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RESEARCH ARTICLE

Clinical Operationalization of the Cell Danger Response: A Five-Phase Treatment Protocol - Outcomes in 100 Patients with Chronic Post-Exposure Illness

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ABSTRACT

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Background: The Cell Danger Response is a unifying mechanistic framework, articulated by Naviaux and colleagues, that explains the persistent multisystem dysfunction observed in chronic post-exposure illness, including illness following exposure to water-damaged buildings, tick-borne pathogens, viral infections, and complex environmental insults. The response proceeds through three sequential biological stages: active defense, hypometabolic repair, and restoration. When the cycle fails to complete, persistent arrest produces the multisystem clinical phenotype now recognized across mold-related illness, post-viral syndromes including long COVID, tick-borne illness, and chronic fatigue syndrome. Although the model is biologically rich and supported by metabolomic, transcriptomic, and proteomic evidence, no published clinical protocol has previously translated this biology into a sequenced, actionable treatment framework with prospective outcome data.

Methods: This retrospective cohort study analyzed 100 consecutive patients with chronic post-exposure illness who received a standardized five-phase clinical protocol grounded in Cell Danger Response biology, delivered in a group format over 12 months at a single specialty practice between 2021 and 2024. Each phase addresses a distinct biological node maintaining the arrested state. The primary outcome was time to the Ready-to-Heal gate, reflecting objective readiness for restorative-phase initiation; secondary outcomes included a 12-question symptom roster, the SF-20 quality-of-life scale, visual contrast sensitivity testing, and a comprehensive biomarker panel spanning innate immune activation, regulatory hormone depletion, mitochondrial stress, and capillary perfusion.

Results: Median time to Ready-to-Heal status was 5.4 months (95% confidence interval 4.8 to 6.1), with 92% of participants reaching the restorative phase within 12 months. Symptom burden decreased by 82% (effect size 1.82, p less than 0.001); quality-of-life scores improved substantially across all seven domains (effect size 1.29 to 1.82, all p less than 0.001); visual contrast sensitivity normalization or clinically meaningful gain was achieved in 88%; and normalization of at least 80% of the biomarker panel was achieved in 85% of participants. Adverse events were mild and infrequent, and no serious protocol-related adverse events occurred.

Conclusion: This study represents the first published prospective evaluation of a structured clinical protocol explicitly translating the Cell Danger Response model into actionable clinical practice. The five-phase protocol produced rapid, consistent, and clinically meaningful improvements in one of the largest reported cohorts of patients with this arrested-response phenotype. The work provides a clinical bridge between mechanism and patient care, and offers a reproducible framework suitable for randomized controlled trials and multi-center replication.

Keywords: Cell Danger Response; mitochondrial integrated stress response; salugenesis; chronic post-exposure illness; biotoxin illness; post-viral syndrome; polyvagal theory; five-phase clinical protocol; vasoactive intestinal peptide; mitokines

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1. Introduction

Chronic post-exposure illness presents one of the most persistent and least well-organized challenges in contemporary medicine: a disabling, multisystem condition that follows an identifiable biological insult yet resists the organ-specific frameworks that dominate clinical practice. This introduction sets out the clinical problem, the unifying biology of the Cell Danger Response and its molecular counterpart the mitochondrial integrated stress response, the neuroendocrine and autonomic signaling network that governs recovery, and the unmet need for a structured clinical translation of this model. It then introduces the five-phase protocol evaluated in this study and the objective gate that governs entry to its restorative phase.

1.1 CHRONIC POST-EXPOSURE ILLNESS: A CLINICAL PROBLEM IN SEARCH OF A UNIFYING MECHANISM

A substantial population of patients experiences persistent, disabling, multisystem illness following an identifiable biological insult — most commonly exposure to the interior environment of water-damaged buildings, but also following tick-borne pathogen exposure, post-viral infection including long COVID, ciguatoxin exposure, exposure to dinoflagellates and cyanobacteria, severe psychosocial trauma, and combinations of these triggers.[1-6] The clinical phenotype is remarkably consistent across these otherwise distinct etiologies: disabling fatigue and post-exertional malaise, cognitive impairment, autonomic dysregulation, environmental and food sensitivities, sleep disruption, musculoskeletal pain, and gastrointestinal and respiratory symptoms that persist for months to years after the initial exposure.[2-6] Functional impairment is substantial; many patients experience loss of employment, social withdrawal, and progressive disability.[5-6]

For decades, this clinical phenotype has been described under multiple labels — mold-related illness, chronic Lyme disease, fibromyalgia, myalgic encephalomyelitis / chronic fatigue syndrome, Gulf War Illness, and post-acute sequelae of SARS-CoV-2 infection (long COVID) — each defined by its trigger or its dominant symptom rather than by a shared mechanistic understanding. The consequence has been a fragmented clinical literature, inconsistent treatment approaches, and limited cross-pollination of evidence between adjacent patient populations. Patients have frequently moved between specialists and frameworks without a unifying biological model to guide treatment sequencing or to predict response.

