Biotoxin Illness Treatment Protocol:

By Dr. Ritchie Shoemaker MD

Initial visit with patient should include:
Thorough history using standardized roster of symptoms. Review this with patient in order to avoid misinterpretation of symptoms. Ask about sleep disturbances, menstrual problems as appropriate, bleeding history and any other symptoms patient might be experiencing. A thorough past medical history is taken which includes diseases previously diagnosed, medicines, herbal and supplements being taken, allergies, surgeries, major traumas, family history, work history, review of systems and extensive environmental history.
A developmental history should be done especially with children asking about school performance and behavior issues.
During this process a differential diagnosis is being compiled and refined. Asking yourself: What are all these symptoms, how do these symptoms cross over, are they the result of a single illness or multiple maladies?

The next step is a nine system head to toe exam looking for evidence of potentially confounding illness. Look for findings found frequently in patients with Chronic Inflammatory Response Syndrome (CIRS). Common findings amongst CIRS include tremor, cool hands and/or feet, discolored hand/and or feet, pallor and unilateral weakness in the shoulder anti-gravity muscles. Checking fatigability factor by pressing down on the hands or distal forearms of the extended arms, checking for strength. Grip strength, shrugging shoulders against resistance are also tested. Recheck the arms in extended position by pressing down with two fingers, looking for weakness. Respiratory symptoms and flexibility should also be included.
After all information has been obtained, labs should be done according to the differential diagnosis. If there is a suspicion of CIRS, labs should be done to confirm or disprove CIRS. Include those that show inflammatory abnormalities as well as those that are always normal in biotoxin illness. Check initial labs: Start with HLA-DR, MMP-9, MSH (should be run through Lab Corp), C3a, C4a (should be run through Quest), TGF beta 1, ADH, osmolality, VIP, and VEGF. If older than age 12 consider ESR, CBC, CMP, CRP, ACTH, TSH, Testosterone, Cortisol, Lipid profile, IgE, Immunoglobulin panel (total IgA and IgM) and Antigliadin. These markers should be checked to help rule out other suspected illnesses, negative results do not rule out Biotoxin Illness. See protocol manual for Pediatric guidelines.
Perform other diagnostic labs to rule out other conditions/illnesses/diseases in your differential diagnosis. Follow abnormal labs during course of treatment. If history of bleeding with WDB exposure, check labs for vWF syndrome along with a Coagulase study (PT, PTT, PT/INR).

Next: Perform VCS screening. Prior to VCS- check visual acuity per protocol
Use proper lighting (> or equal to 70 foot-Lamberts). Use two 15" daylight fluorescent bulbs for best illumination. Perform VCS at 18". See instructions for scoring.

Starting Treatment:

The treatment protocol is simple to understand, but strict adherence is required in the treatment sequence. It is critically important to follow the pathway to health in the order it is prescribed.

First and most important step is removal from exposure. Make sure effort is given in determining the source of the toxin, be it from a Borrelia spirochete, from dinoflagellate food poisoning or from exposure to the interior of water-damaged buildings (WDB). Disease can be triggered by one or a combination of these toxins. Once source of exposure is identified, every effort must be made to remove the potential continued or future exposure.

If exposure to WDB appears to be the source of toxin exposure the patient should be given an ERMI kit. Review process with patient. Give patient handout on explanation of ERMI testing, which includes websites for remediation. Give patient handout on *Inside Indoor Air Quality* by Dr. Ritchie Shoemaker and Dr. King-Teh Lin.

The Environmental remediation score from www.mycometrics.com gives a quantitative measurement of the fungal DNA in a building. Goal: ERMI <or = to 2 if MSH <35; ERMI to < or = to -1 if MSH <35 and C4a>20,000, HERTSMI -2 < 11.

Discuss using consultants as provided on handout. Discuss with patient this may mean moving from their home, altering their workspace or being moved to a different location. Some schools will take mold illness seriously others will ignore remediation requests. Patients may need to relocate to another school or even consider home schooling. Also, discuss with patient about avoiding small brief exposures to WDB that could cause a "sicker quicker" syndrome.

Second step is elimination of toxin from the patient's body. Those genetically predisposed do not recognize the offending toxins as foreign. Without the recognition, the antigen presentation system is never activated against these particles. There becomes no effective way for the body to rid itself of the toxins. That is where the protocol steps in.

