptin levels lower than 7). MMP-9 level should be less than 322ng/mL and can be re-tested at the end of the initial 30 day period. If intensification of symptoms is seen with this approach the protocol can be slowed, and the dose of cholestyramine can be titrated down temporarily. If intensification continues other pathologies may need to be considered, such as ‘Lyme’ species spirochete infection, before other medications such as Actos are utilised. Dr Shoemaker notes that normal ranges of MMP9 have a mean of 150 with a range of 85-322 ng/mL. The goal with this step is to enhance PPAR-gamma production and lower elevated MMP-9.

Step eight relates to vascular endothelial growth factor, which is vitally important for increasing O2 and new blood vessel formation (angiogenesis) and informs as to oxygen delivery in capillary beds. Physiologically it responds to hypoxia and feedback from TGF-beta 1. It is commonly lowest in the worst cases of CIRS where correction of hypo perfusion becomes very challenging as VEGF cannot correct this in part due to mediation by TGF-beta 1. A low level would be less than 31pg/mL. VEGF levels can stabilise with a

low amylose diet and high dose fish oils. Procrit can also be considered at 8000 units with CBC and VCS screened. Symptoms of low VEGF would be exercise intolerance and fatigue with neurological symptoms being common too. Treatment options for VEGF included mild exercise, or VIP can be used to support VO2 max.

Step nine involves C3a. C3a requires membrane attachments for MASP2 to be triggered, so when it is elevated bacterial membranes are present. First line treatment is antibiotics, such as in the case of Borrelia, or elevated lipopolysaccharides where the bacterial trigger has not been identified (bacterial triggers may also respond to an off-protocol herbal anti-microbial programme, especially those that enhance activity of TLR-4[4]), but high dose statins can also be employed (if despite identification and steps to eradicate C3a is still elevated), such as Zocor 80mg daily. Supplementation with CoQ10 at 150 mg/day is advised to minimise muscle fatigue symptoms frequently seen with statin medication (due to effect of HMG-CoA reductase mediation on CoQ10 production). Commencing CoQ10 supplementation 10-14 days prior to statin treatment can support minimisation of side effects. LFTs can be monitored during statin therapy. As a side point, C3a is commonly elevated in early stage Lyme Disease.

Step ten is to normalise C4a. C4a is one of the most important CIRS marker and elevation reflects ongoing activation and PAMP exposure in light of its role as a marker of complement activation. An elevated level would be greater than 2830 ng/mL and elevated levels can link with symptom severity, with the average CIRS patient having a level of around 10,000 ng/mL. An initial rise of C4a could be seen within 4-12 hours of re-exposure and can remain high until treatment commences, with the elevation reflecting ongoing activation.

Unlike C3a there is no membrane attachment required with C4a. Elevations are linked to high lactate and capillary hypo-perfusion. Lactate normalisation tends to resolve associated brain fog. Treatment of elevated C4a has previously been achieved with low-dose erythropoietin (EPO), but the first line therapy recommended now is VIP spray at four times a day.

If C4a is elevated this can contribute to acquired Von Willebrand's Syndrome (vWS) and heavy nose bleeds. So if this symptom is present testing for vWS should be considered at the earliest opportunity. It is estimated that around 1 in 40 CIRS cases will have acquired vWS. DDAVP can be considered in such cases. Anti-cardiolipin antibodies IgA, IgG and IgM can also be tested to further investigate clotting risk. Shoemaker reports that anti-cardiolipin antibodies are present in about a third of paediatric CIRS patients[5].

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[4] Nakaya TA, Kita M, Kuriyama H, Iwakura Y, Imanishi J. Panaz ginseng induces production of pro inflammatory cytokines via toll-like receptor. J interferon Cytokine Res. 2004 Feb 24(2)93-100

[5] Shoemaker RC., Maizel, MS., Exposure to Interior Environments of Water-Damaged Buildings causes a CFS-like Illness in Pediatric patients: a case/control study. Bulletin of the IACFS/ME. 2009;17(2):68-81

Step eleven is to normalise TGF beta-1, which is essential because of its many varied effects related to it being a marker of a dysfunctional immune system; initiating neurological symptoms such as seizures and tremors and other Parkinson's-like related symptoms and can affect collagen. It can also mediate immune function such as T cells as TGF-beta signals T reg cells into tissue to mediate inflammation if ROR receptor is there. If not IL23 is just one T reg example that can be converted into pathogenic T cells which can in turn mediate TGF Beta-1 levels[6]. Inflammatory TH17 lymphocytes can also be triggered. CD4+ and CD25+ are just two other examples of markers that can be tested for and assessed to fully evaluate cytokine immune response. TGF-beta 1 is also notable due to its ability to impair normal T regulatory cells function, which can impede auto-immunity.