The Cell Danger Response, described by Naviaux and colleagues over the past decade, provides such a unifying biological model.[7-9] This framework explains why disparate triggers produce convergent clinical phenotypes; why standard organ-specific interventions often fail; why patients can deteriorate over years despite the original trigger having been removed; and why interventions that interrupt the persistent signaling cascade produce dramatic clinical improvement. The framework has been validated metabolomically in chronic fatigue syndrome,[9] transcriptomically in multiple chronic illness populations,[10-12] and through mechanistic studies of the molecular machinery that drives its persistence.[13-16]

1.2 THE CELL DANGER RESPONSE: A UNIFYING BIOLOGICAL FRAMEWORK

The Cell Danger Response is an evolutionarily conserved cellular defensive program activated by any perceived threat, whether microbial, chemical, mechanical, or psychosocial.[7-8] Upon threat detection, cells coordinate a comprehensive metabolic, immunologic, and signaling shift: energy production transitions from efficient mitochondrial oxidative phosphorylation toward defensive glycolytic metabolism; mitochondria fragment and release intracellular damage-associated molecular patterns; extracellular adenosine triphosphate is released as a molecular alarm signal that activates

purinergic P2X and P2Y receptors on surrounding cells; the innate immune system enters an acute defensive posture; the autonomic nervous system shifts toward sympathetic dominance with parasympathetic withdrawal; and the neuroendocrine system reorganizes around threat management rather than restoration.[7-9,17-18]

The response proceeds through three sequential biological stages, each with distinct metabolic priorities and clinical manifestations.[8] The first stage, active defense, is characterized by maximal purinergic alarm signaling, NLRP3 inflammasome activation, an inflammatory cytokine surge (interleukin 1-beta, interleukin 6, tumor necrosis factor alpha), mitochondrial fragmentation, and sympathetic dominance. The second stage, hypometabolic repair, is characterized by systemic metabolic-rate suppression, mitokine elevation (growth differentiation factor 15 and fibroblast growth factor 21), immune exhaustion, dysregulated signaling through the mechanistic target of rapamycin and hypoxia-inducible factor 1-alpha, and Warburg-like aerobic glycolysis. The third stage, restoration and salugenesis, is characterized by resolution of purinergic signaling, mitochondrial reintegration, polarization of immune cells toward the resolution phenotype, restoration of neuroendocrine output, anabolic metabolic reactivation, tissue repair, stem-cell engagement, and parasympathetic tone restoration.[8-9,17-18]

Normal completion of the cycle returns the cell to a homeostatic baseline. When the cycle cannot complete — typically because purinergic alarm signaling persists in the absence of resolvable danger, or because the cell lacks the substrate and trophic signaling required to exit defense — the cell remains in a self-sustaining hypometabolic state that Naviaux and colleagues have characterized as dauer-like.[9] This state has been documented metabolomically in chronic fatigue syndrome, with approximately 80% of measured plasma metabolites showing depression rather than elevation, consistent with broad metabolic conservation.[9] Notably, the metabolomic signature is shared across affected populations regardless of triggering etiology, supporting the conception of persistent arrest as a final common pathway for chronic post-exposure illness.[1,9]

1.3 THE INTEGRATED STRESS RESPONSE AND THE MOLECULAR MACHINERY OF PERSISTENCE

Convergent with the Cell Danger Response framework, the mitochondrial integrated stress response provides a complementary molecular description of how mitochondrial dysfunction is communicated systemically to maintain a defensive cellular state.[13-16,19] When mitochondria are stressed by infection, toxin, or sustained inflammatory signaling, the inner-membrane protease OMA1 cleaves the mitochondrial protein DELE1, releasing a cytosolic fragment that activates the heme-regulated kinase HRI.[13-14] This kinase phosphorylates eukaryotic initiation factor 2-alpha at serine 51, globally reprogramming cellular protein synthesis toward stress management and away from normal function. The downstream transcriptional program is driven by the activating transcription factors ATF4 and ATF5, which upregulate one-carbon metabolism, serine biosynthesis, asparagine synthetase, and — critically for clinical diagnostics — the mitokines growth differentiation factor 15 and fibroblast growth factor 21, which are secreted into peripheral blood as the systemic signal of active mitochondrial stress.[15-17,20-21]

This machinery provides the molecular substrate by which the persistent danger state is maintained at the cellular level, and it provides accessible peripheral-blood biomarkers that directly report on active mitochondrial stress in chronic illness populations.[20-21] Together, the phenomenology of the Cell Danger Response and the molecular mechanism of the integrated stress response comprise a coherent biology of chronic post-exposure illness that bridges cellular signaling, immune function, neuroendocrine regulation, and the autonomic nervous system.

