Australian
Chronic Infectious &
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Society

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Submission for Inquiry into Biotoxin-related Illnesses in Australia

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The Australian Chronic Infectious & Inflammatory Disease Society (ACIIDS) is a group of registered medical practitioners with a special interest in chronic disease of infectious or inflammatory origin. It is registered as a public company limited by guarantee in New South Wales. Biotoxin-related illness is one of the specific interest areas of the group. The group has approximately 40 members, and is growing.

The primary biotoxin-related condition we will be focusing on is Chronic Inflammatory Response Syndrome (CIRS), which is defined as a multi-system inflammatory response to exposure to biotoxins, in genetically susceptible individuals. The term has been coined and patented by a research team including Ritchie Shoemaker MD, Scott McMahon MD and James Ryan PhD in the United States. There is a growing body of literature on this condition, and biotoxin-related illnesses in general, which we will refer to in this submission[i].

One of the reasons recognition of this condition is considered vitally important by our group is that it not only appears to be extremely common but also has a clearly defined physiology and treatment protocol. Many other chronic diseases characterised primarily by fatigue

tend to be diagnosed primarily by symptoms and signs, but do not have a clearly defined physiology basis, nor clear biomarkers by which to diagnose and track progress on the way to recovery.[ii] The fact that inflammation is at the heart of CIRS is no surprise. The medical literature has been finding an expanding role for inflammation at the centre of a multitude of medical conditions.[iii]

The terms of reference will be addressed one-by-one in this submission starting below.

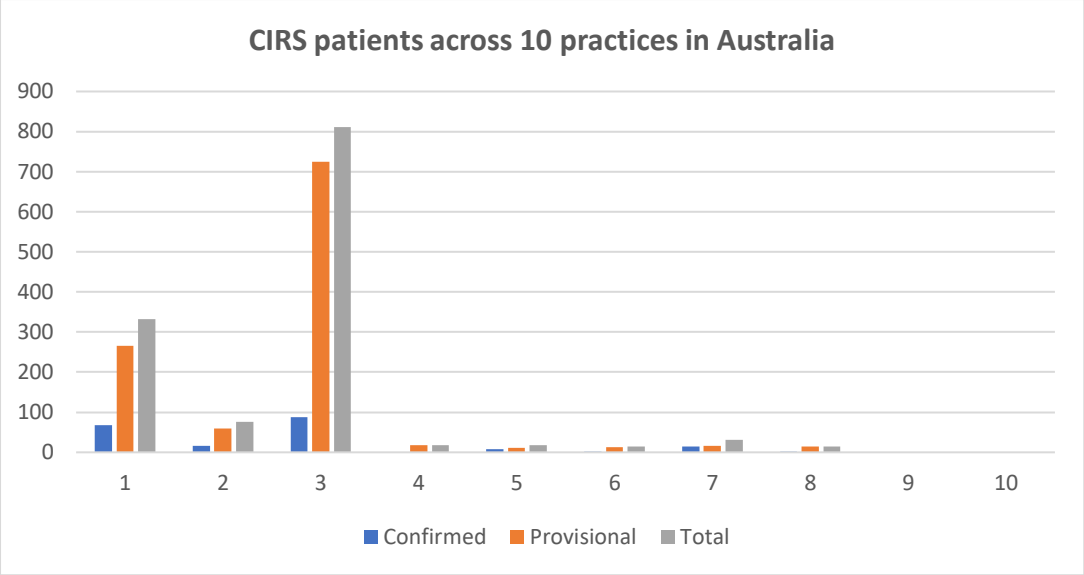
1. *The prevalence and geographic distribution of biotoxin-related illnesses in Australia, particularly related to water-damaged buildings;*

We addressed this question by identifying 30 medical practitioners in Australia who are known to be familiar with CIRS, and who are known or suspected to diagnose and treat the condition. We asked these medical practitioners to search their medical software for the following condition terms:

a. Chronic Inflammatory Response Syndrome
b. CIRS
c. Biotoxin-related illness
d. Mould illness

Out of the patients identified by this search, the doctors were asked to identify whether these patients were diagnosed “provisionally” (i.e. based on clinical history and examination only, including visual contrast sensitivity and cluster analysis testing) or “formally” which generally implied the procurement of the specific diagnostic markers through the approved USA laboratories, as will be discussed later in the submission. Some doctors had to rely on memory in addition to the above search terms, or to search the results from formal diagnostic testing to identify cases.

Due to the short time scale and busy schedule of these doctors, we received responses accounting for eleven medical practitioners distributed in 10 practices, the answers to which are charted below:



The total numbers were 1172 “provisionally diagnosed” cases and 195 “formally diagnosed” cases.

The vast majority of cases were from Dr Janet Kim at N Plus Clinic in Chatswood, NSW and Dr Sandeep Gupta at Lotus Holistic Medicine in Maroochydore, QLD .

