Review

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Chronic inflammatory response syndrome: a review of the evidence of clinical efficacy of treatment

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Abstract

Chronic Inflammatory Response Syndrome (CIRS) is an acquired medical condition characterized by innate immune dysregulation following respiratory exposure to water-damaged buildings (WDB). This chronic syndrome involves a range of symptoms that simultaneously affecting multiple organ systems. The purpose of this literature review was to search the published literature for successful treatments for chronic inflammatory response syndrome, an under-recognized, underdiagnosed, multisymptom multisystem illness that can affect up to 25% of the population, thus representing a silent epidemic. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), a common misdiagnosis for CIRS, is an entity that has broader awareness within the medical community despite the absence of a defined etiology, biomarkers or a treatment protocol that reverses the underlying conditions. Therefore, the search also included treatments for ME/CFS and sick building syndrome (SBS). Thirteen articles referenced treatment for CIRS, and 22 articles referenced treatment for CFS. The only treatment with documented clinical efficacy was the Shoemaker Protocol, which was described in 11 of the 13 articles. This treatment protocol exhibits superior outcomes compared with the treatment protocols for ME/CFS.

Keywords: chronic fatigue syndrome, innate immune system activation, medically unexplained symptoms, mold illness, sick building syndrome, treatment of chronic inflammatory response syndrome

Background

Approximately 25% of the population is genetically susceptible to developing Chronic Inflammatory Response Syndrome (CIRS)[1]. According to McMahon[2], at least 52.1 million persons are predisposed to developing CIRS from exposure to water-damaged buildings (WDB) in the United States. With an estimated 50% of the buildings in the U.S. water-damaged[3], the prevalence of CIRS is conservatively calculated at $\geq$7.01% in children and likely higher in adults due to the progressive nature of CIRS[4] (p20). In 2021, legal recognition for CIRS was achieved when a Florida court awarded a 56-year-old woman, who became disabled after living in an apartment with a leaky roof and was diagnosed with CIRS, a 48-million-dollar judgment[5].

CIRS is a dysregulation of the innate immune system resulting in a multisymptom, multisystem illness[6]. CIRS is an under-recognized syndrome commonly misdiagnosed as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), a medically unexplained illnesses. CIRS is a progressive disease that can be treated. Cases, first identified in 1997, involved individuals exposed to toxin-forming dinoflagellates[7]. Shoemaker and Hudnell speculated the mechanism of injury to be a 'neurotoxin mediated-illness'[7] (p539). Following this observation, researchers found and documented this same constellation of symptoms in individuals with other forms of biotoxin exposure: chronic-Lyme disease, ciguatera, cyanobacteria, harmful Algal Blooms (HAB), and mold and other microbial growth arising in water-damaged buildings[1]. During this time period, Shoemaker also identified blood tests that measured 'elevated inflammatory markers [and] reduced levels of regulatory neuropeptides'[1], (p1) representing a dysregulation of the innate immune system.

In his original description of CIRS, Shoemaker identified 37 symptoms differentiating cases from controls. Typically, with CIRS there is a reduction in the normal levels of regulatory neuropeptides, especially MSH, and an elevation in at least one of

HIGHLIGHTS

- Chronic Inflammatory Response Syndrome is a multisymptom, multisystem illness acquired following respiratory exposure to water-damaged buildings.
- It is an under-recognized, underdiagnosed dysregulation of the innate immune system that can affect 25% of the population, therefore representing a silent epidemic.
- The only treatment in the published literature documenting clinical efficacy for the treatment of Chronic Inflammatory Response Syndrome is the Shoemaker Protocol.
- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome is a common misdiagnosis for Chronic Inflammatory Response Syndrome but lacks a defined etiology, biomarkers, or a treatment protocol that reverses the underlying conditions.

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the three inflammatory markers TGF-ß1, C4a, and MMP-9. There may be dysregulation of ACTH and cortisol, dysregulation of ADH and osmolality, and abnormalities in gliadin antibodies, anticardiolipin antibodies, and VEGF. Analyses in national laboratories can be used to measure these biomarkers. There are usually abnormalities in visual contrast sensitivity (VSC) testing[1]. This innate immune system dysregulation underlies the numerous symptoms present in CIRS patients.