Cholestyramine (CSM) is an anion binding resin which has a quaternary ammonium side chain which creates a localized, net positive charge. The ammonium is of the right size and charge to bind with high affinity to the small ionophore compounds which cause CIRS. It is the drug of choice to start therapy since it contains roughly 4 times as many electrically active sites as does the second choice, Welchol (colesevelam). Give patient information on CSM and have them sign consent form.

Things to consider before prescribing CSM or Welchol:
CSM may not be well tolerated due to gastrointestinal problems. Side effects include: nausea, GERD, belching, bloating, constipation, may have bad taste and mixes poorly. If Cholestyramine is not well tolerated, Dr. Shoemaker recommends using Welchol. Keep in mind Welchol is better tolerated and has fewer side effects but has only 25% of the binding sites found in CSM. It could take longer to normalize labs when treating with just Welchol.
Consider a combination of CSM and Welchol. When in combination CSM can be taken in the morning and at bedtime, take Welchol with lunch and dinner.
Special considerations: If patients are chemically sensitive or have food allergies, consider using Welchol. Watch the use of aspartame in patients with anxiety or depression. Those patients who have a confirmed diagnosis of Candida do not need the added sugar, and others are simply sensitive to food additives. In this case prescribe compounded CSM from Hopkinton Drug, which only contains Stevia. Titrate slowly to a full dose, if necessary.
CSM can be constipating, if patients are already constipated before starting CSM consider starting Welchol instead of CSM. Adding Mag citrate powder to the "Mold Shake" can be helpful for patients with constipation.
To prevent an "intensification" reaction in Lyme patients, pretreat with Low-Amylose diet and Actos 45 mg or high Omega-3 fatty acids for five days prior to starting CSM. In particular if Leptin <7, use 2.4 grams of EPA and 1.8 grams of DHA (fish oil) instead of Actos. Titrate Welchol up slowly for patients who are sicker.
Cholestyramine can decrease the efficacy of Coumadin, thyroid hormones, and thiazide diuretics; therefore these drugs should be administered one hour before CSM or 2 hours after CSM.
CSM can interfere with fat-soluble vitamins A, D, E, and K. Dose these vitamins separately.

CSM treatment:

ADULTS: >120 lbs or > 18 yrs old
Rx Questran (CSM)
Sig: 9 gm (1 scoop) mixed with 6 oz. water PO, QID 30 minutes before food, followed by extra 4-6 oz. water.
Rx Compounded CSM
Sig: 4 gm mixed with 6 oz. water PO, QID 30 minutes before bedtime, followed by an extra 4-6 oz. of water.

PEDIATRICS: (<120 lbs or <18 yo)
Rx CSM
Sig: 60 mg/kg/dose PO, TID mixed with 6 oz. water PO 30 minutes before food.

Follow up:
Recheck VCS one month after starting treatment and then with each step throughout the various Biotoxin Illness Treatment. Treatment durations may vary and are continued until VCS normalizes. Recheck all abnormal labs to see if any have changed in the course of treatment.
See criteria for monitoring VCS in protocol manual

Reexposure Prophylactic Treatment CSM/Welchol:
When VCS is normalized switch to Welchol 625 bid (one tablet per dose) for those out and about. If at home, and home is safe-no medication. Fifty percent of US buildings are identified as moldy by NIOSH, so use prophylactic Welchol often. After going out and there is exposure, use Welchol or full dose of CSM for three days minimum before stopping.

Treatment failure: Consider the patient is continuing to be exposed, possible poor compliance with CSM, or failure to eradicate MARCoNS.

Third Step is the eradication of MARCoNS- multiple antibiotic resistant coagulase negative staphylococcus from the nasopharynx, if present. These bacteria form a biofilm making it hard for many antibiotics to penetrate, sheltering bacteria. They are resistant to more than one class of antibiotics. MARCoNS rarely are found if a patient has a normal MSH, but normal is unusual in CIRS patients. MARCoNS make hemolysins which cleave MSH rendering it ineffective. Inadequate treatment of MARCoNS will reduce efficiency of CSM therapy, perhaps because of continued assault on MSH.
Nasal swab should be done for all patients with baseline labs. A positive result is when the API-Staph nasal culture shows resistance to two or more distinct classes of antibiotics. (Such as Fluoroquinolones and PCN). If positive, after the first month of CSM, treat with one-month high dose BEG (Bactroban/EDTA/gentamicin) nasal spray, dosed 2 sprays to each nostril three times daily.
Counsel patient on use: 2 sprays to each nostril TID, blow nose first. Breathe deeply and spray each nostril. Counsel patient that they may feel worse after starting MARCoNS treatment. This is due to a "die-off" reaction when MARCoNS are being eradicated. In this case, treat patient with Omega 3 fatty acids and or Actos with a low amylose diet for 5 days. Then resume BEG spray along with Omega 3, stopping at 5 days. Rifampin 300 mg bid for one month can be used in resistant cases. Rifampin needs to be used cautiously in patients on a blood thinner. If symptoms worsen after one month, check for re-exposure, recheck VCS, and MMP-9 levels. If better, stop BEG spray: recheck API-Staph nasal culture and VCS.