The geographic distribution is listed in the following table:

Pratice #	**Patient Distribution**							
	QLD	**NSW**	**VIC**	**WA**	**NT**	**SA**	**TAS**	**Unknown**
1	176	79	33	10	3	3	1	
2			76					
3		812						
4								
5		17						1
6								
7			29	1	1			
8								
TOTAL	176	908	138	11	4	3	1	1

The above table documents the number of definite diagnosed cases which can be identified, however it is very clear that this is a vast underestimate of the prevalence, due to the following reasons:

a. Other than three general practitioners (Drs Gupta, Ash and Westaway) who were early signers to the physician training by Dr Shoemaker, medical practitioners have only been aware of this condition since 2015. Only a small number of medical practitioners (predominantly Drs Gupta and Kim) have been regularly utilising the formal diagnostic biomarkers to diagnose people with this condition. This testing is currently out of reach for the vast majority of the Australian population for the reasons documented in section #3.
b. Often cases of CIRS are misdiagnosed with the following conditions: chronic fatigue syndrome (CFS), fibromyalgia, multiple sclerosis, major depression, stress, allergy, post-traumatic stress disorder (PTSD), somatic symptom disorder (SSD), irritable bowel syndrome (IBS) and attention-deficit hyperactivity disorder (ADHD).[iv] In many cases even the CIRS-trained physicians may document the diagnosis as being another diagnosis due to the fact that these diagnoses have been accepted by the treating medical team of the patient, and are more likely acceptable to medical review boards.
c. Many CIRS-affected patients are unable to afford to see a doctor with specialised knowledge of biotoxin-illness as they are only in certain cities of Australia (such as in Sydney, Melbourne and the Sunshine Coast, QLD). Moreover these doctors generally only offer private billing (with a partial Medicare rebate), due to the long and complex nature of consultations on CIRS patients. Not all patients can afford the gap fees. Furthermore the testing and treatment for CIRS are largely out-of-pocket expenses due to the fact that the condition is currently not formally recognised in Australia. Formal recognition will greatly assist this situation.
d. The condition can be subtle and mimic other conditions, such as major depression, chronic fatigue syndrome or fibromyalgia, and can also co-exist with psychiatric conditions such as major depression or post-traumatic stress disorder (PTSD). It is possible that some CIRS patients develop secondary psychiatric conditions as a result of the trauma involved with having to leave their homes, lose significant portions of their financial savings, and in some cases (which have been documented in cases by various ACIIDS members) being left destitute and homeless. This has led to a degree of discrimination and stigma associated with this condition, as referred to in many of the patient submissions to this inquiry. This may occur due to the recognition of the secondary psychiatric illness but not the primary medical condition by medical practitioners in Australia.
e. At least two medical practitioners have endured a notification to the Australian Health Practitioners Regulatory Authority (AHPRA) for treating cases of CIRS with cholestyramine, or ordering diagnostic tests for this condition, and have had to reduce the number of cases of CIRS they treat or totally cease seeing patients with CIRS as a result. This is an extremely difficult situation as if doctors continue to face discrimination for treating this condition, others may be reluctant to start treating it, leading to less and less availability of medical practitioners for having this condition treated.

2. *The prevalence of Chronic Inflammatory Response Syndrome (CIRS) or biotoxin-related illness in Australian patients and the treatment available to them;*

It is highly likely that the prevalence of chronic inflammatory response syndrome (CIRS) and other biotoxin-related illnesses in Australian general practice patients is very high. However there are currently no definite statistics on this prevalence.

Scott McMahon MD, a member of the CIRS research team, documented a prevalence of 7.01% of CIRS in a general paediatric practice in the United States[v]. It is possible that the prevalence of CIRS cases in general practice or paediatric practice in Australia is similar, however it is recommended that a formal research study be performed to determine the prevalence. Proposals for further research are discussed in item #6.

3. *The current medical process of identifying biotoxin-related illness in patients and the medical evaluation of symptom complexes attributed to biotoxins and CIRS;*

To briefly reiterate the above, chronic inflammatory response syndrome (CIRS) is a chronic multi-system, multi-symptom, inflammatory condition associated with exposure to various biotoxins. The primary cause is thought to be exposure to water-damaged buildings (WDB). In this context biotoxins are ionophoric compounds (extremely small compounds capable of moving from cell to cell) weighing approximately 500-1500 Daltons in size. Toxins from botulinium and tetanus toxoid are much larger at around 150,000 Daltons, and therefore not considered biotoxins for the purpose of this condition [iv].

The hypothesis behind this condition has been based on studying the immunology of Systemic inflammatory response syndrome (SIRS), also referred to as sepsis syndrome, a condition often encountered in intensive care units (ICU).

In genetically susceptible individuals, exposure to biotoxins is hypothesised to trigger a chaotic and ineffective immune response characterised by activation of the innate immune system and underactivity of the acquired immune system. There are certain unique inflammatory cytokine, similar to those seen to be elevated in SIRS, which can be found to be abnormal in CIRS patients.

Some of the original research in biotoxin illness occurred in the setting of a pfiesteria outbreak in the estuarine waters of Maryland in 1998. Pfiesteria is a form of dinoflagellate which has been hypothesised to cause large fish kills during outbreaks.