1.4 THE NEUROENDOCRINE AND AUTONOMIC SAFETY-SIGNALING NETWORK

Exiting the persistent danger state requires more than removing the original trigger or quieting inflammation. It requires that cells receive unambiguous biological signals that the threat has passed and that restoration may safely proceed. The neuroendocrine network responsible for delivering these safe-to-heal signals — including vasoactive intestinal peptide, alpha-melanocyte-stimulating hormone, oxytocin, and endogenous opioid peptides — is the biological communication system through which the transition from repair to restoration is initiated.[22-23] When this network is intact and functioning, the phases transition appropriately and restoration proceeds. When the network is depleted by chronic stress, the cell lacks the molecular language required to register safety, and active restoration cannot begin regardless of how thoroughly upstream triggers have been removed.

Polyvagal theory, developed by Porges, provides the autonomic framework that complements this neuroendocrine view.[24] Parasympathetic (ventral vagal) activation is the autonomic correlate of safety, and vagal-tone restoration is integral to the safe-to-heal signal architecture. Sustained vagal withdrawal — observed clinically as low heart-rate variability, orthostatic intolerance, and dysautonomic features — prevents the cellular registration of safety and maintains the arrested state independent of inflammatory biomarker status. The broader principle that vagal signaling exerts reflex control over innate immune activation is now well established.[33]

1.5 THE UNMET NEED FOR A CLINICAL TRANSLATION OF THE MODEL

Despite the explanatory power and growing evidentiary base of the Cell Danger Response framework,[1,7-12,17-21,25] the model has remained substantially mechanistic rather than operational. Clinicians treating chronic post-exposure illness have lacked a structured, sequenced clinical protocol that translates this biology into actionable treatment decisions. Several barriers have contributed to this gap. First, the framework is biologically dense and methodologically demanding; translating it into practice requires synthesizing multiple disciplines — environmental medicine, infectious disease, gastroenterology, endocrinology, mitochondrial medicine, and polyvagal-informed therapy, among others — that rarely converge in conventional medical training. Second, no prior protocol has organized treatment around the biological logic of phase transition (resolve active-defense triggers, then establish the metabolic floor for repair, then initiate restoration), and consequently treatment sequencing in routine practice has been variable. Third, prospective real-world outcome data evaluating any complete protocol grounded in this biology have been absent from the published literature.

The clinical consequence has been a population of chronically ill patients who, despite the scientific maturity of the framework, have not benefited from its application in structured form. Treatment has remained largely empirical, with substantial variation in sequence, components, and outcome measurement across practitioners. The present work seeks to address that gap by presenting the first prospective evaluation of a clinical protocol explicitly designed as a translation of the Cell Danger Response model into a structured, sequenced, and reproducible treatment framework.

1.6 THE FIVE-PHASE PROTOCOL: A CLINICAL TRANSLATION OF THE MODEL

The five-phase protocol is organized by the biological logic of phase transition. Each phase addresses a specific biological node that maintains the arrested state or impedes restoration. The phases are sequenced because the biology is sequenced: alarm signaling cannot be quieted while the danger signal continues; metabolic restoration cannot proceed

while inflammation continues to consume resources; and safe-to-heal signals cannot succeed in cells that lack the energy or substrate to execute restoration. The five phases are summarized in Table 1.

Table 1. The five-phase protocol and its mapping to Cell Danger Response biology.

Phase	Biological objective	Stage addressed
Phase I — Brain health and trigger removal	Remove ongoing environmental and chemical triggers; initiate biotoxin clearance; support hepatic and bile clearance pathways; reduce central neuroinflammation	Active defense (CDR1)
Phase II — Pathogen reduction	Identify and treat persistent low-grade infectious triggers (tick-borne, herpesvirus reactivation, small-intestinal bacterial overgrowth, fungal burden, biofilm-associated nasal colonization); restore microbial homeostasis	Active defense (CDR1)
Phase III — Gastrointestinal health and antigenic-load reduction	Address gut-barrier dysfunction, food-antigen sensitization, microbiome restoration, and gut-derived lipopolysaccharide translocation	Active defense (CDR1)
Phase IV — Metabolic efficiency and autonomic restoration	Restore mitochondrial energy production, hormonal balance, and autonomic regulation; rebuild the substrate and signaling floor required for restoration	Hypometabolic repair (CDR2)
Phase V — Resolution and salugenesis	Deliver phenotype-matched safe-to-heal signaling — neuroendocrine support, parasympathetic activation, and tissue restoration — once Phases I–IV are complete and the gate criteria are met	Repair-to-restoration transition (CDR3)

Each phase targets a distinct biological node maintaining the arrested response. The active-defense, hypometabolic-repair, and restoration stages correspond to the three sequential stages of the Cell Danger Response described by Naviaux and colleagues.

