Keystone First
Family of Health Plans

Chronic inflammatory response syndrome

Clinical Policy ID: CCP.1371

Recent review date: 1/2026

Next review date: 5/2027

Policy contains: Chronic inflammatory response syndrome; dampness and mold hypersensitivity syndrome.

Keystone First VIP Choice has developed clinical policies to assist with making coverage determinations. Keystone First VIP Choice's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First VIP Choice, on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First VIP Choice's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First VIP Choice's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First VIP Choice will update its clinical policies as necessary. Keystone First VIP Choice's clinical policies are not guarantees of payment.

Coverage policy

Chronic inflammatory response syndrome is an investigational/not clinically proven diagnosis and, therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Routine patient evaluation and management by a network health care provider.

Background

The named condition chronic inflammatory response syndrome appears in the medical literature as a proposed clinical entity characterized by multisystem symptoms attributed to biotoxin exposure, particularly from the interior environment of water-damaged buildings containing toxigenic organisms (Shoemaker, 2018). The condition was described by Shoemaker beginning in the early 2000s, with diagnostic and treatment criteria

operationalized in a consensus statement published in 2018 (Shoemaker, 2018; Shoemaker, 2014). A related term, dampness and mold hypersensitivity syndrome, has been used by European researchers to describe a similar clinical presentation in patients with prolonged exposure to indoor dampness microbiota (Valtonen, 2017; Tuuminen and Lohi, 2018).

The condition lacks formal recognition in major disease classification systems. The World Health Organization International Statistical Classification of Diseases, Eleventh Revision does not include a specific diagnostic code for chronic inflammatory response syndrome or dampness and mold hypersensitivity syndrome (World Health Organization, 2024). Proponents of the diagnosis have proposed diagnostic criteria based on symptom cluster analysis, genetic susceptibility markers related to human leukocyte antigen haplotypes, visual contrast sensitivity testing, and a panel of inflammatory biomarkers including complement component four activation product, matrix metalloproteinase nine, transforming growth factor beta one, melanocyte-stimulating hormone, and vasoactive intestinal polypeptide (Shoemaker, 2018; Dooley, 2025). A sequential treatment protocol involving removal from exposure, bile acid sequestrant therapy, eradication of nasal colonization with antibiotic-resistant staphylococci, and normalization of various biomarkers has been proposed (Shoemaker, 2018; Dooley, 2024).

Independent researchers have documented immunologic changes in individuals exposed to damp indoor environments, including complement activation and elevations in inflammatory markers, though these findings have not been shown to constitute a specific disease entity distinguishable from other chronic multisystem conditions (Karhuvaara, 2024; Hyvönen, 2020). While respiratory and allergic manifestations of mold exposure are well-established in the medical literature, the existence of a distinct chronic inflammatory syndrome caused by low-level inhalational biotoxin exposure has been questioned by mainstream medical and toxicology organizations (Chang and Gershwin, 2019; American College of Medical Toxicology, 2025).

Findings

Published evidence does not support recognition of chronic inflammatory response syndrome as a validated diagnostic entity distinct from other chronic multisystem illnesses. Clinical guidelines from major medical societies do not recognize the condition and recommend against the use of proposed diagnostic methods (Hurraß, 2024; American College of Medical Toxicology, 2025; American Academy of Allergy, Asthma, and Immunology, 2024). No systematic reviews or meta-analyses were identified that validate the condition as a distinct diagnostic entity. The primary supportive literature originates predominantly from a small network of affiliated practitioners without independent replication (Dooley, 2024). The proposed biomarker panels lack standardization, validated reference ranges, and demonstrated diagnostic accuracy (Chang and Gershwin, 2019; Centers for Disease Control and Prevention, 2015). Two small randomized controlled trials of cholestyramine conducted by the protocol's originator have been reported, but no large, independent, multi-site trials have validated the treatment protocol, and no randomized trials have evaluated other protocol components (Dooley, 2024; Shoemaker, 2014).