Clinicians and researchers observed that patients exposed to pfiesteria complained of a multisystem illness, had a consistently poorer visual contrast sensitivity (VCS) score (an indirect test of neurological function) and had a positive response to the positively charged bile sequestrant cholestyramine(CSM), a dated anti-cholesterol agent.[vi] [vii]

This research team has observed, accumulated, researched and documented the science behind this condition over 10000 cases in peer reviewed and published journals in the last near 20 years and arrived at a precise case definition for Chronic Inflammatory Response Syndrome (CIRS). The United States patent office accepted a patent application on CIRS in September 2017.[viii]

This condition was introduced to a number of Australian doctors when Ritchie Shoemaker MD visited Sydney in June 2015. Currently there are approximately 30 doctors in Australia (primarly general practitioners) who diagnose and treat CIRS at least occasionally. Out of those only two have been through high level training, the Shoemaker physician training.

Biotoxins exposure in Australia are hypothesised to occur via:

1) exposure to water-damaged buildings (WDB) which contain but are not limited to fungi, bacteria, actinomyces and mycobacteria as well as inflammagens such as endotoxins, beta glucans, haemolysins, proteinases, mannans and possibly spirocyclic drimanes; as well as volatile organic compounds.[ix]

2) tick-borne infections such as with *Babesia microti* and *Borrelia burgdorferii* species[x]. It is noted that a separate senate enquiry investigated the presence and distribution of a Lyme-like illness in Australia. The final report of that enquiry was published in November 2016, titled “Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients”[xi] and included the statement that “the committee noted the weight of evidence on the relationship between tick bites and people becoming ill”. However, currently the distribution and causative species of these infections in Australia is currently unclear. Further research on this topic has been recommended by the senate committee, and is awaited.

3) Ingestion of reef fish such barracuda, snapper, moray eel, grouper, amberjack, triggerfish and parrotfish containing dinoflagellate toxins such as ciguatera. In Australia ciguatera can be acquired in Far North Queensland, New South Wales and the Northern Territory.

4) Blue-Green Algae - aquatic cyanobacteria such as microcystis and cylindrospermopsis species. It is noted that cases of illness due to cyanobacteria have occurred in several locations in Australia, including the Murray-Darling basin area.

Dr Shoemaker’s research group documented that based on international gene registries, approximately 24-25% of the human population with certain HLA gene haplotypes on the 6th chromosome (related to DQB1 and DRB1, DRB3, DRB4 and DRB5 genes) are more susceptible to this illness although 5% of patients with CIRS do not have a gene susceptibility. A recent study on a European population found the incidence may be closer

to 50%[xii]. The exact frequency of the susceptible gene types in the Australian population is yet to be determined.

In Australia the gene typing can be performed by virtually any accredited laboratory but are limited by the reporting process where the Sonic group of laboratories report the haplotype numbers for the DRB1 and DQB1 (while most other labs only report whether the DQ2 or DQ8 haplotype is present or not). However the DRB3, DRB4 and DRB5 haplotypes are only available by asking a local laboratory to submit the specimen to the Red Cross for the full DRB3, DRB4 and DRB5 haplotype.

However even with the report provided by the Sonic group of laboratories by applying the HLA DRB1 and DRQ1 information to the “rosetta stone” Dr Shoemaker’s research team has created, an indication of genetic predisposition to CIRS can be gleaned.[xiii]

The presenting symptoms of CIRS include different combinations of :
1. Fatigue
2. Weakness
3. Aches
4. Muscle cramps
5. Unusual pain
6. Ice pick pain
7. Headache/migraine/facial pain/sinus pain
8. Light sensitivity
9. Red eyes
10. Blurred vision
11. Tearing
12. Sinus problems
13. Cough
14. Shortness of breath
15. Abdominal pain
16. Diarrhoea
17. Joint pain
18. Morning stiffness
19. Memory issues /'foggy brain'
20. Difficulty with focus/concentration
21. Word finding difficulties
22. Decreased assimilation of new knowledge
23. Confusion
24. Disorientation
25. Skin sensitivity
26. Mood swings
27. Appetite swings
28. Sweats (especially night sweats)
29. Temperature regulation or dysregulation problems

30. Excessive thirst despite frequent water intake
31. Increased urination, nocturia
32. Static shocks
33. Numbness
34. Tingling
35. Vertigo
36. Metallic taste
37. Tremors

Key factors in evaluating a patient with possible CIRS is establishing whether the illness is truly multi-system, or simply single or dual system illness. An illness which simply pertains to one or two body systems is not considered to be likely to be CIRS (unless in children who may be unable to express all of the symptoms they are experiencing). This is due to the broad effect caused by the systemic and inflammatory nature of the illness.

Careful history taking is important including history of the patient's home/work/ motor vehicle/school environment (from birth to the current date in time). It should also include the patient's travel history, hobbies and occupational history to elucidate if they could have been exposed to any of the biotoxins mentioned above. A history of exposure to contaminated bodies of water, tick or other vector bites, and of course, to water-damaged buildings is imperative.