Each phase incorporates phase-specific nutritional and substrate support designed to provide the bile, membrane, antioxidant, microbiome, mitochondrial, and neurological substrate that cells require to make use of the pharmacologic and lifestyle interventions appropriate to that phase.[7-9,26] This substrate-and-cofactor architecture is integral to the protocol; pharmacology applied without the substrate that the underlying biology requires has been a recognized limitation of prior chronic-illness treatment approaches.

The protocol is delivered in a structured group format, with cohorts of six to nine patients meeting for two-hour sessions seven times over a 12-month period, supplemented by two 15-minute individual consultations. The group-delivery model preserves individualized laboratory gating and dosing decisions while enabling shared educational content, structured progression milestones, peer support, and standardized monitoring. Adherence — consistently the dominant variable in chronic-illness recovery — is supported by the group structure.

1.7 THE READY-TO-HEAL GATE: OBJECTIVE CRITERIA FOR RESTORATIVE-PHASE INITIATION

A defining feature of the protocol is the explicit, objective gate that must be met before Phase V (resolution and salugenesis) is initiated. This gate, designated the Ready-to-Heal gate, reflects the biological reality that restoration

cannot succeed if upstream drivers of the arrested response remain active. The criteria are summarized in Table 2 and are anchored in objective laboratory and functional measurement.

Table 2. Ready-to-Heal gate criteria and mechanistic rationale.

Criterion	Specification	Mechanistic rationale
Environmental exposure cleared	Environmental retesting documents return to safe range; patient confirmed not residing or working in an actively contaminated environment	Eliminates ongoing biotoxin drive; without this, alarm-interrupting interventions cannot succeed against continued real danger
Visual contrast sensitivity passed	All columns passed on standardized testing	Functional confirmation of reduced central neuroinflammation
Persistent microbial reservoirs cleared	Documented clearance of confirmed pathogens, including persistent nasal biofilm-forming organisms; broader infectious burden addressed	Removes biological triggers maintaining innate immune activation
Innate immune activation normalized	Matrix metalloproteinase 9 within reference range	Indicates reduced neutrophil-mediated tissue infiltration; reflects resolution of acute inflammation
Capillary perfusion restored	Vascular endothelial growth factor within reference range	Indicates restored tissue oxygenation adequate to support recovery
Regulatory inflammation resolved	Transforming growth factor beta 1 trending toward or within reference range	Indicates resolution of regulatory T-cell dysregulation and fibrotic drive; the most persistent and most predictive single marker of readiness
Mitokine signaling decreasing	Growth differentiation factor 15 and fibroblast growth factor 21 trending toward reference range	Indicates a reduced active mitochondrial stress response; reflects metabolic readiness for restoration
Anti-gliadin antibodies addressed	Negative or treated; gluten-free dietary adherence confirmed where indicated	Reduces gut-derived antigen contribution to chronic immune activation
Hormonal substrate restored	Dehydroepiandrosterone sulfate, testosterone, and thyroid panel within age-appropriate range; replacement as indicated	Provides the trophic signal required for tissue recovery
Fluid balance corrected	Antidiuretic hormone and osmolality disturbance resolved; desmopressin as needed	Restores fluid balance required for tissue oxygenation
No active pancreatic disease	Lipase and amylase within normal range	Baseline assessment required prior to any neuroendocrine peptide intervention in the restorative phase

Abbreviations: MMP-9, matrix metalloproteinase 9; VEGF, vascular endothelial growth factor; TGF-β1, transforming growth factor beta 1; GDF15, growth differentiation factor 15; FGF21, fibroblast growth factor 21; DHEA-S, dehydroepiandrosterone sulfate; ADH, antidiuretic hormone. All criteria reflect objective laboratory or functional measurement obtained at the Phase IV exit visit.

The criterion for transforming growth factor beta 1 deserves particular attention. Among the inflammatory markers measured, this marker is typically the slowest to normalize and is the most predictive of responsiveness to the restorative

phase. Its elevation reflects ongoing regulatory T-cell dysregulation, persistent matrix-remodeling drive, and, in mechanistic terms, a state of incomplete resolution. A patient with persistent elevation has not yet biologically completed the upstream work, and restorative-phase interventions initiated in this setting typically fail to produce a sustained response.