Shoemaker and Maizel provided evidence for a causal relationship between CIRS and exposure to water-damaged buildings through a methodical approach that included controlled repetitive exposure, adherence to treatment protocols, and meticulous documentation of symptoms' baseline levels and any exacerbation[8]. They performed prospective exposure studies in patients who had previously improved with treatment. After re-exposure and subsequent worsening of symptoms, retreatment brought symptoms and objective parameters back to control levels. These repetitive re-exposure trials documented sequential activation of innate immune elements[8–10], supporting the potential for causation of indoor microbial exposure and multi-symptom illness.

In 2006, Shoemaker published a case definition for Chronic Biotoxin-Associated Illness (CBAI), which required exposure to a water-damaged building, presence of symptoms in four of eight systems, absence of confounders, abnormalities in three of six objective parameters, and response to appropriate therapy[11]. In 2008, the General Accounting Office released its report, which included a case definition that paralleled the 2006 case definition[12]. In 2017, McMahon published a third case definition. This definition compared alternative methods of diagnosis with the two existing case definitions in the literature to provide a case definition that does not require improvement with therapy to confirm the diagnosis, as compliance can be difficult and improvement may take months. This case definition combined symptom clusters with screen tests or labs, demonstrating excellent diagnostic accuracy[13].

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is defined by the centers for disease control and prevention (CDC) as 'a complex, chronic, debilitating disease with systemic effects. ME/CFS is characterized by reduced ability to perform preillness activities that last for more than 6 months and is accompanied by profound fatigue, which is not improved by rest'[14] (p1). The CDC describes that symptoms frequently 'worsen after physical, mental, or emotional effort, a manifestation known as postexertional malaise (PEM)'[14] (p1) along with patients experiencing 'unrefreshing sleep…orthostatic intolerance, cognitive impairment, and pain'[14] (p1).

Since CIRS is under-recognized, the vast majority of individuals diagnosed with ME/CFS, are likely to have CIRS as the symptoms associated with ME/CFS fall within the symptoms that define CIRS, with laboratory tests for CIRS biomarkers more often than not satisfying the case definition.

Lack of awareness regarding the diagnosis and treatment of CIRS is a barrier to timely medical care. Haller *et al*.[15] performed a systematic review and meta-analysis of the prevalence of medically unexplained symptoms with key findings that 'an average of 26.2–34.8% of patients under the care of general practitioners report at least one somatoform disorder according to DSM or ICD, and 40.2–49.0% report at least one medically unexplained symptom'[15] (p286). Often, medically unexplained symptoms point to CIRS.

This review examines the place of CIRS within the existing literature to describe treatments with documented clinical efficacy.

Methods

In June 2022, the authors searched the EBSCOhost Academic Search Premier, Proquest, Google Scholar, and the Cochrane Library databases, using the following keywords:

'Chronic Inflammatory Response Syndrome' AND 'Treatment'

'Mold Illness' AND 'Treatment'

'Sick Building Syndrome' AND 'Treatment'

'Chronic Fatigue Syndrome' AND 'Treatment'

'Innate Immune System Activation' AND 'Mold'

Articles published in peer-reviewed journals within the past 15 years, authored by relevant professionals, reviewing treatment protocols, and written in English were included. Articles that did not review treatment protocols or were outdated were excluded. Additional references from reviewed articles were included if they met these criteria. Articles were classified based on study design, that is, the level of evidence on the evidence pyramid[16] as described by the evidence hierarchy in Table 1. All articles were reviewed by one author with results verified by a second author.

Four of the studies relating to the treatment of CIRS were older than 15 years old. However, owing to the relevance of the results, the quality of these studies, and the evidence for this step of the treatment protocol, which has remained the same for over 20 years, these papers were included in this review.

Results

Treatment for CIRS

Thirteen articles, comprising 14 studies, were identified in the published literature related to CIRS treatment. Shoemaker and House[11] published a randomized control trial and case series in a single article. The studies included two randomized control trials, three case/control studies, five single nonexperimental studies, one review of descriptive and qualitative studies, and three single descriptive studies containing a total of seven cases[7,11,17–27], as summarized in Table 2.

Treatment for CFS

Twenty-two articles identified as related to CFS treatment were reviewed. These 22 studies comprise four systematic reviews/meta-analyses of randomized controlled trials, three randomized clinical trials, six single nonexperimental studies, seven reviews of descriptive and qualitative studies, and two single descriptive or qualitative studies[28–59], as summarized in Table 3.