Symptomatic improvement on de-exposure from the patient's usual living environment can provide an important clue to the presence of CIRS.

Examination in the context of a possible CIRS diagnosis starts with inspection of the patient from the "end of the bed" looking for evidence of dehydration, a fine tremor, cool hands and/or feet), discoloured hand/and or feet (possible sign of a vasculitic component to the illness, pallor and unilateral weakness in the shoulder antigravity muscles. Respiratory symptoms should be checked through formal spirometry testing looking for evidence of restrictive airway disease. In CIRS patients forced vital capacity (FVC) is usually reduced, and the FEV1/ FVC ratio will be normal to elevated. This is in contrast to asthma in which the pattern is usually obstructive and the FEV1/FVC ratio is generally reduced, even though the respiratory symptoms in a patient with CIRS can mimic asthma.

In CIRS patients various compounds, jointly referred to as "inflammagens", cause damage to a part of nerve fibre that can differentiate white to grey matter, causing deficits in neurological function. This function is tested by measuring the patient's Visual Contrast Sensitivity (VCS). In suspected CIRS patients, the VCS test is carried out as a bedside test.

Dr Shoemaker's research group report 92% of CIRS patients fail, indicating an 8% false positive rate. False negatives are estimated to be about 2%, although the experience by the main physicians diagnosing CIRS in Australia has suggested it may be somewhat higher. Dr Shoemaker observed that despite the illness certain groups such as photographers, interior designers, artists and professional athletes who have trained their vision to better detect fine detail can have false negative results.

VCS testing is hypothesised to be an indicator of neurologic function in the visual pathway from the retina to the cerebral cortex. In the context of CIRS, there are a range of inflammatory and neuroendocrine peptides, such as those studied with regard to sepsis, which are measured, and commonly found to be abnormal.

However in Australia medical practitioners are limited in their ability to order the biomarkers specific for CIRS as most of these biomarkers are not available by any NATA accredited Australian laboratories. Hence diagnostic blood tests need to be forwarded to Quest Diagnostics and/or Laboratory Corporation (Labcorp), United States, with whom the original studies on CIRS were performed.

Currently Queensland Medical Laboratories (QML) in Buderim, QLD is the only venue that provides that service, as logistic difficulties stopped the laboratories in Sydney and Melbourne from providing a collection service on behalf of Quest Diagnostics or Labcorp. It should be noted that the collection process for these tests are more complex than normal due to them needing centrifuging and pipetting into special transport tubes, and then being transported via dry ice, not just standard ice packs.

The biomarkers that are performed by Quest Diagnostics and/or Labcorp in the United States are diagnostic of CIRS when 3 or more of the tests are abnormal (including HLA susceptibility) in addition to a history of likely biotoxin exposure, and a positive cluster analysis, indicating a truly multi-system, multi-symptom disorder. A positive response to a binding agent such as cholestyramine completes the case definition as described by the Government Accountability Office in 2008.[xiv]

The overseas biomarkers for this condition include.
1) Melanocyte Stimulating Hormone (MSH)
2) Transforming Growth Factor Beta-1 (TGF beta-1)
3) Split product of complement 4a (C4a)
4) Split product of complement 3a (C3a)
5) Matrix metalloproteinase-9 (MMP-9)
6) Vascular endothelial growth factor (VEGF)
7) Plasminogen activator inhibitor-1 (PAI-1)

Generally speaking each test in isolation is not specific for CIRS, however the combination of three or more abnormal tests, when combined with a history of exposure to biotoxins, plus a truly multi-system multi-symptom illness, is highly sensitive and specific for diagnosis of chronic inflammatory response syndrome (CIRS). This is the essence of the case definition for CIRS, which has been described above.

Locally, there are some blood tests that can be performed locally in Australia although many of these are not as specific for CIRS. As previously discussed, the HLA DQ/DR (Coeliac) tissue typing can be performed through any laboratory (although the Sonic group of laboratories reports these in a fashion where the exact haplotypes are given and therefore correct interpretation made much easier).

Other blood tests that can be done that assist towards confirming or excluding a diagnosis of CIRS are:

1) Vasoactive intestinal polypeptide (VIP) (a neuroregulatory peptide)
2) Leptin levels (an inflammatory hormone that influences hunger and weight)
3) Anti-diuretic hormone (ADH) (a hormone which regulates fluid balance in the body)
4) Serum and urine osmolalities (a measure of the concentration of blood and urine)
5) Cortisol and ACTH levels (relating to adrenal cortex function)
6) Anti-cardiolipin antibodies (related to anti-phospholipid syndrome, but can be elevated in CIRS)
7) DHEA and testosterone levels (as androgen deficiency may be part of CIRS)
8) Anti-gliadin hormones (as a non-Coelic gluten intolerance may complicate CIRS due to the effects of low MSH levels on the intestinal lining[xv].