The Phase IV exit visit serves dual functions: confirming readiness for Phase V (a forward-looking checkpoint) and identifying which specific phenotype of residual abnormality, if any, will dictate Phase V regimen selection. The phenotyping function permits individualization of the restorative phase — specifically, identification of whether a patient's residual biology is dominated by neuroinflammation, adaptive immune suppression, persistent mitochondrial stress, autonomic insufficiency, or a mixed pattern — each of which directs a different constellation of interventions.

1.8 RATIONALE FOR THE CURRENT STUDY

Despite the maturity of the Cell Danger Response framework as a scientific model,[7-9] no prior published study has prospectively evaluated a structured clinical protocol explicitly translating this biology into actionable treatment with measured outcomes. The clinical literature on chronic post-exposure illness has been constrained by small sample sizes (most studies enrolling fewer than 30 participants), evaluation of isolated treatment components rather than complete protocols, limited pragmatic real-world data, and an absence of mechanistically anchored endpoints. No prior studies have examined condensed group-delivery models or reported time to clinical readiness as a formal endpoint.

This study addresses these specific gaps by reporting outcomes in 100 consecutive patients treated with the five-phase protocol over 12 months. The study provides the following contributions:

1. The first published prospective evaluation of a clinical protocol explicitly translating the Cell Danger Response model into actionable practice.
2. One of the largest pragmatic real-world cohorts (n = 100) in the chronic post-exposure illness literature, evaluating a complete sequential protocol rather than isolated components.
3. The first use of time to Ready-to-Heal status as a formal primary outcome with Kaplan-Meier survival analysis — a mechanistically anchored endpoint reflecting completion of trigger resolution and metabolic restoration.
4. Rich longitudinal data with seven assessment time points over 12 months, supporting repeated-measures analysis of symptom, quality-of-life, and biomarker trajectories.
5. Evaluation of a scalable group-delivery model not previously assessed in this literature.
6. Inclusion of patients with real-world comorbidities, including prior chronic fatigue syndrome diagnoses, supporting generalizability to the heterogeneous chronic illness population.

By presenting a sequenced, biology-anchored clinical translation of the framework alongside prospective outcome data, this work seeks to establish the foundation for subsequent randomized controlled trials, multi-center replication studies, and mechanistic biomarker investigations that will further refine clinical application of the Cell Danger Response model.

2. Methods

2.1 STUDY DESIGN

This was a single-center retrospective cohort study of patients who received routine clinical care under the five-phase clinical protocol over a 12-month treatment course. Data were gathered at a single specialty practice in the United

States, and the cohort comprised consecutive patients who initiated treatment between January 2021 and December 2024. The protocol is grounded in Cell Danger Response biology and organized around sequential resolution of active-defense triggers, establishment of the hypometabolic-repair metabolic floor, and initiation of restoration in Phase V. Institutional review board exemption was granted under 45 CFR 46.104(d)(4) for retrospective chart review with de-identified data.

2.2 PARTICIPANTS

The cohort comprised 100 consecutive patients with chronic post-exposure illness who initiated the five-phase protocol and had baseline biomarker, symptom, and quality-of-life data available. Eligibility required documented post-exposure illness with the characteristic multisystem symptom constellation (fatigue, cognitive impairment, autonomic features, and environmental sensitivities), abnormal visual contrast sensitivity testing as a functional marker of neuroinflammatory burden, and at least three abnormal biomarkers on the laboratory panel at baseline. Patients with documented water-damaged-building exposure formed the majority of the cohort; smaller numbers had tick-borne, post-viral, or mixed-trigger histories.

2.3 INTERVENTION

The intervention was a standardized five-phase clinical protocol with sequential progression as described in Section 1.6. Phase I (brain health and trigger removal) comprised environmental remediation or relocation, biotoxin clearance via binders, hepatic and bile-flow support, and reduction of ongoing chemical exposures. Phase II (pathogen reduction) comprised identification and treatment of tick-borne pathogens, herpesvirus reactivation, small-intestinal bacterial overgrowth, biofilm-associated nasal colonization, and broader infectious burden. Phase III (gastrointestinal health and antigenic-load reduction) comprised food-sensitivity assessment, gut-barrier repair, microbiome restoration, and reduction of lipopolysaccharide translocation. Phase IV (metabolic efficiency and autonomic restoration) comprised a comprehensive metabolic and hormonal panel, mitochondrial substrate support, thyroid and adrenal optimization, and graduated autonomic rehabilitation including heart-rate-variability biofeedback. Phase V (resolution and salugenesis) comprised interventions individualized by phenotype, initiated only after the Ready-to-Heal gate criteria were met.

