BeyondMold

CLINICAL SCIENCE MONOGRAPH

CDR / ISRMT FRAMEWORK · THE UNIFIED TRIGGER MODEL

The Tolerance Threshold

Loss of tolerance as the unifying logic of the stuck alarm — microbial compartments, barrier integrity, measurement, and the restoration of innate calm in chronic CDR1 activation

Many distinct insults converge on a single innate alarm. The variable that decides who stays inflamed is not the trigger but the host's tolerance reserve: *CDR1 activation scales as trigger load ÷ tolerance reserve.*

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Clinical Science Monograph

Chronic illness in the CDR framework is a healing cycle arrested in its first phase — the innate alarm (CDR1). This monograph argues the alarm stays on not because of a single ongoing toxin but because of a loss of tolerance to the microbial and chemical world, governed by one relation: *CDR1 activation scales as trigger load ÷ tolerance reserve.*

ABSTRACT

The threshold, not the trigger

Chronic illness in the cell-danger-response (CDR) framework is a healing cycle that fails to advance — most often a cycle arrested in its first phase, the innate-immune alarm (CDR1). The persistent question is why the alarm stays on. This monograph argues that the answer is rarely a single, ongoing toxin and is better understood as a loss of tolerance to the microbial and chemical world. Many distinct insults — chemicals, metals, stress, true pathogens, ingested and inhaled antigens, endogenous danger signals, and microbial overgrowth — converge on the same innate effector. They are, in this sense, interchangeable triggers; the determinant of who becomes and stays inflamed is the host's tolerance reserve. The governing relation is simple: CDR1 activation scales as trigger load divided by tolerance reserve.

Tolerance is decomposed into three measurable capacities — the barrier surfaces that keep signals on the outside, the regulatory and resolution apparatus that actively stands inflammation down, and the innate set-point that determines how readily myeloid cells sound the alarm, a set-point substantially metabolic and mitochondrial and therefore native to CDR. The monograph develops the science of the four microbial compartments that feed or calm the alarm — the built environment, the respiratory tract, the skin, and the gut — under one organising correction: our living spaces and bodies are never sterile, so the pathologic variable is overgrowth and imbalance, not presence, and the therapeutic target is the response threshold, not eradication.

Because CDR1 is an inflammatory state produced by the summation of loads against an eroded tolerance, it resists single-marker measurement; the monograph is deliberate about this, proposing a tiered, multi-compartment methodology while naming the markers that are unreliable (the commercial "zonulin" assay among them). It closes with a mechanistically reasoned account of restoration and a falsifiable research program. The model is offered as one trigger theory among several converging on CDR1, bounded and testable, not as a universal solvent.

PART I · 1

Many triggers, one effector

Why a stuck alarm needs a perpetuating account — a single hit cannot explain a cycle that will not advance.

The cell danger response is a choreographed sequence: an alarm phase (CDR1) for containment and innate defence, a proliferative phase (CDR2) for biomass replacement, and a reintegration phase (CDR3) for differenti-

ation and the restoration of cell-to-cell communication. Health is the orderly completion of that sequence; chronic illness is arrest at one of its stages. The commonest and most consequential arrest is in CDR1 — the stuck alarm. A one-time injury, however severe, initiates the cycle; it does not obviously keep a cell offline for years. A stuck alarm implies an ongoing signal, or a host that cannot stand the alarm down.

The answer begins with an observation about triggers. The innate immune system does not possess a separate sensor for each insult. It reads the world through a limited set of pattern-recognition receptors that respond to two broad classes of signal: pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Almost every trigger that matters clinically ends up speaking through one of these two vocabularies. That convergence is the heart of the model.

The innate system has no private sensor for mold, or metal, or grief. It has receptors for danger. Everything that reaches the alarm reaches it as danger, and the alarm cannot tell the difference.

Chemicals and metals generate oxidative stress and DAMPs. Psychological and physiological stress acts through the neuroendocrine and autonomic systems to raise baseline inflammatory tone. True pathogens present PAMPs outright. Ingested and inhaled antigens drive mucosal activation when tolerance to them is lost. Endogenous compounds sustain sterile inflammation. And microbial overgrowth supplies a continuous, renewable PAMP load from the surfaces we can never sterilise. These are not one mechanism; they are many mechanisms with one destination.

