Mold Toxicity

A Chronic Inflammatory Response Syndrome

Keith Berndtson, MD
Chronic Inflammatory Response Syndrome:
CIRS is the adopted name that refers to the underlying pathophysiology of an increasingly well understood multi-symptom, multi-system illness.

Other Names for CIRS:

• **Biotoxin Illness**
  Refers to the currently understood common denominator cause: toxins made by living things.

• **Mold Toxicity Syndrome**
  Underplays the importance of inflammagens that combine with mold toxins to create indoor air capable of making susceptible people chronically ill. Sometimes called toxic mold sickness.

• **CIRS-WDB**
  The mold-driven version of CIRS associated with.

Data suggest that 80 percent of human biotoxin illness is driven by indoor air contaminated with mold toxins and other inflammagens.

Ritchie Shoemaker, MD

• First to link a toxin produced by *Pfiesteria* to the Mid-Atlantic outbreaks of human illness in the late 1990s. (1)

• First to determine that most cases of biotoxin illness are due to toxins produced by certain molds known to grow in water-damaged buildings. (2)

• First to clarify the underlying pathophysiology of biotoxin illness and to develop a stepwise protocol to treat it. (3)


Stachybotrys: nature’s solution to the human problem?

- Perhaps the most toxic mold of them all.
- Requires sustained moisture.
- Makes tricothecene toxins:
  - T2 toxin
  - Satratoxin H
- T2 toxin allegedly added to the chemical weapon known as yellow rain (this is disputed).
- Stachy toxins often found in heavily water-damaged buildings.

Stachybotrys chartarum
Copyright Dennis Kunkel / print available thru Astrographics.com
Trichotheecenes: how toxic are they?

**Mechanisms of toxicity**

- Cell-cycle arrest
- Mitosis disruption
- Protein synthesis inhibition
- Oxidative cell stress with DNA damage
- Cell membrane disruption and permeability
- Immunostimulatory and immunosuppressive
- Induction of apoptosis and programmed cell death
- Increased expression of inflammatory and apoptotic mRNAs
- Ribotoxic stress response producing MAPK induction of cytokine release
- Endoplasmic reticulum stress with protein misfolding and blocked unfolding

*Toxicology Letters, 217(2):149-158.*

Deoxynivalinol (DON) is ingested with wheat contaminated by *Fusarium* mold species.
Tricothecenes: brain damage anyone?

Satratoxin H (SH) causes a leaky blood-brain barrier. (1) BBB changes naturally vary depending on the nature of the situation. (2) A mouse experimental allergic encephalitis (EAE) model studied the effects of tricothecenes on neuroinflammation. Can SH cause brain interstitial microedema?

- SH disrupts brain endothelial cells and the integrity of the blood-brain barrier.
- SH induces an initial anti-inflammatory response from astrocytes. Chronic exposure results in local oxidative stress and neuronal apoptosis like that seen in lupus, multiple sclerosis, and Alzheimer’s disease.
- Results suggest that a chronic immune response to inhaled SH could produce neuronal hypersensitivity and damage, which could be additive with exposure to other airborne toxins or inflammagens.

Modern SBS began after the 1973 OPEC oil embargo prompted builders to seal the indoor environment off from the outdoors as a way to reduce energy consumption.

This allowed even minor flooding or leaks to foster indoor fungal growth giving rise to new combinations of toxin-producing indoor molds.

Molds release toxin-laden spores in response to contact with inflammatory man-made building chemicals. Inflammmagens from gram-negative bacteria and mycobacteria can add to the toxic mix.