Clinical guideline

Clinical guidelines from established medical societies and government agencies do not recognize chronic inflammatory response syndrome or dampness and mold hypersensitivity syndrome as validated diagnostic entities. The Association of the Scientific Medical Societies in Germany published an updated consensus guideline in 2023 addressing medical clinical diagnostics for indoor mold exposure, developed by twelve German

and Austrian medical societies representing allergy, pulmonology, occupational medicine, dermatology, hospital hygiene, mycology, and pediatric specialties (Hurraß, 2024). This guideline achieved greater than ninety-five percent consensus on all recommendations (Hurraß, 2024). The guideline states that for conditions including chronic fatigue syndrome, multiple chemical sensitivity, sick building syndrome, neuropsychological effects, and neurotoxic effects, the evidence for association with indoor mold exposure is “inadequate or insufficient” (Hurraß, 2024). Although the guideline does not use the specific term “chronic inflammatory response syndrome,” these listed conditions overlap substantially with those attributed to the proposed syndrome.

The German guideline specifies that diagnostic methods commonly used in the evaluation of patients with suspected mold-related chronic inflammatory illness shall not be performed due to insufficient scientific evidence (Hurraß, 2024). These methods include visual contrast sensitivity testing, cytokine determinations, lymphocyte subpopulation testing, lymphocyte transformation tests, and mycotoxin testing in biological samples (Hurraß, 2024). The guideline states: “The following diagnostic methods shall not be used for indoor mold exposure because there is insufficient scientific evidence: detection of molds in the blood, determination of IgA antibodies directed against molds, determination of lymphocyte subpopulations, determination of cytokines, determination of oxidative stress, visual contrast sensitivity test, tear film break-up time” (Hurraß, 2024).

The American College of Medical Toxicology published a position statement in 2025 addressing medical toxicology considerations in patients with concerns about mold-related inhalation exposures (American College of Medical Toxicology, 2025). This statement endorses the conclusions of both the 2004 National Academy of Medicine report and the 2023 German guideline (American College of Medical Toxicology, 2025). The position statement emphasizes that environmental mycotoxin concentrations are orders of magnitude lower than those known to cause toxicity in controlled studies, that detection of mycotoxins or antibodies in patients is not an accepted diagnostic approach, and that diet rather than inhalation represents the dominant source of human mycotoxin exposure (American College of Medical Toxicology, 2025).

The American Academy of Allergy, Asthma, and Immunology has stated that available evidence is insufficient to support a relationship between mycotoxin inhalation and the range of nonspecific symptoms reported as toxic mold syndrome or chronic inflammatory response syndrome (American Academy of Allergy, Asthma, and Immunology, 2024). The organization noted that many reports of mold-related illness suffer from lack of controls and potential bias, and cautioned against unvalidated tests and interventions (American Academy of Allergy, Asthma, and Immunology, 2024).

Systematic reviews

No systematic reviews meeting Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards were identified that validate chronic inflammatory response syndrome as a diagnostic entity or evaluate the accuracy of proposed diagnostic criteria. A narrative review by Dooley searched multiple databases for chronic inflammatory response syndrome treatments and identified thirteen publications addressing the topic, eleven of which described the Shoemaker protocol as the only therapy with documented clinical efficacy (Dooley, 2024). However, this review did not meet systematic review methodological standards, did not assess risk of bias, did not include meta-analytic pooling, and drew predominantly from publications by the protocol’s originators (Dooley, 2024). The authors disclosed affiliations with organizations that provide chronic inflammatory response syndrome diagnosis and treatment services (Dooley, 2024).

Independent researchers in Finland have published narrative reviews proposing clinical diagnostic criteria for dampness and mold hypersensitivity syndrome (Valtonen, 2017; Tuuminen and Lohi, 2018). These reviews explicitly acknowledge that no unanimously accepted laboratory tests exist for diagnosing dampness and mold

hypersensitivity syndrome and that diagnosis remains purely clinical (Valtonen, 2017). The proposed diagnostic criteria include history of water-damaged building exposure, recurrent infections, sick building syndrome symptoms, multiple chemical sensitivity, and heightened odor sensitivity, but these criteria have not been validated against an independent reference standard (Valtonen, 2017).

Meta-analyses

No meta-analyses were identified that evaluate diagnostic accuracy, treatment efficacy, or clinical outcomes for chronic inflammatory response syndrome or the proposed Shoemaker diagnostic and treatment protocol. Meta-analyses addressing indoor dampness and mold exposure have examined associations with respiratory outcomes including asthma and rhinitis but have not evaluated chronic inflammatory response syndrome as a distinct diagnostic entity or validated the specific biomarker panels proposed for its diagnosis (Quansah, 2012; Jaakkola, 2013).