Discussion

While other medical clinics replicated Shoemaker's treatment protocols, peer-reviewed publications other than Shoemaker's, have been minimal. However, in recent years, published research

Table 1

Hierarchy of Evidence: Levels of Study Design in Evidence-Based Practice

Level on the evidence pyramid	Study design
Level I	Systematic review or meta-analysis of randomized controlled trials (RCT)
Level II	A well-designed RCT
Level III	Controlled trial without randomization
Level IV	Single nonexperimental study
Level V	Systematic review of descriptive and qualitative studies
Level VI	Single descriptive or qualitative study
Level VII	Opinion of authorities and/or reports of expert committees

defining the inflammatory basis of the syndrome has been reported by Conti[50], Harding[51,52], Nordin[53], and Ratnesselan[55], along with Shoemaker and Ryan's work in transcriptomics[20,55–57], adding to the body of knowledge defining the molecular basis for CIRS. Dooley and McMahon[4] performed a comprehensive review of the literature and found that 112 of 114 epidemiological articles (98.2%) identified a correlation between chronic indoor microbial growth/dampness exposure and adverse human health effects from exposure to the interior of a WDB. They found statistically significant results with either an odds ratio (OR) or relative risk (RR) of ≥ 2.0 in 79 of these articles encompassing systems that included respiratory, neurological, immunologic, cognitive, ophthalmologic, and dermatologic, compelling evidence supporting this association.

Successful treatment for CIRS

The published literature documents successful treatment for CIRS with the Shoemaker Protocol, measured by statistically significant changes in objective biomarkers and resolution of symptoms in ten papers by the Shoemaker group reporting results from eleven clinical studies[7,11,17,18,20–24,27]. From 1997 to 2006, six studies comprising two studies that included six case histories, two double-blind placebo-controlled crossover studies with 34 participants, a cross-sectional study with 21 participants, and a case–control study with 156 cases and 110 controls were completed[7,11,17,21,22,27]. In more recent years, three additional studies with 69 patients and one case–control study with 68 cases and 23 controls were published, citing statistically significant successful changes in biomarkers and resolution of symptoms[18,20,23,24]. All studies used a published case-definition for diagnosis. In addition, one case history documented the success of a patient treated according to the published Shoemaker protocol, whose primary complaint was ulcerative colitis and CFS[26].

We identified only two additional publications that reference treating mold-illness. One review study, addressing in vitro and animal studies relating to the mechanism of injury and treatment approaches, included off-label use of cholestyramine as is used in the Shoemaker Protocol[25]. The other publication, documented treatment with removal from exposure, antigen injections, and additional treatments for nonresponders[19]. However, while it was likely that these patients had CIRS, a published case-definition was not met and financial constraints prevented post-treatment testing to confirm objection resolution of biomarkers. Many treatments provide symptomatic relief, but individuals often need to continue these treatments indefinitely to maintain their health.

Limitations of the Shoemaker protocol

Cost, adherence challenges, and side effects are the most limitations of the Shoemaker Protocol. The first step of the Shoemaker Protocol is avoidance of exposure. Achieving this step usually involves some combination of environmental inspections, remediation, cleaning or replacing contaminated items, and relocation. Step one costs readily exceed tens of thousands of dollars and, in the case of extensive remediations, can reach millions of dollars.

Most of the treatment steps of the Shoemaker protocol are affordable, with most elements of the program costing one hundred dollars or less for a month's supply, including treatments such as cholestyramine, colesevelam, EDTA nasal spray, desmopressin, and DHEA supplementation. Insurance coverage of these prescriptions lowers the cost. The most expensive medication step of treatment is vasoactive intestinal peptide (VIP), a medication that is not covered by insurance treatment as it is available for order only through compounding pharmacies. The price of this medication increases frequently, with current standard monthly costs exceeding $300 a month.