The mold/bacterial/chemical mix can induce a chronic multi-symptom illness in people who are genetically susceptible to poor toxin clearance.
<table>
<thead>
<tr>
<th>Mold species</th>
<th>Toxin types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus penicilloides</td>
<td>aflatoxin, ochratoxin</td>
</tr>
<tr>
<td>Aspergillus versicolor</td>
<td>chaetosin</td>
</tr>
<tr>
<td>Chaetomium globosum</td>
<td>deoxynivalinol, T2 toxin</td>
</tr>
<tr>
<td>Penicillium corylophilum</td>
<td>gliotoxin</td>
</tr>
<tr>
<td>Stachybotrys chartarum</td>
<td>T2 toxin, satratoxin H</td>
</tr>
<tr>
<td>Trichoderma viride</td>
<td>T2 toxin, DAS</td>
</tr>
<tr>
<td>Wallemia sebi</td>
<td>walleminol</td>
</tr>
</tbody>
</table>

- **Aspergillus versicolor**
- **Chaetomium globosum**
- **Penicillium corylophilum**
- **Trichoderma viride**
- **Wallemia sebi**
Toxic Bioaerosol Dispersal

- Mold toxins are undetectable with conventional sampling methods due to their unusually small size (0.001 to 0.005 microns).
- Less than 2% of mold toxins are attached to mold spores (10 to 30 microns). The remainder are attached to fungal fragments or exist as free-floating particles. Like other aerosol particles, they are dispersed by vibration and air turbulence.
- Aerosolized mold toxins mixed with volatile organic compounds are major threats to indoor air quality and this warrants collaborative research. (1,2)

2. Indoor mold: better coordination of research on health effects and more consistent guidance would improve federal efforts. United States Government Accountability Office; 2008:1–60.
Toxin-Inflammmagen Synergism in the Air of Water Damaged Buildings

- Mold toxins
- Volatile organic compounds
- Actinomycetes
- Endotoxins

Homes
Schools
Offices
Other buildings
The Environmental Relative Moldiness Index Test (ERMI)

Recovery from mold toxicity syndrome is likely only if routinely visited building structures (home, office, and/or school) manifest ERMI scores less than 2 on a scale from -10 to 20. The ERMI test is currently the only mold inspection method with predictive value concerning clinical recovery.

ERMI does not account for non-mold inflammagens including VOCs, endotoxins, actinomycetes, glucans, glycoproteins, and other noxious incitants.
<table>
<thead>
<tr>
<th>Fungal ID \ Sample ID</th>
<th>EC1261 Basement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus flavus/orage</td>
<td>4</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>28</td>
</tr>
<tr>
<td>Aspergillus niger</td>
<td>26</td>
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<tr>
<td>Aspergillus ochraceus</td>
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<tr>
<td>Aspergillus penicilloides</td>
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<tr>
<td>Aspergillus restrictus*</td>
<td>63</td>
</tr>
<tr>
<td>Aspergillus sclerotium</td>
<td>21</td>
</tr>
<tr>
<td>Aspergillus sydowii</td>
<td>27</td>
</tr>
<tr>
<td>Aspergillus unguis</td>
<td>9</td>
</tr>
<tr>
<td>Aspergillus versicolor</td>
<td>680</td>
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<tr>
<td>Aureobasidium pullulans</td>
<td>130</td>
</tr>
<tr>
<td>Chaetomium globosum</td>
<td>97</td>
</tr>
<tr>
<td>Cladosporium sphaerospermum</td>
<td>170</td>
</tr>
<tr>
<td>Eurotium (Asp.) amstelodami*</td>
<td>830</td>
</tr>
<tr>
<td>Paeonilomyces variotti</td>
<td>7</td>
</tr>
<tr>
<td>Penicillium brevicompactum</td>
<td>53</td>
</tr>
<tr>
<td>Penicillium coryneum</td>
<td>260</td>
</tr>
<tr>
<td>Penicillium crustosum*</td>
<td>5</td>
</tr>
<tr>
<td>Penicillium purpurogenum</td>
<td>4</td>
</tr>
<tr>
<td>Penicillium spinulosum*</td>
<td>1</td>
</tr>
<tr>
<td>Penicillium variabile</td>
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<tr>
<td>Epicoccum fischeri/flavum</td>
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<tr>
<td>Cladosporium cladosporioides 1</td>
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<tr>
<td>Cladosporium cladosporioides 2</td>
<td>73</td>
</tr>
<tr>
<td>Cladosporium herbarum</td>
<td>200</td>
</tr>
<tr>
<td>Epicoccum nigrum</td>
<td>1600</td>
</tr>
<tr>
<td>Mucor amphiborum*</td>
<td>8</td>
</tr>
<tr>
<td>Penicillium chrysogenum</td>
<td>52</td>
</tr>
<tr>
<td>Botrytis stolonifer</td>
<td>20</td>
</tr>
</tbody>
</table>