If TGF beta is elevated then losartan (a blood pressure drug) can be used at 12.5-25mg daily. The blood pressure is stable this dose can be increased to 25mg BID, ideally in no less than 30 days and up to 6months (children split dose 0.6-0.7mg/kg/day). Regular monitoring of blood pressure (both high and low) is crucial for up to six months. If losartan cannot be used then VIP nasal spray can be considered.

Step twelve involves normalising vasoactive intestinal peptide (VIP) and is the final pyramid step, especially if the patient is still symptomatic. VIP is a neuroregulatory polypeptide. It down-regulates MMP9 and MASP complexes and cytokine responses, pulmonary artery pressure and inflammatory response throughout the body, so has a wide ranging influence.

Correction of VIP is dependent on the previous steps being taken with success, and is subject to conditions; VCS should be normal, MARCoNS must be negative, there should be no ongoing exposure to mold (at both home and workplace and anywhere else that the client frequents), with an ERMI score of less than, or equal to two, or HERTSMI-2 less than or equal to ten. As a secondary factor lipase levels should be normal.

When the client is ready for VIP additional testing of TGF beta-1, C4a, VEGF, MMP-9, 25 OH-Vitamin D, estradiol, total testosterone and lipase should be undertaken.

Dosage of VIP spray is begun at 50 mcg, which equates to one spray four times daily. It is recommended that the first dose is taken at the office, with a TGF-beta 1 blood draw done prior to the VIP spray being administered, and again 15 minutes later. Any rise in TGF-beta 1 can be indicative of mold exposure. FBC, LFT and lipase levels (in case of pancreatitis) should then be checked regularly. If there is any abdominal pain/ gastrointestinal discomfort lipase levels should be checked immediately and VIP stopped if levels are elevated. After a month the VIP dose can be adjusted, increased in some to 8

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[6] Manel N, Unutmaz D, Littman D., The differentiation of human Th-17 cells requires transforming growth factor B and induction of the RORγT. Nat. Immunol. 2008 Jun; 9(6) 641-649

sprays/day or more and in orders to less than 4 doses/day (a summary table of medical treatment information can be found in Appendix 6).

Monitoring should then be ongoing, and this involves not just through the steps, but a full symptom review and steps to remediate any other factors that may still be an issue such as capillary hypo-perfusion at the end of the protocol. Capillary hypo perfusion can be measured via VO2 max, and a rise can support VEGF correction.

In suspected cases of re-exposure a VCS test should be considered first. Relapse can occur with any re-exposure and in as little as between 24-72 hours. Cholestyramine or Welchol can be used prophylactically.

The protocol is extensive and the client may need additional support to successfully complete each step. Compliance is a key part of any protocol, but this especially the case with the Shoemaker protocol- however the dividend for completing it can be immeasurable for a clients future quality of life.

Additional References

CIRS State of the Art in CIRS Conference summit 2016, Irvine, CA notes

Indoor Environmental Professionals Panel of Surviving Mold, Consensus Statement, 2016

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Shoemaker, RC, Schaller J, Schmidt P (2005) Mold Warriors. Fighting America's Hidden Threat. Gateway Press: Baltimore, USA

Institute of Medicine of the National Academies Press. Damp Indoor Spaces and Health (2004) The National Academies Press, Washington DC, USA

Appendix 1

The ERMI Test

Group 1 Water Damage Indicators Fungal ID	Sample ID Dust Weight 01 5.0 mg	
	SE*	SE/mg
Aspergillus flavus	ND	<1
Aspergillus fumigatus	4	1
Aspergillus niger	7	1
Aspergillus ochraceus	ND	<1
Aspergillus penicillioides	1	1
Aspergillus restrictus	ND	<1
Aspergillus sclerotiorum	ND	<1
Aspergillus sydowii	ND	<3
Aspergillus ungula	ND	<1
Aspergillus versicolor	1	1
Aureobasidium pullulans	360	72
Chaetomium globosum	1	1
Cladosporium sphaerospermum	1	1
Eurotium (Asp.) amstelodami	260	51
Paecilomyces variotii	1	1
Penicillium brevicompactum	12	2
Penicillium corylophilum	ND	<1
Penicillium crustosum (Group 2)	ND	<2
Penicillium purpurogenum	ND	<1
Penicillium spinulosum	ND	<4
Penicillium variable	ND	<2
Scopulariopsis brevicaulis	ND	<1
Scopulariopsis chartarum	1	1
Stachybotrys chartarum	1	1
Trichoderma viride	1	1
Wallemia sebi	1	1
Sums of the logs	4.1	