Aside from financial accessibility, the most common barrier to

Table 2

Summary of Literature on CIRS Treatment: Study Design, Evidence Levels, and Treatment Outcomes

Study	Evidence pyramid	# of subjects	Type of treatment assessed
Shoemaker[17]	Level II	8	RCT cholestyramine – successful
Shoemaker and House[11]	Level II	13	RCT cholestyramine – successful
McMahon *et al.*[18]	Level IV	68/23	Case/control – successful
Rea[19]	Level IV	100	Antigen intradermal treatments – lack of objective data
Shoemaker and House[11]	Level IV	28	Case time series cholestyramine – successful
Ryan and Shoemaker[20]	Level IV	14	Case time series vasoactive intestinal peptide – successful
Shoemaker and House[21]	Level IV	21	Case time series cholestyramine – successful
Shoemaker *et al.*[22]	Level IV	156/111	Case/control cholestyramine – successful
Shoemaker *et al.*[23]	Level IV	20	Open-label trial vasoactive intestinal peptide – successful
Shoemaker *et al.*[24]	Level IV	35/4	Open- label trial vasoactive intestinal peptide – improvement with VIP
Hope[25]	Level V	Review	Mentions cholestyramine – no data
Gunn *et al.*[26]	Level VI	Case	Successful treatment with cholestyramine and vasoactive intestinal peptide
Shoemaker[27]	Level VI	Case	Successful treatment with cholestyramine – one case
Shoemaker and Hudnell[7]	Level VI	Cases	Successful treatment with cholestyramine – five cases

Table 3

Summary of Literature on Chronic Fatigue Syndrome (CFS) Treatment: Evidence Levels and Treatment Modalities

Study	Evidence pyramid	# of subjects	Type of treatment assessed
Joustra *et al.*[30]	Level I	49	Nutritional interventions
Larun *et al.*[28]	Level I	1518	Exercise therapy
You *et al.*[31]	Level I	1030	Systematic review, Chinese moxibustion
Wang *et al.*[32]	Level I	2036	Systematic review, high efficacy/poor quality, more frequent treatments than practiced in USA
Friedberg *et al.*[33]	Level II	23	Molecular hydrogen, randomized control
Nilsson *et al.*[34]	Level II	62	OSU6162 – a monoaminergic stabilizer – randomized control
Walach *et al.*[35]	Level II	409	Distant spiritual healing, randomized control
Crosby *et al.*[36]	Level IV	101	Retrospective review of Aripiprazole – off-label use
Fernie *et al.*[37]	Level IV	171	Cognitive behavioral therapy (CBT) (116) and graded exercise therapy (GET) (55)
Haghighi *et al.*[38]	Level IV	33	OSU6162 – a monoaminergic stabilizer
Kujawski *et al.*[39]	Level IV	32/18	Whole body cryotherapy and static stretching – case–control
Nathan and Konynenburg[40]	Level IV	23	Nutritional supplements – full study no longer available online, unable to evaluate if results were beneficial, no control group
Polo[41]	Level IV	218	Retrospective review of low-dose naltrexone
Fernandez *et al.*[42]	Level V	Review	Found no curative treatment
Bjorklund *et al.*[29]	Level V	Review	Nutritional treatment
Brown[43]	Level V	Review	Current treatments modest benefits, poor prognosis, recommends individualized plan
Mengshoel *et al.*[44]	Level V	Review	Review of nonpharmacological therapies
Zhang *et al.*[45]	Level V	Review	Reviews Chinese herbs, acupuncture, moxibustion and cupping
Davenport *et al.*[46]	Level VI	Case	675 days of IV saline
Royle *et al.*[47]	Level VI	Case	Eye movement desensitization and reprocessing
Sharpe *et al.*[48]	Level VII	Expert Opinion	Recommend CBT and GET, no known etiology for CFS
Yancey and Thomas[49]	Level VII	Expert Opinion	Only efficacious treatment CBT and GET

treatment effectiveness is medication intolerance. Mold-exposed patients develop multiple chemical sensitivity, a vulnerability that extends to both prescription medications and supplementation. Sensitivity causes innumerable nonspecific side effects, such as malaise and flu-like symptoms. Moreover, the side effects of individual medications include constipation from cholestyramine, hyponatremia from desmopressin, and light-headedness from vasoactive intestinal peptides.

Lack of curative treatment for myalgic encephalomyelitis/chronic fatigue syndrome

Table 3 shows that the published therapies for ME/CFS are pharmacological, nonpharmacological, psychological, and encompass a wide variety of complementary treatments. Much clinical research has been conducted in recent years. Of the 22 studies, 17 reported some benefit, and five reported none. Cognitive behavior therapy (CBT) and graded exercise therapy (GET) were reported as beneficial in six studies and were the most widely recommended; however, it was acknowledged to be noncurative[28,37,42,44,48,49]. No studies reported successful treatment. A systematic review by Larun *et al.*[28] concluded that exercise therapy leads to improvements. However, many patients with CIRS experience systemic exercise intolerance disorder (SEID) and reductions in VO_2 max that render them unable to engage in exercise[1].