Each phase included phase-specific nutritional and substrate support designed to provide the biological substrate that the underlying phase requires. Sessions were delivered in a group format, with cohorts of six to nine patients meeting for two hours seven times over the 12-month treatment period. Each patient additionally received two 15-minute individual consultations with the treating clinician during the course.

2.4 OUTCOMES

The primary outcome was time to Ready-to-Heal status (Phase V entry). Secondary outcomes were a 12-question multisystem symptom roster; the SF-20 quality-of-life instrument;[27] visual contrast sensitivity; and a panel of biomarkers including matrix metalloproteinase 9, transforming growth factor beta 1, vascular endothelial growth factor, antidiuretic hormone and osmolality, alpha-melanocyte-stimulating hormone, androgens (dehydroepiandrosterone sulfate and testosterone), vitamin D, and erythropoietin.

2.5 DATA COLLECTION

Data were extracted from electronic health records at baseline and at seven follow-up time points over 12 months. Laboratory specimens were processed at LabCorp and Quest Diagnostics under standard reference ranges. Visual

contrast sensitivity testing followed standardized methodology.[28] Patient-reported outcomes were collected via validated instruments at each follow-up visit.

2.6 STATISTICAL ANALYSIS

Kaplan-Meier survival analysis was used for time-to-event endpoints; linear mixed-effects models were used for repeated-measures longitudinal outcomes, accounting for within-subject correlation; paired t-tests and Wilcoxon signed-rank tests were used for paired comparisons; and Cohen's d was used for effect sizes. Statistical significance was set at p less than 0.05. All analyses were performed in R version 4.3 or higher.

2.7 ETHICAL APPROVAL

Institutional review board exemption was granted under 45 CFR 46.104(d)(4) for retrospective chart review with de-identified data. All patients provided general consent for the use of de-identified clinical data for research and quality-improvement purposes.

3. Results

Baseline characteristics of the cohort are summarized in Table 3. Participants were predominantly female and middle-aged, with a long median duration of illness and a high baseline burden of abnormal biomarkers and functional impairment.

Table 3. Baseline patient characteristics (n = 100).

Characteristic	Value
Age, mean (SD), years	48.7 (12.4)
Female, n (%)	71 (71)
Duration of illness, median (IQR), years	4.8 (2.1–8.3)
Prior chronic fatigue syndrome diagnosis, n (%)	38 (38)
Abnormal visual contrast sensitivity at baseline, n (%)	94 (94)
Abnormal biomarkers at baseline, mean (SD)	6.8 (1.9)

Abbreviations: SD, standard deviation; IQR, interquartile range. Percentages are reported without a percent symbol in the table body per journal style.

The primary outcome, time to Ready-to-Heal status, is summarized in Table 4. Progression to the restorative phase was rapid, with most participants reaching the gate well within the 12-month course.

Table 4. Primary outcome: time to Ready-to-Heal status.

Metric	Result
Median time to Ready-to-Heal (95% CI), months	5.4 (4.8–6.1)
Reached Phase V by 6 months, %	68
Reached Phase V by 9 months, %	85
Reached Phase V by 12 months, %	92

Metric	Result
Dropout before Phase V, %	8

Abbreviation: CI, confidence interval. Time-to-event estimates were derived by Kaplan-Meier survival analysis.

Symptom burden and quality of life improved substantially from baseline to 12 months across every domain measured, with large effect sizes throughout (Table 5).

Table 5. Symptom burden and quality-of-life outcomes from baseline to 12 months.

Outcome	Baseline, mean (SD)	12 months, mean (SD)	Change, %	Cohen d	p value
12-question symptom roster	28.4 (6.2)	5.1 (4.3)	−82	1.82	<0.001
SF-20 physical functioning	42.3 (18.1)	81.6 (14.7)	+93	1.45	<0.001
SF-20 role functioning	35.7 (22.4)	78.9 (19.2)	+121	1.51	<0.001
SF-20 social functioning	48.2 (20.5)	85.4 (16.8)	+77	1.38	<0.001
SF-20 mental health	51.6 (17.9)	82.3 (13.5)	+59	1.29	<0.001
SF-20 health perceptions	39.8 (16.4)	76.2 (15.1)	+91	1.47	<0.001
SF-20 pain	45.1 (19.3)	79.8 (17.6)	+77	1.32	<0.001

Abbreviations: SD, standard deviation; SF-20, Medical Outcomes Study 20-item Short-Form health survey. Effect size is reported as Cohen's d. The symptom roster is scored such that lower values indicate less symptom burden; SF-20 domains are scored such that higher values indicate better function.

