TREATMENT OF CHRONIC INFLAMMATORY RESPONSE SYNDROME (CIRS)

Today's Integrative Health
L. J. Leo, DO, MS, MBA, FAARM, FICT, FAAO, FACACN, IFMCP
6321 Executive Blvd
North Bethesda, MD 20852
Phone: (301) 770-6650; Fax: (301) 770-6252
Email: DrLJLeo@todaysintegrativehealth.org
Website: www.todaysintegrativehealth.com

INTRODUCTION

This document is an overview, background, diagnosis and proposed treatments of Chronic Inflammatory Response (CIRS). In the world of medicine, this concept of CIRS is in its very young stages. Therefore, as more evidence-based information is discovered, some of the information, protocols, etc...are subject to change. Appropriate updates will be made to this document and available for review.

OVERVIEW

CIRS is an underdiagnosed multi-system, multi-symptom illness with increasing prevalence throughout the world. This illness is found to occur through an illness due to biotoxins. These biotoxins can be from exposure to water damaged buildings, tick bites (i.e. Lyme disease) or other exposures (e.g. contaminated drinking water, volatile organic compounds, eating contaminated fish).

Once the CIRS illness is identified, the physician will go through a methodical, stepwise protocol to resolve the symptoms. This detail will be provided later in this document. Fortunately, there is help for this elusive and debilitating illness.

BACKGROUND

In 1997, Dr. Ritchie Shoemaker, from the Eastern Shores of Maryland happened upon patients from his area that had an unidentifiable, complex illnesses. He ultimately discovered that these patients were exposed to salt marsh fish that were contaminated by a dinoflagellate called Pfisteria. Subsequently, after recognizing this as a biotoxin that caused a multi-system, multi-symptom illness he was able to evaluate these patients with special labs. Once the illness was confirmed by these labs a treatment protocol was developed.

Potential Exposures

Inhalation: Air in buildings that have suffered water damage create mold, mycotoxins and bacteria along with their byproducts. Upon inhaling these toxins from a water damaged building by a genetically compromised person will cause serious illness

Ticks: People may have suffered a tick bite and received the toxins that create Lyme Disease. These toxins make a person susceptible to an inflammatory illness.

Ingestion: Some salt marsh fish may be contaminated by dinoflagellates. If a genetically susceptible person eats these fish it will predispose them to CIRS.

Contaminated Water: If a water source is contaminated by cyanobacteria or other biotoxins and a person either drinks this water or swims in it they also may be predisposed to CIRS.

Diagnosis and Treatment

There are fourteen (14) steps involved in diagnosis and treatment of CIRS.

1. Differential Diagnosis
2. ERMI/HERTSMI-2 Testing
3. Removal from prior exposure
4. Correcting toxins in the body with Cholestyramine (CSM)
5. Eradicating biofilm forming Multiple Antibiotic Resistant Coagulase Negative Staph (MARCoNS)
6. Eliminate gluten if needed
7. Correct Androgens
8. Correcting elevated Matrix Metalloproteinase 9 (MMP9)
9. Correcting Anti-Diuretic Hormone (ADH)/Osmolality
10. Correcting low Vascular Endothelial Growth Factor (VEGF)
11. Correcting elevated C3a
12. Correcting elevated C4a
13. Reducing elevated TGF beta-1
14. Replacing Vaso-Active Intestinal Peptide (VIP)
15. Final check to verify stability off medications

1. Differential Diagnosis
    a. A detailed History and Physical Exam
    b. The following tests must be ordered to direct physician in with the diagnosis of CIRS
        i. Visual Contrast Sensitivity Test (VCS) (Positive Test = Not meeting susceptibility criteria in Columns C and D of the test; Negative Test = Meeting susceptibility in Columns C and D of test. Positivity in Columns C and D suggest inability detect contrast and have some exposure to biotoxins)
        ii. This test measures the neurological function and perfusion of the optic nerve.

    c. Environmental Relative Mold Index/Health Effects Roster of Type Specific Formers of Mycotoxins and Inflammagens (ERMI/HERTSMI-2) Testing (Normal <11)
        i. HERTSMI-2 Test is the preferred method of testing the suspected affected environment (home and/or office) for mold or biotoxin exposure.

