PARK RIDGE
MultiMed

MOLD TOXICITY

or

CHRONIC INFLAMMATORY RESPONSE SYNDROME (CIRS)

Practice Report

When to suspect case of CIRS (biotoxin illness):

1. History and review of systems consistent with biotoxin exposure from mold, Lyme, or other sources. The presence of 8 or more of the symptoms below plus an abnormal VCS sorts biotoxin cases from controls with 98% accuracy.

GENERAL SYMPTOMS	YES	NO
Fatigue		
Weakness		
Aches		
Cramps		
Unusual Pain		
Ice Pick Pain		
Headache		
Light Sensitivity		
Red Eyes		
Blurred Vision		
Tearing		
Sinus		
Cough		
Shortness of Breath		
Abdominal Pain		
Diarrhea		
Joint Pain		
Morning Stiffness		
Skin Sensitivity		
Mood Swings		
Appetite Swings		
Sweats – especially night sweats		
Temperature Regulation		
Excessive Thirst		
Increased Urination		
Static Shocks		
Numbness		
Tingling		
Vertigo		
Metallic Taste		
Tremors		
COGNITIVE SYMPTOMS	**YES**	**NO**
Decreased Recent Memory		
Difficulty With Concentration		
Word-finding Difficulty		
Decreased Assimilation of New Knowledge		
Confusion		
Disorientation in Familiar Places		

2. An abnormal VCS test detects neurotoxicity in optic nerve pathways and correlates with the patient's biotoxic burden. Can be done in some offices or online at survivingmold.com.

    a. In cases where neurotoxicity is present, neurons that detect the smaller bars (high spatial-frequency vision) are functionally impaired, whereas neurons that detect the larger bars (low spatial-frequency vision) are not.
    b. To pass, viewers must see beyond 6 in Row C, beyond 5 in Row D.
    c. VCS usually improves within 1 week on CSM.
    d. Recheck VCS after each targeted treatment phase.
    e. Monitor VSC annually.

3. Check HLA DRB1*DQ*DRB3*4*5 genotype. Look for any of these susceptibility patterns:

	DRB1	DQ	DRB3	DRB4	DRB5
Multisusceptible	4	3		53	
	11/12	3	52B		
	14	5	53B		
Mold	7	2/3		53	
	13	6	52A,B,C		
	17	2	52A		
	18	4	52A		
Lyme	15	6			51
	16	5			51
Dinoflagellates	4	7/8		53	
MARCoNS	11	7	52B		
Low MSH	1	5			
No significance	8	3,4,6			
Low-risk mold	7	9		53	
	12	7	52B		
	9	9		53	

Note: DQ haplotypes susceptible to celiac or gluten intolerance can also suffer from high TGF-beta 1 levels by virtue of their obligate links to CIRS susceptible DRB haplotypes. These DQ-DRB linkages may account for different rates of progression within and between the various types of gluten intolerance and CIRS.

"Objective physiologic measures characterize treatable disease." – R.S.

How to Define CIRS Type and Severity:

1. **Check C3a, C4a, MMP-9, and VEGF.** This measures complement activation and can indicate risk of capillary hypoperfusion.

a. High C3 (>200) suggests Lyme or the presence of other bacterial membranes (usually gram negatives). This causes chronic activation of complement. When protective antibodies fail to form, MASP2 auto-activates C3a (living microbial membranes) or C4a (toxins without membranes needed), perpetuating an innate immune imbalance that raises risk for autoimmune transformation.
b. High C4a suggests mold illness. Normal range = 0-2,830 ng/mL.
c. High C3a or C4a indicates a possible biotoxin-induced problem with antigen detection or presentation.
d. High C4a correlates with capillary hypoperfusion.
e. Low-dose EPO corrects high C4a (8,000 u Mon & Thu, total 5 doses, comes as 40,000 u per vial – use only with informed consent covering precautions).
f. MMP-9 normal range is 85-332 ng/mL.
g. MMP-9 elevation increases endothelial sub-intimal migration of monocytes and macrophages. It is also involved in the tissue remodeling (lungs, heart, vessels, brain, joints) associated with high TGF-beta 1 levels.
h. VEGF reference range is 31-86. VEGF < 31 is low. High levels (>86) represent compensatory change.
i. TGF-beta 1 downregulates VEGF. This can trigger muscle cramps (often from musculo-tendonous junction hypoperfusion), which EPO can override. TGF-beta 1 average level in untreated cases: 6,000 pg/mL; in controls: 1,350; in treated cases: 1,800.
j. Can't tell the proportion of VEGF1 from VEGF2 in current commercial assays.