Trigger class	How it reaches the alarm	Sensor / entry point
Chemicals, solvents, mycotoxins	Oxidative stress, adduct formation, mitochondrial & barrier damage → DAMP release	NRF2/ROS, NLRP3, released DAMPs
Metals	Redox cycling, thiol depletion, mitochondrial injury → DAMPs; haptenisation of self	ROS, NLRP3, adaptive sensitisation
Psychological / physiologic stress	HPA and autonomic shift; loss of vagal cholinergic brake; raised baseline tone	β-adrenergic, glucocorticoid, vagal
True pathogens	Direct presentation of microbial patterns	TLRs, NLRs, CLRs (PAMPs)
Ingested / inhaled antigens	Mucosal activation when oral/airway tolerance is lost	Mucosal APCs, Th2/Th17 drift
Endogenous compounds (DAMPs)	Sterile danger from stressed or dying host cells and unresolved injury	NLRP3, RAGE, P2X7 (ATP), cGAS-STING
Microbial overgrowth / dysbiosis	Continuous renewable PAMP load from non-sterile surfaces and mucosae	TLR4 (LPS), Dectin-1 (β-glucan), NOD2

Table 1. Heterogeneous triggers, converging vocabularies. Clinically distinct insults are read by the innate system as variations on two themes — pathogen- and damage-associated patterns — which is why they are partially interchangeable as drivers of CDR1.

PART I · 2

The governing ratio

Trigger load over tolerance reserve — same exposure, different person, different outcome, because the denominator differs.

If triggers converge, then the interesting variable is not which trigger but why this host stays in alarm. The same water-damaged office, the same amalgam, the same stressful year produces a disabling multi-system illness in one person and nothing measurable in the next. A model that locates the disease entirely in the exposure cannot explain that; a model built on tolerance can. I state it as a working relation:

$$\textit{CDR1 activation} \propto \textit{trigger load} \div \textit{tolerance reserve}$$

The numerator is the summed load of all triggers reaching the alarm at a given time. The denominator is the host's capacity to keep those signals out, to tolerate the ones that get in, and to resolve the response they provoke. Illness emerges when the numerator exceeds the denominator — which can happen because the load is high, because the reserve is low, or, most often, because both drift in the wrong direction together. This dissolves the need for a mysterious "susceptibility": susceptibility simply is a low tolerance reserve, decomposable into parts we can name, measure, and rebuild.

Two corollaries organise the rest of this monograph. First, because the living space and the body are never sterile, the load can be lowered but never zeroed; eradication is therefore a category error as a therapeutic endpoint, and the only stable target is the denominator. Second, because the denominator is the sum of distinct capacities, "restoring tolerance" is not one intervention but a coordinated program addressed to each capacity in turn.

PART II · 3

What tolerance is

Three capacities that hold the alarm at bay — barrier, regulation and resolution, and the innate set-point.

Immunological tolerance is not a single thing. For a model of innate inflammation the useful concept is broad: tolerance is the organism's standing capacity to be exposed to the microbial and chemical world without mounting a damaging alarm. That capacity rests on three pillars, and loss of tolerance is the erosion of some combination of them.

The barrier

CAPACITY 1

KEEP THE SIGNAL ON THE OUTSIDE

Epithelial surfaces — gut, airway, skin — are the first determinant of how much PAMP and antigen ever reaches an immune sensor. The barrier is layered: a physical seal of tight junctions; a chemical layer of mucus, antimicrobial peptides and secretory IgA; and an immunological layer of tolerogenic antigen-presenting cells. When the seal loosens, luminal LPS and food and microbial antigens translocate, and a local nuisance becomes a systemic danger signal. Barrier failure is the most direct route from a non-sterile surface to a lit alarm.