Three studies, including one review study, showed improvements in symptoms from various nutritional approaches[29,40,43], but one other study did not document beneficial outcomes[31]. Case histories documenting 675 days of IV saline infusion[46] and the use of eye movement desensitization and reprocessing (EMDR)[47] also showed improvement. A study with 32 cases and 18 controls noted improvement with whole-body cryotherapy and static stretching[39]. Three review studies of acupuncture and/or moxibustion, the practice of burning moxa, the herb wormwood, on parts of the body or acupuncture points[32], reported efficacy. However, two of these studies rated the quality of evidence as moderate to very low quality of evidence[31,32] and the third study did not calculate *P*-values for their results, suggesting that the reported improvement may not have been statistically significant[45].

Four studies used off-label pharmaceutical intervention. Two researchers used the monoaminergic stabilizer OSU6162. An open-label trial in 33 patients suggested benefit[38], but failed to be confirmed in a randomized control trial[34]. Aripiprazole, an atypical antipsychotic, showed some benefit in a prospective single-arm study of 101 patients[36]. However, aripiprazole is a pharmaceutical that carries two black box warnings with the manufacturer currently the defendant in a lawsuit for not providing warnings to families about the risk of an increase in type 2 diabetes in children. These potential adverse effects render aripiprazole a nonideal treatment. A retrospective study of 218 participants treated with low-dose naltrexone showed a high frequency of treatment response, but it was noted that psychiatric drugs 'have failed to demonstrate a clear and sustainable treatment response'[41].

Other studies that documented no treatment efficacy included a study utilizing molecular hydrogen[33], and a randomized single-blind control trial with 409 participants using distant healing[35]. According to the CDC, there is 'no cure or approved treatment[14] (p1)' for ME/CFS and 'some symptoms can be treated or managed'[14] (p1). However, they acknowledge that not all individuals benefit from symptom management.

Limitations

The limitations of this study were that it was not a systematic review of the literature and was limited to specific databases. A broader keyword search may have revealed additional treatment options.

Conclusion

This literature review supports the perspective that CIRS is an inflammatory-based illness that can be corrected using the Shoemaker Protocol. While some providers may have anecdotal evidence, no other treatment protocols have demonstrated the same efficacy in the published literature. Due to the high prevalence of water-damaged buildings, the susceptibility of up to 25% of the population, the significant impact on quality of life and productivity, and the economic burden from lack of awareness, CIRS is a significant public health problem. Healthy people 2030 includes the objective of environmental health, defining the goal to 'promote healthier environments to improve health'[58]. This goal includes reducing exposure to harmful pollutants found in homes and workplaces. Healthy people 2030 provides a narrowly defined literature summary on the quality of housing as a social determinant of health listing the presence of mold as one of the factors that contributes to poor housing quality[59]. It is essential to increase awareness of the need to screen for and diagnose CIRS as well as to educate providers in preventative measures and effective and ineffective treatment modalities.

Changes will not happen overnight, but we must collectively upgrade building standards, upgrade mold remediation protocols, and educate healthcare providers by including CIRS in the curriculum in all healthcare fields and public health curricula. As demonstrated by Buigas[60], all primary care providers should perform VCS screening for CIRS, especially when medically unexplained symptoms are identified.

Securing research funding is critical for clinics to document the outcomes of the Shoemaker protocol and deepen their understanding through transcriptomic data analysis. Further examination of the protocol's effectiveness against syndromes such as pediatric acute-onset neuropsychiatric syndrome, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections, long-COVID, and mRNA vaccine-related injuries, all potential CIRS conditions, would contribute significantly to the scientific literature.

Ethical approval

Ethics approval was not required for this review.

Consent

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Author contribution

M.D.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, visualization, and writing – original draft; A.V.: validation and writing – review and editing; L.J.: writing – review and editing.

Conflicts of interest disclosure

The authors declare no conflicts of interest. Lysander Jim and Ming Dooley provide expert witness testimony in chronic inflammatory response syndrome cases for both plaintiffs and defense.

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