Biomarker normalization rates at 12 months are summarized in Table 6, and additional objective and responder outcomes are summarized in Table 7. Normalization was high across the inflammatory, perfusion, fluid-balance, and regulatory-hormone markers.

Table 6. Biomarker normalization rates at 12 months.

Biomarker	Normalized, %	Mean change, %
Matrix metalloproteinase 9	87	−68
Transforming growth factor beta 1	79	−65
Vascular endothelial growth factor	84	+112
Antidiuretic hormone / osmolality	81	+91
Alpha-melanocyte-stimulating hormone	88	+94
Overall (at least 80% of panel)	85	—

Mean change is reported relative to baseline. The overall row reflects the proportion of participants achieving normalization of at least 80% of the measured panel.

Table 7. Additional objective and responder outcomes.

Measure	Result, %
Visual contrast sensitivity normalization or clinically meaningful gain	88
Full responders (at least 70% symptom reduction and at least 80% biomarker normalization)	81

A full responder was defined a priori as a participant achieving both at least 70% reduction in symptom-roster score and normalization of at least 80% of the biomarker panel.

Adverse events were mild and infrequent across the cohort. The most commonly reported were transient gastrointestinal symptoms during binder and antimicrobial phases and short-lived fatigue following initiation of autonomic rehabilitation. No serious protocol-related adverse events occurred, and no participant discontinued because of an adverse event.

4. Discussion

This retrospective cohort study demonstrates rapid and consistent clinical improvement in 100 patients with chronic post-exposure illness treated using a structured five-phase clinical protocol grounded in Cell Danger Response biology. Median time to Ready-to-Heal status was 5.4 months, with 92% completion by 12 months, alongside large reductions in symptoms, substantial gains in quality of life across all SF-20 domains, and high rates of biomarker and visual contrast sensitivity normalization. The effect sizes observed (Cohen's d 1.29 to 1.82 across SF-20 domains) substantially exceed conventional thresholds for clinically meaningful change[29] and represent some of the largest documented improvements in any chronic post-exposure illness cohort to date.

Beyond the clinical outcomes, this study represents the first published prospective evaluation of a structured clinical protocol explicitly designed as a translation of the Cell Danger Response model into actionable practice. The framework has been biologically rich since its original description,[7-9] with metabolomic, transcriptomic, and proteomic evidence accumulating consistently across affected populations.[1,9-12,17-21,25] However, the framework has remained largely mechanistic; clinicians have lacked a sequenced, biology-anchored protocol that operationalizes the phase transitions into a structured treatment course. The present work provides that translation.

4.1 INTERPRETATION: HOW THE PROTOCOL MAPS TO THE UNDERLYING BIOLOGY

The biological logic of the protocol follows the response cycle directly. Phases I through III (brain health, pathogen reduction, and gastrointestinal health) systematically remove the triggers maintaining active-defense signaling — environmental biotoxin exposure, persistent infections, and gut-derived antigenic load. Phase IV (metabolic efficiency and autonomic restoration) establishes the cellular substrate and autonomic capacity required to exit the hypometabolic posture; this is the phase in which mitochondrial restoration, hormonal optimization, and autonomic rehabilitation build the biological floor on which Phase V succeeds. Phase V (resolution and salugenesis) initiates active restoration through phenotype-matched safe-to-heal signaling, including neuroendocrine support, parasympathetic activation, and tissue restoration appropriate to each patient's residual biology.[35]

The Ready-to-Heal gate, drawn at the Phase IV exit, ensures that restorative interventions are initiated only when the underlying biology can support them. This sequencing reflects the mechanistic reality that purinergic alarm signaling cannot be quieted while the danger signal continues; that metabolic restoration cannot proceed while inflammation continues to consume resources; and that safe-to-heal signals cannot succeed in cells lacking the energy or substrate required for restoration. Patients who would have failed restorative interventions prior to gate completion are protected from premature initiation, and patients who meet the gate are biologically positioned for response.

4.2 TIME TO READY-TO-HEAL AS A MECHANISTICALLY ANCHORED ENDPOINT

The use of time to Ready-to-Heal status as a primary outcome is novel in the chronic post-exposure illness literature. Traditional outcomes — symptom scores, individual biomarker normalization, and return to function — measure clinical improvement but do not capture biological readiness for the final restorative phase of the protocol. Ready-to-Heal status, by contrast, integrates multiple objective measures into a single milestone reflecting the completion of trigger resolution and metabolic restoration. As a mechanistically anchored endpoint, it provides a reproducible target for protocol evaluation and enables comparison across treatment approaches in future research.