If negative for MARCoNS: go to next step in treatment Protocol. Repeat nasal culture after first month of treatment with a positive API-Staph nasal culture for MARCoNS.

Things to remember:

If still positive, consider canine carriage in the home, close facial contact with another person with low-MSH or ongoing mold exposure.

Treatment:

BEG spray (Bactroban, EDTA, and Gentamycin) which dissolves the biofilm clearing the way for a direct attack by the topical antibiotics.
Two sprays 2-3 times a day for 30 days
Children: 1 spray twice a day, alternating nares. (Rarely need to use in children).
If treatment resistant after first month, resume BEG spray along with Rifampin 300 mg, 2 tabs daily for 30 days for adults. Start Rifampin and BEG spray on the same day to discourage new resistance emergence. After treatment, repeat culture- do not assume eradication. This step is important for future success with treatment pyramid, especially if VIP is considered.

Fourth step in the process is the correction of antigliadin antibodies. With low MSH there is a resultant dysregulation of Treg cells, leading to possible inflammation and autoimmune disorders. In particular, serum IgA and IgG anti-gliadin antibodies should be checked. If positive then rule out celiac disease by doing TTG-IGA. Many, but not most will have a positive antigliadin antibody (AGA) in their initial lab work. However, in CIRS patients, TTG is usually negative. This is a result of Treg dysregulation, which led to gluten autoimmunity. In such cases, a tissue transglutaminase antibody test (TTG) should be performed. If this is positive, have the patient come off gluten forever. Treatment of TTG negative patients consists of a gluten free diet for at least three months followed by retesting. If the AGA is negative on retesting, gluten can be reintroduced into the diet still monitoring patient for recurring GI symptoms.

For those with low MSH-associated anti-gliadin antibody (AGA) positivity who stay off gluten for 3 months, recheck anti-gliadin antibodies. If negative, retry gluten. The anti-gliadin antibodies are later rechecked: if they become positive again Dr. Shoemaker recommends patients stay off of gluten indefinitely. If a patient just feels better being off gluten, they should continue to stay off of it.

Fifth Step: Correction of Androgens

Abnormal androgens are usually caused by an upregulated aromatase enzyme. Biotoxin patients often experience dysregulation of their androgenic hormones, especially testosterone. If testosterone replacement is given to these patients, it can result in further suppression of natural testosterone production, making matters worse. Low VIP or inflammation in these patients can cause the enzyme aromatase

to more rapidly convert testosterone into estrogens. This results in continued low levels of testosterone, with concomitant high levels of estrone/estradiol. DHEA can help rebalance androgen levels in these patients.

Treatment:

*Dose: DHEA 25 mg TID, or HCG injections of 125 mg per week (or sublingual) for 5 weeks (*experimental) or VIP (vasoactive intestinal peptide) nasal spray 4 times a day* for 30 *days.*

DHEA levels should be checked to see if it is low, prior to starting DHEA supplementation. While supplementing DHEA, monitor estradiol levels to make sure they are not rising. This is necessary since the conversion of testosterone to estradiol is catalyzed by aromatase, which can be overactive in some Biotoxin Illness patients.

Consider VIP treatment as it can stabilize aromatase in these patients, resulting in a rebalancing of the androgens.

Sixth Step: Correction of Antidiuretic Hormone/osmolality problems.

There are certain cells in the hypothalamus of the brain called osmoreceptors that respond to levels of serum osmolality. When there is high serum osmolality (i.e. dehydration), these osmoreceptor cells shrink and trigger the release of ADH (antidiuretic hormone) from the posterior pituitary. ADH signals for free water to be reabsorbed in the kidneys. As a result, serum osmolality is brought to normal levels again, as cells are hydrated. When serum osmolality is low (i.e. overhydration), the osmoreceptors swell and block the release of ADH; this leads to the loss of free water into the urine.