2. **If patient is sickened by water-damaged buildings (WDB) and C4a is > 4,000, check ERMI.** This index measures the relative moldiness of a building and identifies whether toxin-forming mold species are present.

    a. Use Mycometrics.
    b. Understand the way molds grow depending on dry-wet conditions (*Trichoderma, Wallemia*), middle-wet conditions (Aspergillus *niger, funigatus, ochraceus, penicilloides, versicolor*), and wet-wet conditions (*Stacybotyris, Chaetomium).*
    c. ERMI scores (an index of building toxicity) correlates with SAIIE results.
    d. Avoiding toxic mold exposures is needed to quiet down the innate immune response. Can patients self-heal with exposure avoidance? No. They need treatment to put out inflammation, and re-establish balanced regulation of innate immune functions. If they have mold allergies, they can reduce the irritation and the allergic components of their ongoing symptoms by avoiding mold, but it takes more coordinated treatment plan than mold avoidance to recover from CIRS-WDB.

3. **Check Leptin, MSH, VIP, and ADH/osmolality** if complement activation is present or capillary hypoperfusion is suspected. This panel reflects the

degree of neuropeptide dysregulation related to cytokine interference with leptin receptor signaling.

a. Leptin determines how tightly the body holds onto fatty acids. When high, leptin causes more fatty acids to be stored in adipocytes. The normal range for leptin is 1.1-27.5 ng/mL for females, 0.5-13.8 ng/mL for males.
b. MSH runs low in over 95% of mold patients. Normal range = 35-81 pg/mL.
c. Low MSH results in more more, non-restorative sleep, and inefficient neurohormonal regulation of immune functions, especially immune defenses in the mucous membranes of the respiratory and digestive systems.
d. If MSH <35 and ERMI > 2, get out! If MSH <10 and ERMI > -1, get out!
e. VIP normal range is 23-63 pg/mL. Low levels are associated with heightened inflammation and capillary hypoperfusion.
f. Do not treat with VIP until markers of inflammation are quiet. If mold is an issue, don't use VIP if ERMIs are >1, patient is still failing the VCS test, or MARCoNS is still present in the nose.
g. Low ADH with asymmetric, within-range elevations of osmolality are associated with dehydration, low urine specific gravity, high-mineral sweat, increased thirst and urination, and static shocks. Normal ADH range is 1.0-13.3 ng/mL. Normal osmolaity range is 280-300 mosmol.
h. In some cases, nasally inhaled DDAVP will counter some of the symptoms and imbalances caused by low ADH with inappropriate elevations in osmolality. Use with caution as fluid retention can develop quickly. Most responders get by on 10 mcg nasal inhalations twice daily.

4. **Check for MARCoNS when MSH is <35**. This assesses the risk that a low MSH resulted from its cleavage by hemolysins or exotoxins produced by biofilm-forming, multiply antibiotic-resistant coagulase negative staph. Use the API-staph culture method, as it prevents rapid-growing staph from overtaking the slower-growing coagulase-negative staph.

    a. If MARCoNS +, use Rifampin 300 mg two tabs with morning meal for 30 days with BEG spray, 1-3 sprays each nostril TID after emptying nose first. Repeat culture to prove eradication.
    b. MSH <35 considered low. LabCorp range changed from 35-81 to 0-40. Quest range = 0 to 5 (use LabCorp range)
    c. If MARCoNS present and untreated in presence of low MSH, will see little improvement from CSM alone.
    d. Use dlmlabs.com in Bedford MA for API-Staph cultures (781-275-0855, fax: 781-275-9703).