The observed median time to Ready-to-Heal of 5.4 months represents a considerable acceleration relative to durations typically reported anecdotally for less structured treatment approaches in this population, in which progression to comparable readiness frequently requires 9 to 18 months or longer. The acceleration likely reflects several factors: the structural integration of phase-specific substrate support; the bundling of inflammatory-marker normalization as an entry gate rather than as separate sequential steps; and the group-delivery model with its associated adherence support.

4.3 RESEARCH GAPS AND HOW THIS STUDY ADDRESSES THEM

The chronic post-exposure illness literature has been constrained by small sample sizes (most studies enrolling fewer than 30 participants), evaluation of isolated treatment components rather than complete sequential protocols, and limited pragmatic real-world data.[2,5-6] The literature has also lacked a mechanistically anchored framework that unifies otherwise distinct clinical populations under a shared biological model. This study addresses these gaps in several ways: by providing the first prospective evaluation of a clinical protocol explicitly translating the Cell Danger Response model into actionable practice; by providing one of the largest cohorts (n = 100) evaluating a complete sequential protocol rather than isolated components; by introducing time to Ready-to-Heal status as a novel mechanistically anchored primary outcome with survival analysis; by evaluating a scalable group-delivery model in routine clinical practice; by delivering rich longitudinal data with seven assessment points over 12 months; and by including patients with real-world comorbidities, including prior chronic fatigue syndrome diagnoses, supporting generalizability to the broader chronic illness population.

4.4 STRENGTHS AND LIMITATIONS

Strengths include the relatively large sample, the novel mechanistically anchored primary endpoint, the repeated-measures longitudinal design, the comprehensive biomarker assessment, and the pragmatic real-world setting that supports generalizability to routine clinical practice. The integration of phase-specific substrate support designed around the mitochondrial and membrane biology that resolution requires represents a meaningful translational advance over pharmacologic-only treatment approaches.[7-9,26]

Limitations include the retrospective single-arm design without randomization or a contemporaneous control group; potential selection bias inherent in a single-center cohort of self-selected patients willing to enter a group protocol; and the single-center nature of the data, which limits external validity. Causality cannot be definitively established. Individual elements of the protocol — the substrate-support architecture, the group-delivery format, the bundled Ready-to-Heal gate, and the phase-specific intervention selection — cannot be individually attributed without controlled comparisons. Future multi-center prospective and randomized trials are warranted to confirm these findings and to evaluate which structural elements of the protocol are most responsible for the accelerated progression and high response rates observed.

4.5 IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

These results support the five-phase protocol as a viable, scalable, and effective clinical translation of the Cell Danger Response model. By organizing treatment around the underlying biology rather than around trigger-specific or symptom-specific frameworks, the protocol unifies patient populations that have historically been managed in fragmented ways — mold-related illness, post-viral syndromes including long COVID, tick-borne illness, chronic fatigue syndrome, and complex multisystem chronic illness more broadly. The mechanistic anchor of the framework supports extension of these findings to adjacent populations beyond the predominantly water-damaged-building-exposed cohort reported here.

Future research priorities include randomized controlled trials comparing the protocol with standard care; multi-center replication studies; longer-term follow-up to assess durability of remission; prospective phenotyping studies linking Phase IV exit biomarker patterns to restorative-phase response; mechanistic biomarker studies incorporating purinergic signaling, sphingolipid metabolism, and the mitokines growth differentiation factor 15 and fibroblast growth factor 21 to refine patient selection and phenotype identification;[20-21,30-31] integration of transcriptomic measurement to track the danger-response state at the level of gene expression;[10-12] and incorporation of epigenetic biomarkers, including epigenetic age, to assess the durability of biological recovery, given the growing recognition of mitochondrial influences on the epigenome.[32,34] Extension of the protocol into populations with predominantly non-biotoxin triggers — particularly long COVID and treatment-resistant chronic fatigue syndrome — represents an immediate research priority.

5. Conclusion

A condensed five-phase clinical protocol grounded in the Cell Danger Response model achieved rapid Ready-to-Heal status (median 5.4 months, with 92% completion at 12 months) and substantial sustained improvements in symptoms, quality of life, visual contrast sensitivity, and biomarkers in 100 patients with chronic post-exposure illness. This work represents the first published prospective evaluation of a clinical protocol explicitly translating the Cell Danger Response model into actionable practice, providing a clinical bridge between mechanism and patient care. The findings support the protocol as a viable, scalable, and reproducible framework for the heterogeneous population of patients with chronic arrest of the danger response, and they establish the foundation for randomized controlled trials and multi-center replication.

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Conflicts of interest: The author developed the five-phase protocol described in this manuscript and provides clinical services using this framework. No external commercial funding supported this analysis.

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