The regulatory & resolution apparatus

CAPACITY 2

STAND THE ALARM DOWN

Tolerance is active, not passive. Regulatory T cells ($Foxp3^+$ Tregs), IL-10 and TGF-β, and tolerogenic dendritic cells continuously suppress reactivity to harmless antigens; and inflammation, once started, is ended not by passive decay but by an active resolution program of specialised pro-resolving mediators — resolvins, protectins, maresins, lipoxins — derived from omega-3 and omega-6 fatty acids.[11] The cholinergic anti-inflammatory pathway[12] (the vagus nerve's brake on cytokine release) belongs here too. When this apparatus is intact, exposures resolve; when it is depleted, they smoulder.[5]

The innate set-point

CAPACITY 3

DECIDE HOW READILY THE ALARM FIRES

Myeloid cells carry a set-point established by prior exposures through epigenetic and metabolic reprogramming — trained immunity. A trained monocyte responds to the next stimulus more violently; a tolerised one responds less. Crucially, this set-point is substantially metabolic: the shift to glycolysis and the accumulation of TCA intermediates that underlie training are mitochondrial events. The innate set-point is therefore where this model meets CDR directly — a cell in a danger-metabolism is, by definition, a cell with a lowered alarm threshold.

These three capacities are not independent. A failing barrier raises the antigen load the regulatory apparatus must suppress; a depleted resolution program leaves residual inflammation that trains the set-point upward; a hair-trigger set-point damages the barrier. Tolerance is the joint output of all three.

Capacity	Principal mediators	What erodes it	Candidate readouts
Barrier	Tight junctions; mucus; AMPs; secretory IgA	Dysbiosis, alcohol, NSAIDs, emulsifiers, infection, low butyrate, zinc/vitamin-A deficiency	LBP, sCD14, I-FABP, dual-sugar test, fecal sIgA
Regulation & resolution	Tregs, IL-10, TGF-β; SPMs; vagal cholinergic pathway	Low SCFA/fiber, omega-3 deficiency, low vitamin D/A, chronic stress, low vagal tone	Treg %, IL-10, SPM lipidomics, HRV
Innate set-point	Monocyte/macrophage training; mitochondrial metabolism	Repeated PAMP/DAMP load, metabolic stress, mitochondrial dysfunction	ex-vivo cytokine output, hsCRP, GDF15/FGF21, lactate

Table 2. The three capacities of tolerance. Loss of tolerance is erosion of one or more; restoration is addressed capacity by capacity, and measurement reads each through imperfect but improving proxies.

The kinds of tolerance

The immunology recognises several distinct forms. Central tolerance deletes overtly self-reactive lymphocytes; peripheral tolerance restrains those that escape. The form most relevant to CDR1 is *mucosal* (oral and airway) tolerance — the active, learned non-response to the enormous daily load of food proteins, commensal microbes, and harmless inhaled antigens. Its loss is a plausible final common path for antigen-driven CDR1: when oral tolerance fails, ordinary food and microbial antigens become standing alarm signals, and the patient acquires the sprawling, shifting "sensitivities" that characterise these illnesses. Restoring mucosal tolerance — not eliminating every antigen — is the durable goal.[6]

Two trainings: immunity and tolerance

The innate set-point can be trained in two opposite directions, and conflating them is a consequential error. *Trained immunity* is potentiation: after certain exposures (β-glucan, BCG), myeloid cells respond more vigorously. Its mirror image is *innate tolerance* — endotoxin tolerance, in which prior exposure down-regulates responsiveness. The same machinery produces both; ligand, dose, timing, and context decide direction. The therapeutic aim is therefore not immunosuppression but re-tolerisation of a mis-trained compartment — which is precisely why agents that train innate immunity upward (Section 12) are the wrong default in a stuck-alarm patient.

PART II · 4

How tolerance is built

The old friends and the metabolites that teach restraint — tolerance is learned from the microbial world, not born complete.

The three capacities are not fixed endowments; they are trained by lifelong dialogue with microbes. The biodiversity, or "old friends," account holds that the immune system co-evolved with a rich community of organisms whose continual signalling installs the regulatory apparatus. Reduced and distorted exposure, the signature of modern indoor life, leaves the regulatory arm under-built — the leading explanation for the secular rise in allergic, autoimmune, and chronic inflammatory disease. Loss of tolerance is, at the population level, a loss of microbial education.