**ERMI score: 25.58**

- Aspergillus penicilloides = 33,000 (10)
- Aspergillus versicolor = 680 (10)
- Chaetomium globosum = 97 (6)
- Stachybotrys chartarum = 51 (6)
- Wallemia sebi = 2,100 (6)

(HERTSMI-2 score: 38)

**Get out ASAP!**
Case Criteria for a Diagnosis of Mold Toxicity Syndrome

1. Multiple unexplained or non-responsive symptoms.
2. Evidence for HLA genetic susceptibility.
3. Evidence for the documented pattern of abnormal findings seen in exposed HLA-susceptible patients.

- Patient presents with multi-symptom, multi-system illness.
- Past history of exposure to a water damaged building (optional).
- Failed visual contrast sensitivity testing (8% false negative).
- Current ERMI Score >2 in home, office, and/or school.
- Markers for HLA genetic susceptibility (see Rosetta Stone).
- Pattern of abnormal findings seen in biotoxin illness.
Visual Contrast Sensitivity Testing

Most biotoxins are neurotoxic. The optic nerve’s superolateral rim carries the fibers responsible for edge-detection needed for visual contrast sensitivity (VCS). For vascular supply reasons, this rim is more vulnerable to neurotoxic effects. Neurotoxicity thus causes a decrease in VCS that self-corrects with a sufficient reduction in toxin carriage. Age-related decreases in VCS are not reversible, or so it is assumed.

Biotoxin illness: reversible

Age-related: irreversible?
Who gets sick: HLA susceptibility to poor clearance of biotoxins.

The **Rosetta Stone** for interpreting HLA nomenclature in biotoxin illness:

<table>
<thead>
<tr>
<th>DRB1</th>
<th>DQB1</th>
<th>DRB3</th>
<th>DRB4</th>
<th>DRB5</th>
</tr>
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<tbody>
<tr>
<td>4</td>
<td>3</td>
<td></td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>11/12</td>
<td>3</td>
<td>52B</td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>14</td>
<td>5</td>
<td>53B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2/3</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>6</td>
<td>52A,B,C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>2/3</td>
<td>52A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>4</td>
<td>52A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>6</td>
<td></td>
<td>51</td>
<td></td>
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<td>16</td>
<td>5</td>
<td></td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>52B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HLA haplotypes in each row are associated with at least twice the risk of treatable biotoxin clearance susceptibility problems compared to controls.**

Genes Load the Gun...

- Specific haplotypes affect susceptibility to poor clearance of biotoxins.
- More research needed to clarify relative risks of the homozygous 8-4 haplotype.

Exposures Pull the Trigger.

- Biotoxin exposures call out the genetic vulnerability to poor clearance.
- Molds, blue-green algae, and dinoflagellates are the main sources of biotoxin exposure.
# Key Biomarker Abnormalities in Mold Toxicity Syndrome