A deep nasal swab (inserted at least 5-7.5cm into the nasal passages) which is cultured for at least five days may show evidence of Multiple Antibiotic Resistant Coagulase Negative Staphylococcus (MARCoNS). This is a type of staphylococcus bacteria which is postulated to colonise patients with CIRS and further perpetuate some of the neuro-endocrine changes, specifically lowering of MSH levels, due to the production of haemolysins. Generally this is performed by Microbiology Dx in Massachusetts, USA, due to their expertise, but in theory any accredited laboratory could perform this testing by culturing the samples for more than normal duration.

Patients are commonly advised to organise testing of their home and work/study environments with the Environmental Relative Moldiness Index Testing (ERMI) or Health Effects Roster of Type Specific fungal producing-Mycotoxin and Inflammagens (HERSTMI-2) methodologies. Obtaining a HERTSMI-2 or ERMI analysis of dust from a building costs a patient somewhere between $188 to $446 if performed in Australia.
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ERMI testing is mould-specific quantitative polymerase chain reaction

(PCR) testing for the total mould (36 species) burden in a particular building. It is a well studied methodology, although still not considered the Gold standard in the indoor environmental professional (IEP) world. A recent consensus statement by the IEP committee of www.survivingmold.com endorsed this testing as the Gold standard for CIRS cases[xvi].

The HERTSMI-2 index is an ERMI derivative which has been found to be more specific for predicting relapse in CIRS patients, and looks at five organisms from group I or pathogenic species on the ERMI. The result of the HERTSMI-2 test can help predict whether a premises is safe to reoccupy for the patient, with at least 95% accuracy[xvii].

Those with a high ERMI/HERTSMI-2 and a firm diagnosis of CIRS may need to consider remediation of their home or work environment or face the onerous task of relocating their home or work premises before formal treatment can be undergone. This step can lead to some degree of emotional trauma for the patient and experience has shown that a great deal of psychological support is required by patients during this stage.

A computerised volumetric analysis of a targeted brain MRI scan named 'NeuroQuant' has also been researched by Dr Shoemaker's research group. This can potentially show changes in the brain due to the inflammation to the brain by biotoxins[xviii].

When a firm diagnosis of CIRS is established at any stage, the following 14 treatment steps can be taken to address CIRS as per Dr Shoemaker's research team. In many cases implementing all steps is not necessary for recovery.

1. **Remove from exposure to biotoxins.** It is imperative that patients are removed from an environment in which exposure to biotoxins is taking place before medical treatment can be taken place. If inflammatory blood markers are available, then as a general rule, ERMI levels should be <2 if the patient's C4a less than 20,000. If the C4a is more than 20,000, the ERMI must be less than -1. The following are common fungal types found per ERMI depending on moisture levels in the building in question:
In very moist areas: (water saturation 90-100%): Stachybotrys and Chaetomium.
In moderately moist areas:(water saturation 80-90%): Aspergillus vesicolor and Aspergillis penicilloides spp.
In slightly moist areas: (saturation of 60-80%): Wallemia and Trichoderma.

2. **Binding of biotoxins**. After proper informed consent, the use of a bile acid sequestrant such as cholestyramine (CSM) or coleveselam should be considered.

In Australia cholestyramine is available commercially as the product Questran Lite but it does contain the artificial sweetener aspartame. If patients are averse to using this preparation due to concerns about aspartame, one can also use compounded cholestyramine which is available from several compounding pharmacies in Australia. The standard dosage of cholestyramine is 4g on empty stomach four times a day. This means half an hour before food, or at least hours after food. Thyroid medications and warfarin must be taken up to 4 hours away from cholesytramine. There are numerous other drug interactions to be aware of. The paediatric dosage is 60mg/kg three times daily.
Patients can experience difficulty with this preparation due to the frequency of medications and side effects such as bloating or constipation, gastro-esophageal reflux and triggering the gag reflex. In these cases it is recommended that coleveselam be used as an alternative at the dosage of 1.25g three times daily with food. This is hoped to be available via a major compounding pharmacy in Sydney by the end of August 2018. VCS testing should be performed monthly, and binders continued until the VCS has returned to normal, and the patient is in a safe residence, usually heralded by a HERTSMI-2 score of <11.

3.**Eradicate MARCoNS**
This bacteria colonise the nasopharynx and and have a direct relationship with MSH levels as previously mentioned. Dr Shoemaker has found early on that 80% patients deficient in MSH have MARCoNS which produce endotoxin A and B that split MSH resulting in perpetuating low levels of this hormone[xix]. MARCoNS are treated by using a silver and EDTA preparation which is available from several compounding pharmacies.

4. **Eliminate anti-gliadin antibodies**.
Due to low MSH levels, dysregulation of T-reg cells occurs, triggering an autoimmune reaction to gliadin, a component of gluten. This should not be confused with Coeliac disease. Checking for transglutaminase antibodies is advised to screen for Coeliac disease as well, given the common HLA genetic subtypes in some cases. T-reg cell dysregulation is also hypothesised to cause a widening in tight gut junction causing intestinal hyperpermeability in these patients. Patients are advised to eliminate gluten-containing foods for three months if they develop this condition, after which type antibodies are checked again, along with a possible retrial of gluten-containing foods.