Other evidence

Primary studies evaluating diagnostic criteria, biomarkers, and clinical outcomes for chronic inflammatory response syndrome originate predominantly from a small group of affiliated practitioners. The Dooley review identified two randomized controlled trials of cholestyramine with a combined total of thirty-four participants, both conducted by the protocol's originator (Dooley, 2024). These trials reported improvements in visual contrast sensitivity scores but have not been independently replicated, and no randomized trials have evaluated other components of the treatment protocol including intranasal vasoactive intestinal polypeptide, nasal antimicrobial therapy, or the sequential multi-step algorithm (Dooley, 2024).

A transcriptomic study by Ryan examined gene expression profiles in eleven patients with chronic inflammatory response syndrome attributed to ciguatoxin exposure compared with eleven controls, identifying differentially expressed genes with high classification accuracy (Ryan, 2015). However, this study addressed marine biotoxin exposure rather than mold, included a small sample size, involved the originator of the chronic inflammatory response syndrome construct as a co-author, and has not been replicated by independent investigators (Ryan, 2015). A neuroimaging study reported structural brain differences in seventeen patients with mold-attributed chronic inflammatory response syndrome compared with eighteen controls, but this study likewise originated from the same research group and has not been independently confirmed (Shoemaker, 2014).

Independent Finnish researchers have documented elevated complement component three activation product and C-reactive protein in individuals exposed to damp indoor environments compared with controls (Karhuvaara, 2024). This study provides some support for immune activation with mold exposure but did not evaluate the specific biomarker panel proposed for chronic inflammatory response syndrome diagnosis, did not measure complement component four activation product, and did not validate any diagnostic criteria (Karhuvaara, 2024). A separate Finnish study documented higher rates of neurological symptoms in workers exposed to moisture-damaged buildings compared with controls but employed a cross-sectional design that cannot establish causation (Hyvönen, 2020).

The proposed biomarkers for chronic inflammatory response syndrome lack independent validation of diagnostic accuracy. No studies were identified that establish sensitivity, specificity, positive predictive value, or negative predictive value for complement component four activation product, matrix metalloproteinase nine, transforming growth factor beta one, melanocyte-stimulating hormone, or vasoactive intestinal polypeptide in distinguishing chronic inflammatory response syndrome from other chronic multisystem illnesses. The Centers for Disease Control and Prevention has cautioned that commercial urinary mycotoxin assays used in some diagnostic

protocols are not clinically validated and that mycotoxin detection does not establish causation by inhalational exposure given dietary sources of exposure (Centers for Disease Control and Prevention, 2015). A critical review by Chang and Gershwin characterized commercial mycotoxin testing laboratories as lacking scientific credibility and concluded that the evidence does not support toxic mold syndrome as a diagnostic entity (Chang and Gershwin, 2019).

A single case report described improvement in symptoms and biomarkers in one patient treated with hyperbaric oxygen therapy as an alternative to standard protocol components, but this represents anecdotal evidence without control comparison (Coletti Giesler, 2025).

In 2026, we revised the background and findings sections. We updated the policy references to include the Association of the Scientific Medical Societies in Germany mold guideline (Hurraß, 2024), the American College of Medical Toxicology position statement (American College of Medical Toxicology, 2025), an independent critical review (Chang and Gershwin, 2019), and an independent biomarker study (Karhuvaara, 2024), and clarified the scope of evidence from randomized trials reported in the literature (Dooley, 2024).

References

On December 6, 2025, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “chronic inflammatory response syndrome” and “dampness and mold hypersensitivity syndrome.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

3/2018: initial review date and clinical policy effective date: 5/2018

4/2019: Policy references updated.

1/2020: Policy references updated.

1/2021: Policy references updated.

1/2022: Policy references updated.

1/2023: Policy references updated.

1/2024: Policy references updated.

Related Codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1353. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code Description
86160	Complement; antigen, each component (e.g., C4a)
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, NOS (Used for MMP-9, TGF-beta-1, VEGF)
83519	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (RIA) (Used for MSH)
84586	Vasoactive Intestinal Peptide (VIP)
84588	Vasopressin (Antidiuretic hormone, ADH)
81370–81383	HLA Class I and II typing (HLA-DR/DQ)