<table>
<thead>
<tr>
<th><strong>Biomarkers</strong></th>
<th><strong>Physiology</strong></th>
<th><strong>What it Means</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>High C4a, Low C3a</td>
<td>Innate immune system in overdrive due to toxins</td>
<td>A biotoxin burden is present.</td>
</tr>
<tr>
<td>High MMP-9</td>
<td>Tissue barrier disruption and remodeling</td>
<td>Neuroimmune stress and/or injury is likely.</td>
</tr>
<tr>
<td>High TGF beta-1</td>
<td>Immune suppression + activates Th17-driven inflammation</td>
<td>Imbalanced innate-adaptive immune response is likely.</td>
</tr>
<tr>
<td>Low MSH</td>
<td>Disrupted neuropeptide regulation of immune function</td>
<td>Impaired tissue-based immune defenses.</td>
</tr>
<tr>
<td>Low ADH</td>
<td>Dysregulation of ACTH and kidney water conservation</td>
<td>Impaired stress response, chronic dehydration.</td>
</tr>
<tr>
<td>Low or High VEGF</td>
<td>Chronic tissue hypoxia</td>
<td>Imbalanced response to capillary hypo-perfusion.</td>
</tr>
<tr>
<td>Low VIP</td>
<td>Poorly controlled inflammation and blood flow</td>
<td>Impaired regulation of multiple functions.</td>
</tr>
<tr>
<td>Low Treg cells</td>
<td>Poorly suppressed inflammation</td>
<td>Chronic inflammatory response syndrome.</td>
</tr>
</tbody>
</table>
High C4a, Low C3a
Zhou W. The new face of anaphylatoxins in immune regulation. *Immunobiology*. 2012;217(2):225-34 (C3a up-regulates Th2-driven antibody responses to foreign particles. We await more research into C4a-specific effects on the activation or inhibition of Th1, Th2, Th17, and/or T reg cell activities).

High MMP-9

High TGF beta-1

Low MSH

Low ADH

Low or High VEGF
Mayer G. Capillary rarefaction, hypoxia, VEGF, and angiogenesis in chronic renal disease. *Nephrology, Dialysis, and Transplantation*. 2011;26(4):1132-7 (If VEGF-induced hypoxia counter-regulatory factors can exert beneficial or harmful effects in chronic kidney disease, they likely do so in other tissues as well).

Low VIP

Low T reg cells
CIRS Reduces Levels of Key Regulatory Neuropeptides

**Adrenocorticotropic hormone (ACTH)**
Pituitary ACTH induces release of cortisol. Low levels reduce inflammation control and stress resilience.

**Alpha melanocyte stimulating hormone (MSH)**
Pituitary MSH coordinates mucous membrane-based immune defenses. Low levels may result in leaky barriers, low ADH, and chronic membrane inflammation.

**Anti-diuretic hormone (ADH)**
Hypothalamic ADH induces kidneys to conserve water. Low levels result in dehydration and osmolality changes that aggravate inflammation.

**Vasoactive intestinal polypeptide (VIP)**
Down-regulates Th1 responses, up-regulates tolerogenic dendritic cells and antigen-specific Treg cells, and improves microcirculatory blood flow.
Multidrug Resistant Coagulase Negative Staph (MRCoNS)

Long-considered non-pathogenic for lacking an enzyme that coagulates plasma, coagulase-negative staph (CoNS) are now considered pathogens for other reasons, including:

- **Their ability to participate in biofilm communities** that host a range of other bacteria and that may also include fungal and protozoal species.
- **Their ability to differentially active gene expression.**
- **Their ability to make and release hemolysins** - pore-forming toxins that can disrupt cell membranes.
- **Their ability to make and release exotoxins** that interfere with host immune defenses that can incapacitate MSH.
- **Their ability to develop multidrug resistance** (MRCoNS).

If MSH is low, obtain deep nasal culture for MRCoNS!