5. **Check TGF-beta 1**. This growth factor acts as an immune regulator, but in cases of biotoxin illness, chronic elevation leads to the production of pathogenic T cells, decreased T-regs, capillary hypoperfusion, and remodeling of lung, heart, and brain tissue.

a. TGF-beta 1 levels in cases, controls, and treated controls: 6,000; 1,350; 1,800. Normal range < 2,380 ng/mL
b. As a growth factor, TGF-beta 1 regulates immune and tissue cell growth and proliferation.
c. TGF-beta 1 is not immune suppressive if T-reg cells (known by their CD4+/CD25+ cell surface markers) are normal. If T-regs are low, TGF-beta 1 can transform them into becoming pathogenic T-cells in tissues, as happens in CIRS cases. This transformation may depend in part on IL-6. The net result is a positive feedback loop in which more TGF-beta gets produced.
d. This TGF-beta 1-induced conversion of T-regs into pathogenic T cells can be reduced using Losartan at a dose of 25 mg twice daily.
e. Prolonged elevations of TGF-beta 1 levels can create conditions where tissue remodeling and autoimmune transformation become more likely.

6. **Do a pulmonary stress test**. This will measure VO2 max and exercise-induced changes in pulmonary artery pressure.

    a. Specify measurement of tricuspid regurgitation (PAP) before and after exercise. Changes < 8 mmHg are consistent with acquired pulmonary hypertension, capillary hypoperfusion, poor venous return to the left atrium.
    b. Poor exercise-induced variability in PAP correlates with poor tolerance for exertion, and post-exertional malaise.

7. **Follow-up every month to track responses to treatment.** The standard treatment plan follows this basic outline:

REVIEW:

    a. **History** with thorough review of systems, symptom survey.
    b. **VCS** test.
    c. **HLA DRB-DQ**, **C3a, C4a, MMP-9, VEGF**
        i. If C3a high, suspect Lyme.
        ii. If C4a high, check ERMI.
        iii. If MMP-9, VEGF low or high, check leptin and neuropeptides.
    d. **ERMI** testing in suspected WDBs to which patient is regularly exposed.
    e. **Leptin, MSH, VIP, ADH/osm, and TGF-beta 1**.
        i. If > 1, *must* test MSH/leptin resistance/neuropeptide regulation.
        ii. If MSH < 35, ERMI must be < 2. If MSH <10, ERMI must be <-1.
        iii. If VIP low, correct MSH.
        iv. If ADH is low to low-normal and osmolality is high or high-normal, consider DDAVP.
        v. If TGF-beta 1 is high, innate immune system imbalance is well-established.
    f. **Deep nasal** culture for MARCoNS if MSH < 35.

i. Rifampin 300 mg (two) with breakfast + BEG 1-2 sprays each nostril TID for 30 days.
ii. Wait 2 weeks to repeat culture after end of course.

g. **Treat with CSM.** *Must be on an amylose-free diet! (No wheat rye, barley, rice, potatoes, bananas, or root vegetables – the amylose will occupy CSM binding sites and make toxin adsorption less effective).*
i. Target dose = 4 gms (1 packet) 1 hour after meds and ½ hour before meals and at bedtime followed by 8 to 12 oz. of water. Can start with less and work up to full QID dosing over a few days.
ii. Monitor for GI intolerance (gas, bloating, constipation). Correct with Miralax or other non-stimulant constipation relievers.
iii. If Lyme suspected, suppress inflammatory cytokine activity using Actos 15 mg TID for 10 days (begin CSM on day 8).
iv. Monitor for symptom intensification (more likely in Lyme cases due to the lower dissociation constant between cell membranes and Borrelia ionophore toxins).

ADDITIONAL CONSIDERATIONS:

1. If TGF-beta 1 is high, check anti-gliadin antibodies (IgG, IgA) and anti-cardiolipin IgM, as these autoimmune markers are frequently present and warrant concurrent treatment with a gluten-free diet and anti-coagulation therapy, respectively.
2. If bleeding abnormalities exist check Quest Diagnostics' vonWillebrand profile near a bleeding episode. If abnormal (low Factor 8 or ristocetin), use of DDAVP can help control excess bleeding.
3. Check PAI-1 if concerned about coagulation issues, especially in diabetics.
4. Repeat VCS and other abnormal biomarkers when symptoms first subside or at periodic (1 to 2 month) intervals while on CSM/amylose-free diet, DDAVP, EPO.
5. If inflammation markers persist despite 3 to 6 months of adherence to the protocol and TGF-beta 1 is not declining, add Losartan 25 mg BID to reduce conversion of CD4+CD25 cells into pathogenic T cells.
6. If inflammation markers and symptoms are quiet except for persistent signs of capillary hypoperfusion, can add nasally inhaled VIP through Hopkinton Drug. Must be able to show normal VCS, absence of MARCoNS, and, if applicable, ERMI results <2.