In Biotoxin Illness patients, a lack of regulation of salt and water is signaled when ADH is low (or too high) but osmolality is relatively high (or low). These patients may have excessive thirst and may need to urinate every 30 minutes or so, due to low ADH causing them an inability to retain water they drank. As salt levels in blood rises due to the lack of free water, some salt is released on their skin, sweat glands, creating a battery-like electrical potential that increases susceptibility to static electric shocks. Some people may have migraine-like headaches due to dehydration with high osmolality.

Besides affecting kidneys, ADH also interacts with VIP and MSH in the suprachiasmatic nucleus of the hypothalamus. Without these three hormones working in concert, hypothalamic dysfunction will be increased.

Chronic neurotoxic illnesses, including Lyme disease have shown elevated serum osmolality.

Treatment:

DDAVP 0.2 mg tab every other night for five doses: monitor for side effects, especially weight gain. The day after last dose, measure serum osmolality and serum electrolytes sodium to ensure both are normal. If both are in normal range and symptoms still persist (especially on off days), increase DDAVP 0.2 mg to every day for 10 days.

Remeasure serum osmolality and serum sodium to ensure they are still normal after 10 days of the increased dose. Some patients may need to increase to 2 doses per day if tolerated.

Pediatrics: 1 spray of DDAVP spray based on child's weight and age. Caution use with kids.

DDAVP can be discontinued once serum osmolality stays normal in sequential lab testing. Continue to follow serum osmolality and ADH during treatment. If odd symptoms occur during DDAVP treatment, discontinue treatment and check electrolytes and serum osmolality for abnormalities. Make sure patients understand the need to measure serum sodium and osmolality. Follow electrolytes (CMP) and ADH/Osmolality.

This treatment corrects labs but also polydipsia, polyuria, orthostatic hypotension, recurrent headaches, and static shocking that patient's experience.

Dr. Shoemaker states that 60% of Biotoxin Illness patients have dysregulated ADH/osmolality. After mold remediation, biotoxin carriage correction, improvement in VCS, and eradication of MARCONS, low ADH in many patients will normalize. There is a certain percentage that will need further treatment.

Lab results:

High serum Osmolality- High ADH-normal
Low Serum Osmolality- Low ADH- normal
High serum Osmolality compared to ADH consider DDAVP

Seventh Step: Correction of MMP-9 (matrix metalloproteinase 9).

In the Biotoxin pathway, cytokines activate receptors, resulting in the release of MMP-9 from the endothelium into the bloodstream. MMP-9 aids in bringing certain inflammatory molecules into the brain, nerves, muscles, lungs, and joints. Therefore if MMP-9 is elevated, treatment must be done to bring it down to normal. It is important to make sure the blood draw is done properly. A prechilled SST tube should be used. Following the lab draw, the specimen should be immediately centrifuged and frozen. These steps help prevent the release of MMP-9 from white blood cells in the blood specimen. The release of MMP-9 could elevate the MMP-9 level. Goal is to up regulate PPAR-gamma production and reduce MMP-9 expression.

Care should be taken with Diabetic patients as to not interfere with their other therapies. You may need to consult with their Primary Care Provider and communicate treatment.

Treatment:

Actos 45 mg once daily for thirty days along with "No Amylose" diet for the same period of time. Those with Leptin <7, or under 18 years of age or cannot tolerate Actos, use 2.4g/day of EPA with 1.8g/day of DHA in its place .

As with all steps, abnormal labs should be repeated at the end of the therapeutic trial. This therapy may also correct abnormal VEGF.

Watch kidney functions. Actos also has an increased risk for bladder cancer with long-term use. May cause hypoglycemic symptoms even if BS is normal. Slender patients with Leptin <7 may not tolerate Actos since Actos lowers leptin. If patients do not tolerate Actos or if Leptin <7: Use 2.4 mg EPA/1.8 mg DHA daily. Takes longer to work but just as effective. Still low amylose diet required.

FYI: MMP-9 patients may get worse when starting CSM, and Herxheimer reaction (*when a patient feels as though their disease symptoms have suddenly gotten worse. They may describe reactivation of previous symptoms, exacerbation of current symptoms, or new symptoms*), often involves an increase in MMP-9 with a fall, or worsening, in row E of the VCS test.