1. These tests may be purchased through Mycometrics. Their website can be found at www.mycometrics.com
2. Air sampling has a very high false negative rate and is not recommended for testing suspected exposure areas.

d. Nasal Swabbing for MARCoNS
e. Labs
   i. Complete Blood Count
   ii. Comprehensive Metabolic Panel
   iii. Urinalysis
   iv. Hs-CRP and ESR – if negative in the setting of biotoxin exposure, there is an increase concern for CIRS
   v. Melanocyte Stimulating Hormone (MSH) (Normal: 35 – 81 pg/ml)
   vi. Transforming Growth Factor Beta -1 (TGF beta-1) (Normal: <2380 pg/ml)
   vii. Multiple Antibiotic Resistant Coagulase Negative Staph (MARCoNS) (Normal: none present)
   viii. C4a (Normal: 0 – 2830 ng/ml)
   ix. C3a (Normal: 55 – 486 ng/ml)
   x. Matrix Metalloprotienase 9 (MMP9) (Normal: 85 – 332 ng/ml)
   xi. Vasoactive Intestinal Polypeptide (VIP) (Normal: 23 – 63 pg/ml)
   xii. ACTH/Cortisol (Absolute high: ACTH >45 or Cortisol >21; Absolute Low: ACTH <5 or Cortisol <4)
   xiii. ADH/Osmolality (Absolute High: ADH > 13 or Osmolality >300; Absolute Low: ADH < 5 or Osmolality <275); symptoms of recurrent headaches, static shocks, polyuria, polydipsia, orthostatic hypotension.
   xiv. Antigliadian Antibodies (AGA) (Normal: 0 – 19)
   xv. Vascular Endothelial Growth Factor (VEGF) (Normal: 31 – 86 pg/ml)
   xvi. Human Leukocyte Antigen (HLA) Genetic Testing
   xvii. Leptin (Normal: 0.5 – 13.8 ng/ml; men, 1.1 – 27.7 ng/ml women)
   xviii. Von Willebrand Profile
   xix. D-Dimer
   xx. Coagulation Studies (PT, PTT, INR)
f. Imaging
   i. NeuroQuant/MRI (NQMRI)
      1. CIRS due to Mold –
         1) Increased in: forebrain parenchyma, cortical gray, hippocampus and pallidum
         2) Decreased in: Caudate
      2. CIRS due to Lyme –
         1) Increased in: Thalamus, cerebellum
         2) Decreased in: Forebrain parenchyma, putamen
   ii. Other testing
      1. Pulmonary Function Test (PFT's)

2. Stress Echocardiogram
3. VO2 Max

2. Environmental Relative Mold Index/Health Effects Roster of Type Specific Formers of Mycotoxins and Inflammagens (ERMI/HERTSMI-2) Testing (Normal <11)
    a. HERTSMI-2 Test is the preferred method of testing the suspected affected environment (home and/or office) for mold or biotoxin exposure.
        i. The five (5) specific molds that are tested are: Aspergillius penicilloides, Aspergillus versicolor, Chaetomium globosum, Stachybotrys chartarum and Wallembia sebi.
        ii. Any score over 15 is considered too dangerous for previously sickened people to occupy
        iii. Score of 11 – 15 is borderline
        iv. Score <11 low recurrence rate of CIRS
        v. Score <8 likely not to impact patient regarding CIRS
    b. ERMI is done by standardized DNA Mold-Specific Quantitative Polymerase Chain Reaction (MSQPCR). The collection method is done by vacuuming and/or Swiffer cloths as a means of dust collection.
    c. These tests may be purchased through Mycometrics. Their website can be found at www.mycometrics.com
    d. Air sampling has a very high false negative rate and is not recommended for testing suspected exposure areas.
3. Removal from Exposure
    a. Due to the heightened immune response, removal of the patient from the contaminated environment is extremely important. It will be very difficult, if not impossible to progress past step one in the process without removal from exposure. If Lyme is the offending agent, considering treating the infection.
    b. Mold remediation of the building with a designated, qualified and reliable indoor environmental professional (IEP) and a qualified CIRS physician are important to achieve resolution of the CIRS.
4. Correcting the biotoxins in the body with CSM
    a. CSM is a bile acid sequestrant with a positive charge. It is not a true binder like charcoal, bentonite etc. CSM binds to negatively charged biotoxins and excreted with the bile. CSM should be taken on an empty stomach preferably, 30 – 60 minutes before meals.
    b. The biotoxin clearance can be monitored with the VCS test. As the body begins to clear the biotoxins, the VCS will trend better ultimately becoming Negative.
    c. If CSM is not tolerated, may use the tablet form of Welchol.
    d. Dosing
        i. Adults – CSM - 9 grams mixed in 6 oz of water followed by 6 oz of water three times per day.
            Welchol – 625 mg (2 tablets) three times per day
        ii. Children – CSM – 60 mg/kg in 6 oz of water followed by 6 oz of water three times per day.