Rapidly Changing Markers of Biotoxin Exposure

Based on Re-exposure Trials

<table>
<thead>
<tr>
<th></th>
<th>day 1</th>
<th>day 2</th>
<th>day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4a</td>
<td>rises</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGFb1</td>
<td>rises</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td>rises</td>
<td></td>
<td>falls</td>
</tr>
<tr>
<td>Leptin</td>
<td></td>
<td>rises</td>
<td></td>
</tr>
<tr>
<td>MMP-9</td>
<td></td>
<td></td>
<td>rises</td>
</tr>
</tbody>
</table>

This 3-day Sequential Activation of Innate Immune Elements (SAIIE) panel is a CIRS health index that answers the question, “Did the building cause the patient’s symptoms and abnormal biomarkers?” Results correlate well with ERMI results. As a test, SAIIE must be done in the genetically susceptible who achieved a healthy baseline by toxic mold avoidance and use of cholestyramine or welchol.

Shoemaker R, House D. Sick building syndrome (SBS) and exposure to water-damaged buildings: Time series study, clinical trial and mechanisms. Neurotoxicology and Teratology 2006; 573-588.
## Interpreting C4a Levels

<table>
<thead>
<tr>
<th>Level</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,380-5,000</td>
<td>concerning</td>
</tr>
<tr>
<td>5,000-10,000</td>
<td>worrisome</td>
</tr>
<tr>
<td>&gt;10,000</td>
<td>needs prompt reduction</td>
</tr>
<tr>
<td>&gt;20,000</td>
<td>indicates repeated exposures, “sicker, quicker” sensitivity, MASP1 + MASP2 activation</td>
</tr>
</tbody>
</table>

Shoemaker R, House D. Sick building syndrome (SBS) and exposure to water-damaged buildings: Time series study, clinical trial and mechanisms. Neurotoxicology and Teratology 2006; 573-588.
The Roles of C3a and C4a in Host Defenses

The lectin pathway of the complement system serves as a first line of defense against microbial intruders. The innate immune system recognizes danger signals presented by the pathogens (pathogen-associated molecular patterns) or altered host cells (damage-associated molecular patterns) by means of germline encoded cell-surface bound or soluble pattern recognition molecules. These pattern recognition molecules have evolved against evolutionarily conserved structures of microorganisms, such as carbohydrates and acetylated compounds.

The pattern recognition molecules do not act alone - they are associated with other proteins, mainly serine proteases. These serine proteases (MBL-Associated Serine Proteases), or MASPs, become activated to initiate the complement cascade when the recognition molecules bind to their target. Activation of the complement cascade culminates in the destruction and elimination of pathogens or dangerous molecules via direct cell lysis or opsonization, respectively.

C3a and C4a are anaphylatoxins. C3a reacts to bacterial membrane molecules. C4a reacts to biotoxins. Lyme disease can raise C3a and C4a levels. CIRS-WDB raises C4a and tends to lower C3a levels.

How MASP-1 and MASP-2 are activated by the Mannose Binding Lectin (MBL)-Associated Complement Pathway

The dual regulatory roles of TGF beta-1

**Pro-inflammatory Th17 cells vs. Anti-inflammatory Treg cells**

Activated Th17 cells supply their own TGFb1 to help maintain their pro-inflammatory posture in antigen-challenged tissues like mucous membranes. T reg cell-derived TGFb1 helps maintain the immune suppressing action of T reg cells in the body’s periphery.

Th17 cells secrete cytokines IL-17, IL-21, and IL-22, shown to be more active in autoimmune and inflammatory disease.

T reg cells delete autoreactive T cells, induce tolerance, and dampen inflammation. Natural T regs are thymus-derived. Inducible T regs are present in the periphery. TGFb1 recruits both types.

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Physical Effects of High C4a Levels

C4a reduces capillary perfusion, producing the following well-documented pathophysiological effects:

• Reduces VO2 Max and thus lowers anaerobic threshold.
• Lowers ratio of glutamate/glutamine (G/G) as measured by magnetic resonance spectroscopy (MRS).
• Raises lactate as measured by magnetic resonance spectroscopy.