Eighth Step: Correction of C3a.

Increase of C3a can cause anaphylaxis through immune responses, which cause smooth muscle constriction, capillary hypoperfusion, increased vascular permeability, and WBC release of oxidants, leukotrienes, and enzymes.

C3a can be elevated in Lyme disease. Acute Lyme must be ruled out if patient has a high C3a. Remember: C3a will be low unless there is an available microbial cell membrane, such as found in Lyme disease.

Treatment:

High dose Statins: showed reduction in T cell activation, macrophage infiltration, and vascular wall inflammation. Statins inhibit an enzyme called HMG-CoA reductase that controls the rate of cholesterol production in the body. Statins like Lipitor, Crestor, Zocor have been shown to shut down the production of one of the most important nutrients in the body, Co-Enzyme Q10 (CoQ10). CoQ10 is needed by the mitochondria of the cell to make energy in the form of ATP from carbohydrates and fatty acids. During Statin usage-low levels of CoQ10 are seen not only in the serum but in the muscle and may result in myalgias. This is why a supplement is used (see dosage below)

Treatment:

CoQ10 150 mg daily for 10 days, then start Statin dose while continuing CoQ10. High dose at 80 mg/day-some require divided dosing. Pravastatin, Atorvastatin, Fluvastatin, Rosuvastatin, and Lovastatin. Watch for recommendations of availability, specific dosing parameters, side effects, and drug-drug interactions.

Prior to starting Statin, check liver functions and renal function. Continue to monitor renal function during treatment.

Inform patients of possible increase in blood sugar levels, reversible memory loss, and confusion, and very rare liver problems when taking high dose Statins. Remember: FDA recommends patients avoid Statins if they are taking Cytochrome P450 3A4 inhibitors such as itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, teleprevir, nefazodone, gemfibrozil, or cyclosporine. With Lovastatin do not exceed 20 mg daily if patients are on danazol, diltiazem, or verapamil. Do not exceed 40 mg Lovastatin/day with amiodarone. Patients should also avoid ingesting large quantities of grapefruit juice (more than 1 quart a day) while on statins.

Ninth Step: Correction of elevated C4a.

This split product of the MBL (mannose binding lectin) pathway of the complement system is a key marker of how severe a patient's CIRS is. Like C3a, C4a is an anaphylatoxin. It can activate mast cells, and basal cells, increase smooth muscle contraction and vascular permeability, and cause release of chemotactic factors.

Procrit (erythropoietin) is used to reduce C4a.**** Has a black box warning.

Informed consent must be obtained. Complete blood count and iron studies (as well as C4a, TGF beta-1, d-dimer, and T regulatory cells labs) are obtained before each dose and after completion of the trials to insure no polycythemia develops, potentially increasing risk for thrombus formation, as well as to document efficacy.

Treatment:

Five shots of 8000 units are given in a supervised manner, twice a week (Monday and Thursday) for a total of five doses. *****Recheck C4a, monitor D-dimer, hemoglobin, and blood pressure with each dose of Procrit.

Patients keep track of symptoms as they go. At the end,patient and provider go over symptoms to see if there is improvement, (i.e. is patient feeling better, breathing easier, increased mental clarity). People with high C4a can have decreased cognitive function due to hypo- perfusion. Treating C4a has shown improvement in: memory, concentration, word finding, assimilation of knowledge, confusion and disorientation.

There is no established dosing of Procrit for children. For those recalcitrant to Procrit, VIP therapy can also be used at 4 sprays a day.

MRI of the brain (Nuero Quant) with MR Spectroscopy can show changes in brain volumes that correlate with hypo-perfusion caused by high C4a. Changes include high lactate levels (>1.29) in the frontal lobes and hippocampus and a low glutamate/glutamine ratio(<2.19). These changes are seen with cognitive dysfunction and may improve when C4a is normalized.

Treatment:
Assess for the above 6 executive functions.
If abnormal, check MRI Spectroscopy
If MRI is abnormal showing a low glutamate/glutamine ratio (sign of capillary hypo perfusion) then patient meets eligibility for Procrit.