5. Eradicating MARCoNS
    a. If MARCoNS positive, treat with either Bactroban, EDTA, Gentamicin (BEG) spray or Bactroban, EDTA, micronized nanoparticle Silver.
    b. Dosing – 2 sprays in each nostril three times per day for thirty days.
    c. Repeat MARCoNS testing after one cycle and determine if resolved.
    d. If not resolved continue for second cycle. If not resolved after two cycles, consider other sources.
6. Eliminate Gluten if Anti-gliadin Antibodies (AGA) are positive
    a. An elimination diet from gluten would be initiated for ninety days.
    b. Retest AGA after removal of gluten for 90 days.
    c. If AGA still positive, consider other sources (i.e. functional intestinal disorder, small intestinal bowel overgrowth, dysbiosis)
7. Correct androgens
    a. A low MSH may indicate abnormal androgens and excess aromatase
    b. Testing for hormone imbalance will indicate any dysregulation of cortisol, testosterone or Hypothalamic-Pituitary-Adrenal (HPA) axis abnormalities.
    c. If androgens/testosterone are low a consideration of elevated aromatase is in order
    d. Avoid testosterone replacement and consider higher up the pathway with DHEA.
    e. Monitor testosterone and estradiol levels every ninety days for any abnormal reactions or unwanted elevations
8. Correct elevated MMP 9
    a. The upregulation of PPAR-gamma will help to reduce the MMP 9 levels.
    b. Some options for this action are: high dose omega 3 fatty acids, pioglitazone, low amylose diet
    c. Dosing of each:
        i. Pioglitazone (Actos) – 45 mg daily for thirty days. Caution in long term use to cause bladder cancer, reduce renal function and low leptin levels (<7)
        ii. Omega 3 Fatty acids – 2.4 mg of EPA and 1.8 mg of DHA daily.
        iii. Low amylose (sugar type) diet
    d. Re-test in thirty days for improvements or resolution
9. Correcting ADH/Osmolality
    a. If ADH and Osmolality are high use DDAVP.
    b. Dosing – Initial: 0.2 mg every other night; must watch for adverse side effects
    c. After five doses, repeat labs for ADH, electrolytes and serum osmolality.
    d. If conditions for elevated ADH/Osmolality persists, increase dose to 0.2 mg per day. Consider twice a day dosing if symptoms are problematic. Must monitor labs and for adverse side effects closely in this population.
    e. Discontinue DDAVP in a reducing taper once ADH and osmolality are achieved.
10. Correcting VEGF
    a. Retest VEGF at this step before attempting to correct. MMP 9 correction may have addressed this problem.

b. If not improved, have patient perform anaerobic exercises for forty-five minutes per day.
c. Ideally, this will have the patient perform with an "oxygen deficit" and the muscles will use the oxygen more efficiently.