Neuronal cells synthesize glutamate from glutamine. Glutamate is a substrate for the neuronal TCA cycle. Thus, in addition to its excitatory neurotransmitter role, glutamate is involved in neuronal energy production. A reduced glutamate/glutamine ratio indicates capillary hypoperfusion, reduced neuronal energy, loss of glutaminergic excitatory activity, and possibly micro-interstitial edema in the brain. Correction of C4a levels correlates with improved VO2 max, MRS G/G ratio, MRS lactate, and with improvements in cognitive function, tolerance for exertion, and other symptoms associated with CIRS.


The role of C4a in Coagulation

In a diagnostic re-exposure trial, Ristocetin-associated factor, von Willebrand’s (vW) antigen, and multimers of von Willebrand’s antigen all fell by day 3.

In cases where vW factors initially rose, they included factor VIII, von Willebrand’s antigen, and ristocetin-associated factor.

Rising levels of C4a prevent the formation of the fibrin multimers that are needed to form the scaffolding for proper blood clotting. Without these multimers, mucosal bleeding becomes more likely.

The drug desmopressin (also known as DDAVP) helps correct the bleeding problem by enhancing the ability of fibrin monomers to form multimers.
Biotoxin Illness is a Cause of Pulmonary Hypertension.  
Vasoactive Intestinal Polypeptide can Reverse It.

**The pathophysiology of PAH:**
Proliferation of pulmonary vascular endothelium resulting in elevation of right heart pressures and peripheral hypoxemia.

**Non-invasive diagnosis of PAH:**
Stress echo with calculation of right atrial pressure pre- and post-exertion:

\[(\text{tricuspid regurg}) \times 4 + \text{right atrial pressure}\]

**Treatment of CIRS-PAH with VIP:**
Nasally inhaled VIP, 4-6 times daily to reduce TGFb1-induced airway remodeling.

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Stepwise Treatment Protocol for CIRS

Early Steps
- Treat with cholestyramine or welchol
- Eradicate multidrug resistant CoNS
- Treat with cholestyramine or welchol
- Remove from ongoing mold toxin exposure

Middle Steps
- Correct anti-gliadin antibodies
- Correct MMP-9
- Correct ADH/osmolality
- Normalize androgen levels
- Correct VEGF
- Correct C4a
- TGFb1
- VIP

Final Steps
Early Treatment Steps for CIRS

Remove from ongoing mold exposure or the deal’s off

The first step is often the most difficult because recovery is not possible without strict avoidance of exposure to toxic molds. To get well one must produce toxin egress while stopping toxin ingress.
Early Treatment Steps for CIRS

Treat with cholestyramine (CSM) or Welchol

Patients must adhere to detailed guidelines in order to obtain the best possible results. Should be monitored by a physician with experience in the treatment of chronic inflammatory response syndrome.

Shoemaker R, House D. Sick building syndrome (SBS) and exposure to water-damaged buildings: Time series study, clinical trial and mechanisms. Neurotoxicology and Teratology 2006; 573-588.
Early Treatment Steps for CIRS

Test for MRCoNS and eradicate its presence

MRCoNS and other biofilm-associated microbes in the deep nasal space cause various troubles for the immune system and the brain.

Early Treatment Steps for CIRS

Hasten binder-mediated toxin clearance with a gluten-free, amylose-free diet

Strict adherence to dietary guidelines leaves more bus seats open for clearance of toxins. The Welchol bus is slower and smaller than the CSM bus but it’s more user friendly.
Early Treatment Steps for CIRS

Androgen levels tend to self-correct with toxin clearance.

If estradiol is high an aromatase inhibitor may be indicated. Testosterone replacement causes more problems than it solves.
Mid-Treatment Steps for CIRS

If ADH rise lags, consider additional measures.

- Replete minerals when osmolality is low.
- Use DDAVP (desmopressin) only with close physician supervision.

Drinking more water doesn’t work because the kidneys aren’t able to conserve water when the ADH level is low.

Dehydration alters blood viscosity, the delivery of oxygen and nutrition to cells, and tolerance for exertion.
Mid-Treatment Steps for CIRS
If MMP-9 fall lags, consider additional causes for elevation.