Procrit therapy:
Have patient sign consent form. RX: Procrit 8,000 units SQ, Monday and Thursday for 5 doses along with baby ASA. Recheck C4a and monitor D-dimer, hemoglobin, and blood pressure with each dose. Recheck MRI Spectroscopy, which should show Normal G:G, normal lactate, and improvement in 6 executive cognitive functions.

Tenth Step: Correction of TGF-beta1 (transforming growth factor beta 1)
An innate immune cytokine which is also a key marker of illness severity is often elevated in Biotoxin Illness patients. TGF- beta-1 affects autoimmunity through turning on differential gene activation. TGF-Beta 1 turns on Treg cells, which regulate TH1, TH2, TH17 cells. To help Biotoxin Illness patients, not only must the cellular basis of immunity be fixed by increasing low numbers of CD4+CD25++ Treg cells, but the humoral basis of immunity must be improved by lowering the TGF-Beta1.
Reduction is actuated by giving Cozaar (Losartan) up to 25 mg twice a day for 30 days in adults or 0.6-0.7 mg/kg/day divided BID for children. As many adult patients are on multi-therapy for hypertension, care should be given when using this and communication with patient's primary care provider is warranted. Self-monitoring of blood pressure should occur daily, and with the start of symptoms such as orthostasis. As with all other therapies, abnormal labs should be redrawn at the completion of therapy. For those recalcitrant to Cozaar, VIP therapy can also be used at 4 sprays a day.
Elevations of TGF-Beta 1 have been seen in various disorders. HIV and cancer patients, elevated TGF-Beta 1 apparently suppresses protective immune responses. TGF-Beta 1 is elevated in connective tissue disorders. TGF-Beta1 has also been shown to remodel lung tissue by transforming lung cells from smooth muscle cells into thick, tough fibroblasts. High TGF beta-1, as well as low MSH, contribute to gastrointestinal dysfunction. However, digestive function can improve when these immune markers are normalized.

To get an accurate measure of TGF Beta-1, the lab requires using platelet poor plasma. If the result is >40,000 the lab likely mishandled the specimen. If TGF-beta1 is truly high in Biotoxin Illness, it can be an indication that the patient is having a difficult time recovering. Accurate lab testing is important.
<2,380 - Normal
>5,000- Various symptoms seen
>10,000- Restrictive lung disease, tremor, cognitive issues and joint problems

Lab values: CD4+CD25++blood levels quantify Treg cells; if levels are low, then TGFbeta-1 would be expected to be high. While low levels of CD4+CD25++ Tregs alone are not enough to make a Biotoxin illness diagnosis, they can be helpful in measuring how the immune system is responding to treatment. VIP will cause CD4+CD++25Treg levels to increase, but reexposure to biotoxins will cause Tregs to drop again.

Treatments:
If CD4+CD25++Treg cells <4.66% and TGF beta-1 >2,380
Low blood pressure – No
Treat with Cozaar (losartan) 25 mg daily (start with 12.5 mg daily)
(use pediatric dosing if necessary)
Increase Cozaar to 25 mg BID as tolerated
Monitor TGF beta-1 and blood pressure monthly
If low blood pressure
Use VIP 50 mcg intranasal spray
(*Patient must meet criteria to use VIP)

Eleventh step: VIP (vasoactive intestinal peptide)
The final step. By this time, most patients will already have become much better with reduction or resolution of at least 75% of their baseline symptoms. Some will require this last effort. VIP is the crown therapy that must not be misused.
VIP is not appropriate for patients who still have significant exposures or MARCoNS. It won't work. As such, Environmental Relative Moldiness Index (ERMI) of <2 or an updated Health Effects Roster Type Species Mycotoxin and Inflammagen test (HERTSMI-2) not >10 is required to prove lack of exposure.
Patients should have a negative nasal swab and a normalized VCS screen. These document the patient's body has been relatively cleared of toxin, that there is no major exposure and indirectly, that MSH is moving in the right direction (though MSH seems to be the last of the compounds to correct and may need VIP therapy instead, in some cases, to reach normal levels, if possible).
Passing these three tests demonstrates the effectiveness of the previous 10 steps.

VIP is a 28 amino acid regulatory neuropeptide neuroimmune modulator that can down regulate cytokine levels and can have a positive effect on the entire Biotoxin Pathway. VIP has been found to be low in most Biotoxin Illness diagnosed with CIRS-WDB. Watch fasting lipase levels and if patient develops abdominal pain discontinue VIP.