5. Correction of Androgens
Both male and female CIRS patients are often found to have low testosterone levels associated with a higher than normal conversion of testosterone to estrogen. This is hypothesised to be due to an over activity of the aromatase enzyme, which converts testosterone to estrogen.

Replacing testosterone in these patients will only cause more conversion to estrogen. Many female CIRS patients are observed to have concomitant gynaecological complaints such as endometriosis, adenomyosis and menorrhagia.
Replacing the hormone DHEA is one of the options used in the CIRS treatment protocol to overcome androgen deficiency in CIRS patients.

Another treatment mode for androgen deficiency is human chorionic gonadotropin (HCG) treatment, which is often administered via subcutaneous injection.

6. Correction of ADH/Osmolality

Dr. Shoemaker's research team have observed that 60% of patients with CIRS have dysregulated levels of anti-diuretic hormone (ADH) which is a hormone which regulates fluid balance in the body.

Low ADH leads to excessive thirst, frequent urination and decreased blood volume. Static electricity shocks due to the high concentration of sodium on the skin can occur, as can headaches and dizziness due to relative dehydration.

The treatment is to replace low ADH with desmopressin, if possible under the Pharmaceutical Benefits Scheme (PBS) if criteria are met.

7. Correction of Elevated MMP-9

MMP-9 is a cytokine released by white blood cells when an inflammatory process is triggered, such as which occurs in CIRS.

Elevated MMP-9 levels cause damage to nerves, muscles, the lungs, joints and blood vessels. It can bind with another protein, PAI-1, to cause damage to endothelium of blood vessels in the presence of oxidised LDL.

Reducing MMP-9 involves low amylose diet plus either high dose fish oil /or short term use of the anti-diabetic medication pioglitazone if necessary. Pioglitazone is only available on the Pharmaceutical Benefits Scheme (PBS) for treatment of type 2 diabetes.

Pioglitazone has the published side effect of bladder cancer with long-term usage hence informed consent needs to be obtained and should be used short term only in CIRS patients.

8. Correction of Lowered VEGF

Vascular endothelial growth factor (VEGF) is an important growth factor which has been extensively studied in cancer pathogenesis. In contrast to the high levels seen in many cancer patients, VEGF is often lowered in CIRS patients, often contributing to poor oxygen delivery to tissues, and resulting in symptoms such as fatigue and muscle pain. The treatment here is the same as correction of MMP-9 above. Implementation of a low amylose diet along with either high dose fish oil or short term use of pioglitazone is the recommended procedure. Again, pioglitazone is often not required.

9. Correction of Elevated C3a

Production of C3a is a result of activation of the C2 and C4 complements as part of a complex lectin pathway activation, in the presence of a microbial cell membrane. Hence presence of C3a implies the presence of an underlying infection, usually a bacteria.

C3a is an anaphylatoxin that can cause smooth muscle contraction, decreased oxygen delivery to tissues and increased vascular permeability.

This is treated with a HMG-coA reductase inhibitor such as atorvastatin or rosuvastatin, whilst monitoring liver function and CK levels.

Statins used in this setting has shown to lower T cell activation, macrophage infiltration and vascular wall inflammation. coQ10 is used to prevent side effects of these medications.

10. Correction of Elevated C4a

C4a is another split complement that is more commonly elevated than C3a in CIRS patients. Like C3a, C4a is also an anaphylatoxin and can activate mast cells, increase smooth muscle contraction, increase vascular permeability and lead to lower oxygen delivery to tissues.

Elevated C4a levels are a significant cause of cognitive dysfunction which includes loss of memory, impaired concentration, decreased assimilation of new knowledge, difficulty with word finding, confusion and disorientation.

MRI spectroscopy in CIRS patients with elevated C4a have been found to show an increase in inhibition and reduction in glutamate/ glutamine ratio, and oxygen deprivation. This results in high lactate levels. Low dose erythropoietin (EPO) has been trialled by Dr Shoemaker's research team however due to it being a high-risk product, a nasal spray containing the hormone vasoactive intestinal polypeptide (VIP) is recommended for use in the Australian setting due to medicolegal and safety issues. HCG subcutaneous injections has also been trialled for lowering of elevated C4a levels in a small case series by Dr Sonia Rapaport. The case series was presented at a conference in Irvine, California in October 2016 and may also be trialled in some circumstances to lower residually elevated C4a levels.

11. Correction of Elevated TGF beta-1

TGF beta-1 is a destructive cytokine that is often elevated in biotoxin-illness patients. TGF beta-1 regulates regulatory T cells which are important for regulating the various pathways of immune response. When TGF beta -1 is activated T-reg cells are hydrolysed to release pathogenic effector T cells which in turn induce more TGF-Beta-1 causing more destruction, whilst TGF beta- 1 needs to be reduced to minimise the damage. The hydrolysed T-reg cells and high TGF beta-1 cause a vicious cycle of tissue destruction.