Interacting MMPs and TIMPs* released by varied cell types in a Breast Ca tumor nodule.

MMPs and TIMPs engage in ongoing skirmishes in tissue inflammation zones.

MMP-9 is a gelatinase involved in collagen breakdown and tissue remodeling processes. If high despite reduced toxin carriage, consider the possibility of infectious, autoimmune, or neoplastic disease. VIP may succeed in lowering MMP-9.

Mid-Treatment Steps for CIRS

If VEGF or C4a correction lags, consider other drivers for abnormal levels.

Lyme disease and lupus can elevate C4a levels. VEGF can remain high or low despite treatment when there are separate causes for capillary hypoperfusion.


Final Treatment Steps for CIRS

If TGFβ1 remains high or if symptoms persist despite normal VCS, clean ERMI, and (-) MRCoNS, treat with nasal VIP.

Vasoactive Intestinal Peptide (VIP) is a neuropeptide, expressed by lymphoid as well as neural cells, which has diverse effects on the cellular mediators of inflammation and immunity and is also a potent neurotransmitter. As a neurotransmitter, VIP exerts a potent bronchodilatory and vasodilatory effect and also induces the house-keeping of mucus secreted by submucosal glands. It has immunomodulatory functions which include humoral immune response suppression and inhibition of vascular and bronchial remodeling.

Benefits and Side Effects of VIP

**Beneficial Effects of VIP**
- lowers high C4a
- lowers high TGFβ1
- raises low VEGF
- lowers high VEGF
- lowers high MMP-9
- raises low vitamin D3
- lowers high vitamin D3
- raises thymus-derived and induced T reg cells
- reduces reactivity to WDB

**Potential Side Effects of VIP**
- may raise lipase levels
- may cause stomach or abdominal discomfort by reducing gastric hydrochloric acid secretion
- may cause excessively low blood pressure (is a vasodilator)
- may cause a rash

For use only with physician supervision. Stop use of VIP if lipase rises or if abdominal pain, hypotension, or rash occur(s).
How CIRS-WDB results in a multisymptom, multisystem illness *made worse* by usual medical care:

Mold toxins and inflammagens from sick indoor air trigger MBL-related MASP activation in the genetically susceptible, raising C4a, TGFb1, Leptin, and MMP-9 levels, producing a variety of symptoms.

Inflammatory cytokines disrupt the balance of regulatory neuropeptides, producing more symptoms. TGFb1 goes higher to suppress immune up-regulation, but balance may shift from T reg cells to pathogenic Th17 cells, producing more inflammation, making symptoms worse.

Patients present with a multisymptom, multisystem illness that persists despite “excellent” medical care from various specialists, at great expense. They have been told that there is nothing wrong, that “all is explained” by depression, that they need to get a life or exercise more. Some are discharged from care for being “chronic complainers” or “high maintenance.” Meanwhile, even the most well-intentioned specialists are guaranteed to keep missing the data they’re not looking for.

*This needs to stop.*
Estimated scope of the CIRS-WDB problem:

US population: 315 million
One in four = 80 million at risk for CIRS-WDB

NIOSH estimate of percent of US buildings with water damage: 50% = 40 million exposed to WDB

Conservative estimate of percent harboring toxic molds: 10% = 4 million with CIRS-WDB

That’s 40 Michigan Wolverine football stadiums filled with 100,000 people needlessly suffering from lack of access to competent medical care.

Access to competent medical care for people with CIRS-WDB needs to be a national health care priority.

Thomas G, Burton NC, Mueller C, Page E. Comparison of mold exposures, work-related symptoms, and visual contrast sensitivity between employees at a severely water-damaged school and employees at a school without significant water damage. CDC Workplace Safety and Health: Health Hazard Evaluation Report. 2010.
Calling all health care professionals!

Climb the CIRS-WDB learning curve with the resources below:

All of the above available for purchase through:

www.survivingmold.com
Patient-centered systems medicine.