Following criteria must be met before using VIP: Normal V.C.S. , no exposure to ERMI>2 or HERTSMI -2> or= 10, MARCoNS negative on API-Staph nasal culture and normal fasting Lipase levels

If these four criteria are met:

Check for tricuspid regurgitation (pulmonary artery systolic pressure) with a stress echocardiogram prior to starting VIP. PASP should not rise more than 8 mm Hg during exercise. Biotoxin illness patients will often have >8 mm Hg elevation of PASP. Elevated PASP can be a source of palpitations and of dyspnea that is not responsive to beta-2 agonists.

Ordering physicians should request tricuspid regurgitation and do not accept a general impression of a "normal study."

VIP is a human regulatory neuropeptide that is "designated" by the FDA for orphan use. It can be compounded from Hopkins Compounding Pharmacy in Hopkinton, MA.

Treatment:

Provide patient with handout regarding use of VIP

Monitor following labs before VIP replacement: VIP, MSH, C4a, TGF beta-1, MMP-9, VEGF, testosterone, estradiol, CD4+CD25++Tregs and lipase. Get a baseline stress echo to measure PASP (verify it is >8mm Hg). First dose should be administered in office: observe for hyper-acute changes in symptoms, in some cases improvements can be seen within 5 minutes: joint pain, breathing, and cognition may improve. Other things to monitor are blood pressure, signs of rash and other symptoms.

If patients tolerate first dose, continue VIP 50 mcg/ml at four times per day.

Redraw labs after 30 days: C4a, TGF beta-1, and fasting lipase. Watch blood pressure along with a repeat stress echo. VCS should be repeated and an assessment done for dehydration. If elevated lipase or abdominal pain appear, discontinue VIP dose and check gallbladder dysfunction.

If TGF beta-1 and VCS are stable, lipase is normal, and symptoms are improving, then VIP can continue for 30 more days tapering down to twice daily, followed by 30 days, and then discontinue VIP. Continue to check for abdominal pain and check lipase monthly while patients take VIP. Recheck patients at 6 months for stability off of VIP. Some patents have used VIP for up to four years without adverse effects. Patients with multiple chemical sensitivities improved over time. Most chronic fatigue patients have low VIP.

VIP is dispensed in a brown bottle, must be refrigerated in an upright position. If stored correctly and used regularly, it will last up to 90 days.

Patients should blow their nose to remove mucus, dust or debris prior to administration of VIP into the nostrils.

Treating Capillary Hypoperfusion-VO2 Max (post exertional malaise)

With high cytokine levels and often low VEGF levels, Biotoxin patients may have lower threshold for hypoxia than other people. These patients still need to exercise to improve oxygenation to their cells. The key is to have these patients stay below their anaerobic threshold to prevent depletion of glycogen stores.
Perform a cardiopulmonary stress test to determine anaerobic threshold by measuring VO2 max. O2 uptake and CO2 output are measured.
If VO2 max is >35- Normal
<20 Some biotoxin illness patients
12-15 Stage IV CHF

Treatment options to improve Hypoperfusion
Graded exercise that stays below the patient's anaerobic threshold.
Correction of low VEGF
Procrit and VIP- can increase VO2max (protocol in manual)

Extra information:
The HPA (Hypothalamic-piuitary adrenal) axis is an area that can be dysregulated in Biotoxin Illness. Normally the hypothalamus axis is tightly regulated. The peptide hormone known as CRH stimulates the release of ACTH (adrenocorticotropic hormone) from the anterior pituitary gland. ACTH signals cortisol production in the adrenal glands. Sufficient cortisol directly suppresses further release of CRH from the hypothalamus and ACTH from the anterior pituitary gland. Cortisol is normally tightly regulated and released in response to stress. It gives a good reflection of how the neuroendocrine system is working. Cortisol regulation is lost in 50% of patients with low MSH. Early in Biotoxin illness and as patient's improve with treatment, high ACTH and cortisol levels are seen when measured simultaneously.
Early in illness and as MSH begins to fall, high ACTH is associated with few symptoms; a marked increase in symptoms is associated with a fall in ACTH.
Patients who are very ill can have an ACTH and cortisol levels that are also very low.
In early illness or patients who are improving with treatment ACTH and cortisol can be high. If not improving rule out tumor.
Normal regulation: ACTH is high and Cortisol is low

See end of treatment and follow up care in protocol manual