11. Correct C3a
    a. Primarily for Lyme patients. Proposed mechanism is to reduce T cell activation, macrophage infiltration and vascular wall infiltration.
    b. Corrected with statins and CoQ10 simultaneously.
    c. Monitor liver function tests and avoid CYP3A4 metabolism substrates. (i.e grapefruit juice, other medications, etc)
12. Correct C4a
    a. VIP is used with the proposed action of downregulating MASP2.
    b. Procedure for administering VIP
        i. Draw blood
        ii. Initial test dose of 50 mcg sprayed into one nostril
        iii. Take vital signs and monitor every 5 min for three cycles
        iv. Observer for rash, anaphylaxis, other adverse reactions
        v. Draw C4a after fifteen minutes. If there is a twofold increase there may be other occult mold or biotoxin issues.
        vi. If aforementioned is satisfactory, give second dose of VIP in other nostril and repeat same monitoring as above.
        vii. If well tolerated and no adverse side effects noted, the patient may depart.
    c. Consider Erythropoietin as an additional technique to reduce C4a
        i. Dosing – 8000 units twice per week.
        ii. If used, should consider using before starting VIP and TGF beta-1
13. Reduce elevated TGF beta-1
    a. Treatment is Losartan
    b. Losartan reduces TGF beta-1 by its breakdown products preventing conversion of T reg cells therefore, lowering TGF beta-1
    c. Dosing – 12.5 mg per day. Can increase to 25 mg per day if needed
    d. Monitoring
        i. Test TGF beta-1 monthly
        ii. Blood pressure; Losartan tends to lower pulmonary artery pressure
14. Replacing VIP
    a. This is the "Secret Sauce" in the entire protocol
    b. After all steps are successfully completed with the stated results
    c. Assuming VIO procedures were followed in step 12
    d. Dosing – 50 mcg (one spray) four times per day for thirty days
        Repeat labs, lipase and VCS
        If needed, increase dose to 100 mcg (2 sprays) four times per day
    e. Once TGF beta-1, VCS are normalizing, and symptoms improve
    f. Continue VIP for thirty days
    g. Then taper to twice per day to once per day then discontinue the VIP
15. Final Check to verify stability off of medications

a. Once symptoms are normal
b. Repeat all labs and VCS
c. Plan a follow up at six months after completing VIP treatment
d. Education about re-exposure and staying away from further biotoxin exposure.

Evidence-Based Medicine

What Evidence-Based Medicine (EBM) is:

The original concept of EBM began in the 1980's with some investigators attempting to put medicine on a more solid scientifically based foundation. Ultimately, producing clinical guidelines based on current (at the time) related developing science. (1) The actual concept of EBM has been in the medical lexicon since the 1990's. Initially, EBM was being implemented to educate physicians/clinicians to understand the importance of integrating their understanding of the literature and science into clinical medicine. The currently accepted definition of EBM in medicine today is: "...the care of patients using the best available research evidence to guide clinical decision-making..." (2,3)

There are four basic elements of EBM. 1. Formulate a clinical question, 2. Finding the best available evidence, 3. Assessing the validity of the evidence (including internal and external validity), 4. Applying the evidence in practice, in conjunction with clinical expertise and patient preferences). (2,4)

1. Formulating a clinical question is a critically important part of EBM. This will allow the investigator and physician to zero-in on a specific area of scientific concern. This step is important to maintain focus on a specific area and not to become distracted by confounding outliers when searching for an answer. In medicine, a common method of maintaining this focus is to use the **PICO** method.

P: What is the relative **P**atient population? Is the study being considered related the individual patient(s) being treated? (5)

I: What **I**ntervention is being considered? A specific intervention must be considered. However, having an intervention (diagnostic test, medication, etc...) may cause the physician to rely too much on subgroup analysis. This reliance may have skewed results and not comport with the medical condition related to the study. Therefore, the scope of the intervention may need to be widened.

C: What is the **C**omparison intervention? When considering double-blind randomized controlled treatment trials, the comparison group in the study must be considered. For example, if the placebo control is not related at all to your patient population or treatment considerations, alternative interventions must be considered. (7)

O: What **O**utcomes are of interest? Outcomes should be well defined, measurable, reliable, sensitive to change and actually assess clinically relevant aspects of a patient's health. (2). There are three types of outcomes when consideration of clinical studies:

a. Composite endpoints – If there are multiple combined endpoints in a study, this may increase the studies reliability and statistical relevance. However, if these composite endpoints are not all equally relevant to your patient or treatment plan the endpoints are only marginally useful. In order to make sense of the studies endpoints, an analysis of the individual endpoints must be assessed to determine if the studies outcomes are relevant.
b. "Soft" outcomes – These outcomes are related to the more subjective measurements in a study (i.e. function, pain, quality of life, etc…). Soft outcomes are likely much more important to the patient and the empathic physician. However, they are subjected to expectation bias also known as the placebo effect.
c. Surrogate outcomes – are usually used when clinically important outcomes are either unable or too difficult to measure. Hence, these larger metrics tend to make the trials extremely expensive and make the cost of development prohibitive. (i.e., drug development). Surrogate outcomes are largely indirectly related to patients. This is akin to an associative effect not a cause and effect. Therefore, in the interest of using fewer patients and reducing costs, the studies results are subject to errors in interpretation of the outcomes. Ultimately, approving medications that produce either direct or indirect harm to patients. For example, if a drug was approved to address a specific medical problem and the drug did not have any effect on the population, the drug would not have a positive outcome. Consequently, if a drug was approved for the same medical problem and was the cause of increased morbidity or mortality, then that outcome would not be acceptable either.

2. Finding the best available evidence in today's technological environment is amazingly easy. In fact, the plethora of information available to physicians can be overwhelming. Since the advent of the internet, searching for information is quick, easy to search and most of the times at a reduced or zero cost to the user. There are many services available that sort and evaluate the volume of research available and will provide relevant summaries or abstracts for the physician's review.

In search of the evidence, there are three levels of complexity to be considered when reviewing the data.

a. Primary (original) research – this is data collected from groups of people that are defined by the researchers. Providing, the study is designed appropriately, this type of research will minimize the risk of bias. The best type of primary research studies are double-blind randomized control studies.
b. Systemic reviews – are designed to answer one specific question. Unlike traditional reviews, the systemic review is very specific in its selection of previously published studies and carefully evaluates if there are any bias or conflicting results.
c. Summaries and guidelines – are considered the highest level of complexity. This is due to the development of summaries and guidelines that are a synthesis of systemic reviews, original research, clinical expertise and patient preferences. (2). Subsequently, the guidelines are produced and vetted amongst multiple organizations and committees prior to publication.

3. Assessing the validity of evidence is using all the critical skills a physician has learned to evaluate the information presented to determine if the evidence is to be considered in the treatment of the medical problem the physician has in question. Critically evaluating the evidence is not only important but essential for the physician. To evaluate the evidence these areas must be assessed.

a. Internal validity – Is the study being reviewed, are the results of the study pertinent to the patients in the study. A few considerations will impact the internal validity. Bias and Chance to name two.
b. External validity – Are the results of a particular study applicable to patients outside the study being evaluated. (i.e. does the study apply to the patient the

physician is trying to treat). A few considerations will impact the external validity are: Indirect evidence, Subgroup analysis; Reporting bias, Multiple comparisons, Lower Statistical Power.

Assessing validity is a learned skill that improves with time and effort. The physician should work to develop their critical reading skills and work to maintain their knowledge in their respective fields of medicine.

4. Applying the evidence in practice is the ultimate goal with EBM albeit one of the most difficult tasks to undertake and implement.

a. The know-do gap – this is likely the most common problem implementing EBM in a clinical practice. This is due mainly to the gap in recommendations from best evidence and actual clinical practice. (8). As mentioned before, there is an overwhelming amount of research available. With only so many hours in an extremely busy day, sometimes there is little time to properly assess the evidence. Therefore, the know-do gap is created. The physician does not have a grasp on the evidence but implements a treatment based on gestalt or collegial input. It is incumbent on the physician to implement the appropriate treatment to the appropriate patient in the appropriate manner.

b. Difference in baseline risk – do the results in a particular study apply appropriately to the physician's population? The cliché of "every patient is different" is relevant and important in evaluating the baseline risk of your patient vs the baseline risks of the patients in a specific trial. Caution must be advised when using subgroup analysis of a study which may lead to unclear or improper conclusions.

What EBM is not:

EBM is not a substitute to violate our sacred and precious Hippocratic oath which includes Primum non nocere ('first do no harm'). As physicians, treating a patient blindly following guidelines without critically evaluating for a specific patient or patient population is risky. Especially, when knowingly or unknowingly there may be increased mortality or morbidity to the patient is unethical and unacceptable behavior. It is incumbent upon every physician to remember that once entering one of the most honorable professions, they are

committed to a lifetime of learning. EBM is an amazing method to apply research principles to the practice but only if the evidence is properly evaluated and then implemented.

Endnotes:

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