Group 2 Common Indoor Molds Fungal ID	Sample ID Dust Weight 01 5.0 mg	
	SE*	SE/mg
Acremonium strictum	5	1
Alternaria alternata	ND	<1
Aspergillus ustus	ND	<1
Cladosporium cladosporioides -1	530	110
Cladosporium cladosporioides -2	2	1
Cladosporium herbarum	22	4
Epicoccum nigrum	1	1
Mucor/Rhizopus	4	1
Penicillium chrysogenum-2	7	1
Rhizopus stolonifer	ND	<1
Sums of the logs	2.8	

* SE = Spore Equivalents, ND = Not Detected

Sample	01
ERMI Calculation	4.1 — 2.8
ERMI Result	1

Appendix 2

HERTSMI-2

Patient name	Date					
Date of testing	Location					
	Spore E/mg	Points	Concern			
Aspergillus penicilloides Aspergillus versicolor						
Chaetomium globosum						
Stachybotrys chartarum						
Wallemia sebi						
HERTSMI 2 Score = Total Points awarded =						
We use a point system. Units are Spore E/mg.						
10 points are assigned for						
Aspergillus penicilloides	≥500					
Aspergillus versicolor	≥500					
Chaetomium globosum	≥125					
Stachybotrys chartarum	≥125					
Wallemia sebi	>2500					
6 points are assigned for						
Aspergillus penicilloides	100-499					
Aspergillus versicolor	100-499					
Chaetomium globosum	25-124					
Stachybotrys chartarum	25-124					
Wallemia sebi	500-2499					
4 points are assigned for						
Aspergillus penicilloides	10-99					
Aspergillus versicolor	10-99					
Chaetomium globosum	5-24					
Stachybotrys chartarum	5-24					
Wallemia sebi	100-499					
Interpretation of HERTSMI-2 Score						
<11 Statistically safe for re-entry for those with CIRS						
11-15 Borderline; clean first and re-test before re-entry						
>15 Dangerous for those with CIRS. Do not enter.						
Disclaimer:						
HERTSMI-2 is a building index. No one HERTSMI-2 can possibly show all areas of a given building.						
HERTSMI-2 does not replace careful observation of symptoms and lab results obtained following re-exposure						

Accessed via: http://www.survivingmold.com/diagnosis/hertsmi-2

Appendix 3- Cholestyramine Protocol

CSM Protocol

1. On an empty stomach, take one scoop of CSM (9 grams), mix with water, or juice, 4-6 oz.

2. Stir well and swallow. Add more liquid, repeat 1 above until done.

3. Drink an extra 4-6 oz of liquid.

4. After 30 minutes, you may eat or take meds (wait at least 2 hours before taking thyroxine, digitalis, theophylline, Coumadin and others; ask your doctor for information).

5. Take CSM 4 times a day!

6. If you eat first, wait at least 60 minutes before taking your next CSM.

7. Reflux, constipation, bloating and bowel distress are not unusual.

8. Use acid blocking medications as needed.

9. Use Miralax to relieve constipation

Source: Cholestyramine_Fact_Sheet_SM-5_2011.pdf from wwww.survivingmold.com

The Shoemaker CSM Factsheet will be shared with all clients

Appendix 4- The no-amylose diet

NO-AMYLOSE DIET FORBIDDEN FOODS

- Roots and tubers including white and sweet potatoes, beets, peanuts, carrots, and other vegetables that grow underground. The exception here is onions and garlic.
- Bananas (the only forbidden fruit).
- Wheat and wheat-based products including bread, pasta, cakes, and cookies.
- Rice.
- Oats.
- Barley.
- Rye.
- Foods with added sugar, sucrose, corn syrup, or maltodextrin.

ALLOWED FOODS

Allowed foods include basically anything that is not on the list of forbidden foods including:

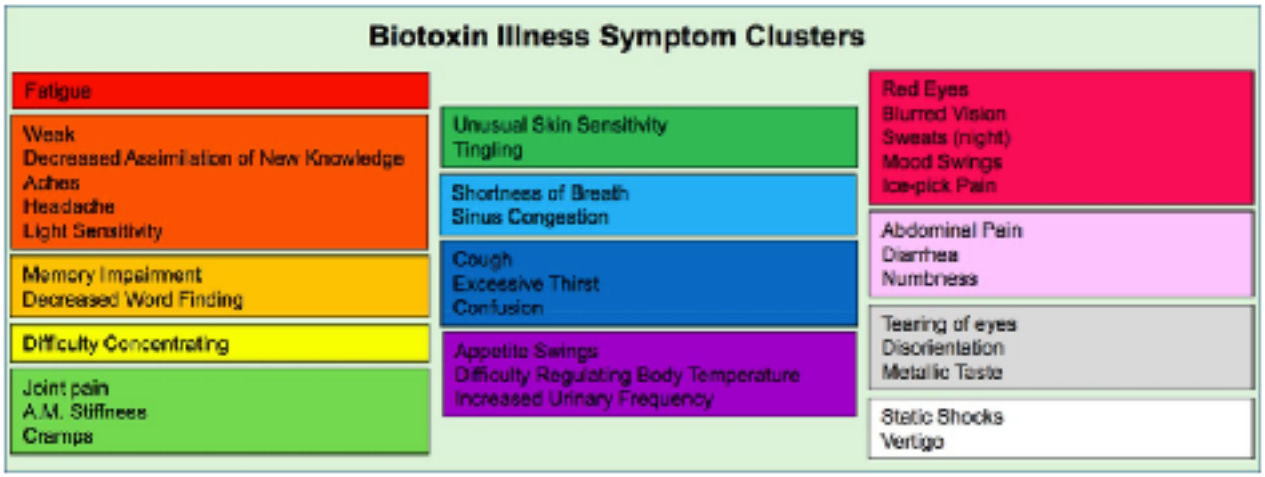
- Corn.
- Onions.
- Garlic.
- All vegetables that grow above the ground including lettuce, tomatoes, beans of all types, peas, cucumbers, and celery.
- All fruits except bananas.
- Meat, fish, and poultry.
- Condiments (avoid low-fat varieties as they usually contain added sugar).
- Spices.
- Eggs.
-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

This diet is based on the 00-2-3 rule and is an easy way for you to remember what should or should not be included in your diet each day. You should have 0 sugars (glucose or sucrose, including corn syrup), 0 amylose, 2 servings of protein that total at least 6 to 8 ounces, and 3 servings each of vegetables that grow above the ground and fruit (except bananas) per day. This diet allows for sufficient quantities of food so that you won't be hungry and can actually enjoy good-tasting, high-quality meals. It just involves adjusting some of our habits and thought patterns when it comes to food. For instance, you can still eat a hamburger, just not the bun. Why not try some melted cheese and a hearty slice of tomato on top instead? Soups can be a nutritious and filling meal or snack but not when they are loaded with pasta, potatoes, or rice. Why not try some delicious black bean soup or maybe a homemade cream-based tomato soup without the added sugar so often found in canned varieties?

The other benefit of this diet is that it is also a gluten-free diet. The avoidance of wheat, oats, rye, and barley is the same for both diets. If you have also been advised to be on a gluten-free diet, no adjustments need to be made in order for you to eat gluten-free. Just follow the 0 amylose rule and you will automatically be avoiding gluten-containing products. One key difference to note is that this diet does not allow rice while gluten-free products often use rice as a substitute for wheat. This makes the no-amylose diet slightly more restrictive than a no-gluten diet.

Source: http://www.survivingmoldillness.com/no-amylose-diet/

Appendix 5 - Symptom Summary Chart



Source: https://www.survivingmold.com/docs
12_STEP_SHOEMAKER_PROTOCOL_FOR_CIRS.PDF