Patients high with elevated TGF beta-1 levels have a myriad of signs and symptoms:

- Lung symptom-disorders: are generally in the spectrum of restrictive lung disease, caused by fibrosis of lung tissue.
- Neurological symptoms: atypical seizures, a fine resting tremor, Parkinson-like symptoms.
- Autoimmune disorders: can lead to a positive anti-nuclear antibody (ANA) level which can cause a lupus-like syndrome, positive anti-nuclear cytoplasmic antibodies (ANCA) which can cause blood vessel inflammation (vasculitis), positive anti-gliadin antibodies (which can cause non-Coeliac gluten intolerance) etc.

- Fibrotic diseases: interstitial lung disease, scleroderma-like illness.
- Nasal and vocal cord polyps: in some cases can this can obstruct breathing.
- Increased pulmonary artery systolic pressure: this can lead to breathlessness and severe stress on the right side of the heart.

The treatment for elevated TGF-beta-1 levels in CIRS patients is to use the blood pressure reducing medication Losartan. Losartan creates a metabolite called EXP 3179 which appears to significantly reduce TGF-beta-1 levels. The side effect of Losartan can be lowering blood pressure and diarrhoea. If patients have a low blood pressure or otherwise unable to tolerate Losartan, then VIP nasal spray can be used to assist with lowering TGF-beta-1 levels.

12. Correction of lowered VIP levels

Vasoactive intestinal polypeptide (VIP) levels have been found to be often be low in CIRS patients.

VIP can be checked through Sydney South West Pathology in Australia, to which any local laboratory can forward blood specimens. A Medicare rebate is available for this assay.
VIP deficiency has shown to cause dysregulation of vitamin D metabolism, upregulation of pulmonary artery pressure, and upregulating the aromatase enzyme in the body.
VIP is a 28 amino acid regulatory neuropeptide with many physiologic effects. VIP can down regulate cytokine levels and can potentially have a potentially calming effect on the whole biotoxin pathway.

However according to Dr Shoemaker following criteria must be met before VIP nasal spray can be used:

- VCS must be normalised.
- No regular exposure to buildings with an ERMI >2 or HERTSMI-2>10
- A negative nasal swab for MARCoNS
- Normal lipase level

VIP nasal spray is prescribed at 50mcg four times daily via the intranasal route.
In Australia VIP spray can be purchased from a compounding pharmacy. A particular compounding pharmacy in Brisbane has a preparation which was personally approved by Dr Shoemaker.

There is a 1% risk of pancreatitis from VIP nasal spray administration. There is a small risk of depression in response to VIP administration as well.
It is imperative to monitor electrolytes, liver function tests and especially the lipase level during treatment, and a significant rise in lipase levels is a contraindication to continued use.

When administered for the first time, the patient is advised to be observed in a general practitioner's office with close observation of BP every 5 minutes for 15 minutes.

VIP nasal spray is currently not on the Pharmaceutical Benefit Scheme (PBS) and therefore is at significant cost to patients.

13. Treat capillary hypoperfusion

With high cytokine levels and low VEGF, CIRS patients have a lower threshold for hypoxia than other patients.
Most CIRS patients experience debilitating post exertional malaise due to poor oxygen delivery to tissues. During the process of inefficient anaerobic metabolism due to lack of oxygen there is a low yield of ATP.
During exercise glucose is broken down to produce ATP in the cell.
Then moves into mitochondria. When there is low oxygen, only 2 ATP is produced. Due to inefficient anaerobic metabolism body switches to glycolysis to breakdown glycogen from liver glycogen stores.
It is important for CIRS patients to stay below their anaerobic threshold to prevent depletion of their glycogen stores.
A specialised cardiopulmonary stress test can assess anaerobic threshold by measuring VO2 max or the maximal oxygen consumption.
The normal VO2 max is >35. Most CIRS patients have levels between 15-20ml/kg/min.
In order to improve capillary hypoperfusion, the exercise regime as following is recommended:

- Start with cardio exercise 5 minutes daily and build up to 15 minutes
- Add floor exercise 5 minutes daily and build up to 15 minutes
- Add free weights 5 minutes daily and build up to 15 minutes
- After one month go back to each step and build up intensity.

It is important to note that if CIRS patients are not correctly diagnosed and are instead diagnosed with chronic fatigue syndrome (CFS) and prescribed graduated exercise therapy (GET) prior to the preceding steps, then it is highly unlikely they will improve, and may even become worsened.

14. Follow up

After the above steps, patients should have a normal VCS test, near normal blood biomarkers and be asymptomatic. Annual follow-up with VCS testing is essential as well as avoiding any further exposure to the source of biotoxins, particularly water-damaged buildings.

4. Any intersection with other chronic diseases;

As referred to above, there are a number of conditions which biotoxin-related illnesses are commonly misdiagnosed as. Furthermore, biotoxin-related illness can co-exist with other conditions, both physical and psychiatric, complicating the diagnostic process.