Appendix 6- Summary table of dose and medication information

Medication	Dose	Duration	Other
Cholestyramine	> 120lbs or > 18 years Questran- 9gm (1 scoop) mixed with 6 oz water PO, QUID 30 minutes before food, followed by extra 4-6 oz water Compounded- 4gm mixed with 6oz water PO, QID 30 min before bedtime, following by an extra 4-6oz water Pediatrics (,102lbs or ,18 years) 60mg/kg/dose PO, TID mixed with 6oz water PO 30 mins before food	30 days	Check VCS- if normalised after 30 days switch to Welchol 625 bit (1 tab/dose) if out and about. If home is safe- no medication. Use Welchol or CSM for 3 days minimum before stopping. Prophelactic use of Welchol can be used.
BEG spray for MARCoNS	Adults- 2-3 sprays to each nostril three times daily Children- 1 spray BID alternating nostrils	30 days	Side effects countered by O3 or actor with low amylose diet for 5 days, then resume spray with O3 stopping at 5 days. Rifampin 300mg BID for 30 days can be used in resistant cases, with caution if on blood thinners.
DHEA to normalise androgens	25mg TID or HCG injections of 125mg/week (or sublingual) VIP nasal spray 4 QID	5 weeks DHEA (experimental) 30 days	VIP can stabilise aromatase
DDAVP- ADH/osmolality	Adults- mg tab every other night for 5 doses Children- 1 spray of DDAVP based on weight/age	10 days total	Then measure serum osmolality and sodium. If normal but sx increase DDAVP 0.2mg to every day for 10 days
Actos for MMP-9	45mg once daily	30 days	Use alongside no amylose diet. Where leptin <7 or under 18 use 2.4g EPA with 1.8g DHA
Statin for C3a	CoQ10 150mg for 10 days, then commence statin 80mg/day poss. divided dose required.	10 days for CoQ10 prior to statin- then until treatment ends	Check LFT and RFT
Procrit for C4a (black box warning)	4 shots of 8000 units twice a week- supervised for adults only.	Total of 5 doses	VIP consideration for children and those resistance to Procrit
Losartan for TGF-beta 1	up to 25mg BID for adults 0.6-0.7mg/kg/day divided BID for children	30 days	Monitor TGF-beta 1 and blood pressure monthly
VIP nasal spray	50mcg at QID.	30 days then 30 days more if required post re-testing	Baseline is important. Redraw labs after 30 days Check lipase levels and abdominal sx regularly

Source: https://www.survivingmold.com/BIOTOXIN_PROTOCOL.pdf

Appendix 7- What else could be considered for future development of the Shoemaker Protocol?

The thoughts below are unproven in relation to the Shoemaker CIRS protocol and are solely the thoughts of the author as areas that could possibly be explored in order to ascertain whether there is any value in considering them for further research relative to the CIRS protocol.

1. Cognitive decline has been highlighted over the past year by Dale Bredesen. Type 3 Alzheimer's, as defined by Dr Bredesen leans heavily on the work of Dr Shoemaker, so the importance of CIRS in relation to cognitive decline is something that could be further explored. Novel markers such as Brain Derived Nuclear Factor (BDNF) due to links to glutamate, leptin and ADH in particular could be considered for addition to the test profile. ACTH, sex hormones including DHEA and melatonin and serotonin also increase BDNF. Dietary factors relating to increasing BDNF may then add to the no amylose approach (such as intermittent fasting, butyrate, fish oil, prebiotic FOS, blueberries, cocoa (flavanoids), soy and salt and chewing). Lactate levels rise to try to compensate for low BDNF so it may be this is part of the pathology as to why we see elevated lactate in CIRS too.

2. The blood brain barrier (BBB) could also be considered for further research to ascertain whether it may be a valid area for testing, especially when thinking about long term neurological effects of CIRS. Endothelial cells and tight junctions can be mediated by inflammatory markers, pericytes and astrocytes. The BBB can be breached by both VEGF and MMP-9 and via its role as an organic anion transport system it supports toxin secretion into bile.

3. Additional lab test information to support the dietary advice given regarding gluten could also be considered. Again Cyrex Labs offer their Array 3 panel, which considers immune reactivity to 20 gluten proteins and Array 4 panel which considers gluten-associated cross-reactive foods. Tests of this type could support longer term dietary planning for patients and help differentiate Coeliac Disease from Non-Coeliac Gluten Sensitivity. Genetic testing for Coeliac Disease/spectrum risk could also be explored for completeness, so that from a dietary perspective the gluten intake advice could be further individualised.

4. Additional off-protocol gallbladder support from a dietary perspective could also potentially add to the no amylose dietary approach. Dietary choline for example could be considered as one example that could be researched for addition of a lecithin enriched diet to support gallbladder function during VIP treatment to mediate risk of gallbladder inflammation by supporting bile secretion[7].

5. Psychological support- CIRS clients can have behavioural issues which can express inappropriately. It can be hard for them to relinquish control to someone as they have had to fight so hard to find a practitioner who can help them, this strength can sometimes be an impediment to building and retaining positive relationships with the practitioner. The client's level of patient-expertise can also be a challenge. At the other

[7] LeBlanc MJ, Gavino V, Pérea A, Yousef IM, Lévy E, Tuchweber B. The role of dietary choline in the beneficial effects of lecithin on the secretion of biliary lipids in rats. Biochim Biophys Acts 1998. Aug 28;1393(2-3):223-34

end of the spectrum some clients may be unable to listen and learn effectively and may under-perform in their ability to advocate for themselves and require additional support from a professional or family member- but recognising this may also require early professional intervention. Additional support tools for practitioners could be developed on this subject.

6. The financial cost of the protocol will be high in the UK where all tests would have to be paid for privately by patients. Further research may have to be undertaken to establish whether/how test costs can be reduced.