It has also been suggested in the literature that CIRS can mimic or intersect with other common medical conditions.

One example of this is the condition recently described as “type 3 or inhalational Alzheimer’s disease” by Professor Dale Bredesen from the University of California, Los Angeles campus. The term “inhalational Alzheimer’s disease” refers to a condition which is related to biotoxin-exposure, and fulfils many of the criteria of CIRS, although it may not meet the formal case definition for CIRS. It generally occurs in younger individuals without a apolipoproteinE gene predisposition to Alzheimer’s disease, who have experienced inhalation of biotoxins due to exposure to one or more water-damaged buildings[xx].

Functional abdominal pain syndrome, functional neurological syndromes and chronic idiopathic headaches in paediatrics have been found to be manifestations of CIRS in many cases, by paediatric Scott McMahon MD[v].

Harvard-trained psychiatrist Mary Ackerley MD, as mentioned in her separate submission, has found a high rate of psychiatric symptoms attributable to CIRS in her practice in Tuscon, Arizona, in the United States[xxi] including anxiety and depression.

Other conditions known to commonly intersect with CIRS:

1. Multiple Chemical Sensitivity (MCS): Many of those with CIRS also have concurrent MCS and this has been described in multiple papers.
2. Mast cell disorders such as mast cell activation syndrome (MCAS).
3. Autism spectrum disorder
4. Sarcoidosis

Conditions known to be associated with elevated TGF-beta-1 levels, and therefore are likely to be worsened by co-existent CIRS include:

a. Endometriosis
b. Inflammatory bowel disease (including Crohn’s disease and ulcerative colitis)
c. Multiple sclerosis
d. Nasal polyposis

e. Various autoimmune diseases
f. Interstitial lung disease of various aetiologies
g. Post-pump syndrome
h. Acute Lyme disease
i. Alopecia universalis
j. Peripheral neuropathy

Conditions known to be associated with elevated C4a levels, and also likely to be worsened by co-existent CIRS include:

a. Chronic fatigue syndrome (post-exertional levels)
b. Systemic lupus erythematosis (SLE)
c. Lyme disease

Conditions known to be associated with reduced MSH levels, and also likely to be worsened by co-existent CIRS include:

a. Acute brain injury
b. Obesity
c. Early post CVA
d. MARCoNS (multiply antibiotic resistant coagulase negative staphylococci)
e. Alzheimer's disease
f. Sepsis

5. *Investment in contemporary Australian research to discover and provide evidence of CIRS as a chronic, multisystem disease;*

ACIIDS is in discussion with the Australasian College of Nutritional and Environmental Medicine (ACNEM), the Australian Integrative Medicine Association (AIMA), leading building biologists and the university sector to design research into biotoxin-related illness in Australia. Proposed topics for research include:

1) a more formal prevalence study for CIRS in Australia
2) a study of the prevalence of water-damaged buildings (WDBs) in Australia
3) a study of the prevalence of HLA gene types in Australia which confer susceptibility to chronic inflammatory response syndrome (CIRS)
4) a study of the effectiveness of currently accepted treatment regimens
5) an assessment of the financial cost to the health care system, which is thought to be considerable.

It is recommended that Royal Melbourne Institute of Technology (RMIT) Department of Health Sciences department be commissioned as the centre for further research on CIRS in Australia.

Included in discussions so far have been Prof. Mark Cohen and Nicole Bijlsma from this department. It is noted that Prof Cohen is a core member of the RMIT Health Innovations Research Institute.

Endorsing research of this nature and providing funding for this research would be a very important outcome of this inquiry.

6. Research into biotoxin-related illness caused from water damaged buildings

There has been extensive research conducted in the United States by the previously mentioned research team. The most robust of these included a small double-blinded placebo-controlled clinical trial into what was at the time termed "Sick building syndrome (SBS)" as it occurred prior to the term CIRS being coined. The intervention was two weeks of therapy with cholestyramine, then subsequent avoidance of water-damaged buildings (WDBs) followed by re-exposure to WDBs. It was found that symptom scores, blood markers (MMP-9, leptin and VEGF) as well as visual contrast sensitivity (VCS) scores improved in the case group, but not in the placebo group. Improvements were sustained throughout the period of avoidance of WDBs followed by relapse when re-exposed to WDBs[xxii].

7. Any related matters.

There are very large barriers for patients being able to access medical professionals to properly diagnose and treat CIRS. Currently there are only two medical practitioners who have had the high-level training and around 20-25 who have had basic training in CIRS diagnosis and management. There is thus a dire need for further training in CIRS for medical practitioners.

indoor environmental professionals (IEPs) who are sufficiently knowledgeable in CIRS and can apply the standards set by ANSI/IICRC S520 Mold Remediation industry standards are few and far betweenxxiii. There is thus a high need for training IEPs in inspection and remediation standards that are acceptable in CIRS patients.

The Australian Government has the opportunity to provide recognition and funding to this condition which will impact the life of countless patients.

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