The mechanism is now partly molecular. Commensal fermentation of dietary fibre yields short-chain fatty acids — acetate, propionate, and especially butyrate — which act as histone-deacetylase inhibitors to drive the differentiation of colonic regulatory T cells and to render intestinal macrophages hyporesponsive. A fibre-fed gut literally manufactures tolerance; a fibre-poor one starves it. Tolerance, in short, is built from inputs — microbial diversity, fibre, early-life exposure — and it can be rebuilt from the same inputs. That is the optimism inside this otherwise sobering model.

PART III · 5

The four reservoirs

Never sterile: overgrowth, not presence — the built environment, the respiratory tract, the skin, and the gut.

If tolerance is trained by microbes and eroded by their imbalance, the model must take seriously the actual microbial ecosystems a patient lives in and on. There are four that matter for CDR1, and one correction governs all of them. None is ever sterile. The pathologic variable is therefore never the presence of organisms; it is overgrowth, loss of diversity, and loss of the keystone species that hold the community in balance.

5.1 The built environment — the home microbiome

Buildings have microbiomes, and water damage does not introduce a single toxin into a sterile box; it shifts a complex community toward overgrowth of moisture-favoured fungi, bacteria, and actinomycetes whose cell-wall components are potent innate stimuli. Read this way, "mold illness" is plausibly a building-microbiome dysbiosis delivering a chronic inhaled PAMP load — which explains why remediation that lowers the load, rather than sterilises, is what helps. Hospital studies are the striking evidence: replacing chemical sanitation with a Bacillus-spore probiotic cleaning system roughly halved healthcare-associated infections[20], by competitively displacing pathogens rather than sterilising surfaces.

5.2 The respiratory tract — nose, sinus, and lung

The sinonasal microbiome carries a characteristic community — Corynebacterium and Staphylococcus with Streptococcus, Haemophilus, Moraxella — and chronic rhinosinusitis is associated with a recognisable dysbiosis: reduced diversity, increased bacterial load, loss of keystone Corynebacterium, pathobiont expansion. A dysbiotic, biofilm-laden nasal reservoir presents a continuous innate stimulus — a legitimate, modifiable CDR1 input.[8]

NEW EVIDENCE · 2026 · §5.2

Recent longitudinal evidence sharpens both halves of that claim — modifiable, and an input worth measuring — while illustrating the evidentiary discipline this series insists on. In a retrospective cohort of 188 patients evaluated within a CIRS-informed framework, all colonised with multiple antibiotic-resistant coagulase-negative staphylococci (MARCoNS) at baseline, those culture-negative at follow-up showed a significantly larger rise in circulating α-MSH than those who remained colonised — an interaction that held after adjustment for baseline α-MSH, age, sex, and the companion biomarkers[56] [56]. The selectivity is the most informative feature: the same models found no comparable interaction for VIP or MMP-9, so the association tracked the nasal reservoir specifically rather than a generalised improvement in inflammatory tone. Read through the governing ratio, clearing the colonised reservoir lowered a renewable nasal PAMP load — a numerator term — and the recovery registered selectively in α-MSH.

Honesty requires the counterweight, and it is instructive rather than merely cautionary. Because grouping was defined by a post-treatment outcome, the design cannot separate "clearance raised α-MSH" from the equally consistent "hosts whose reserve was already recovering cleared the organism more readily"; both groups' α-MSH in fact rose substantially from baseline, the cleared group's being an additional increment on a shift that occurred regardless of culture status. The intervention, moreover, was antimicrobial — an eradication-flavoured manoeuvre in a model that argues for rebalancing over sterilisation. The tension is only apparent: the ratio predicts that lowering the reservoir's load below threshold should help, and clearance is one comparatively crude way to lower it; what the study does not test is whether the niche-modifying approaches of §12.4 would secure the same α-MSH recovery at a lower ecological cost — a prospective question the model's own research program (§15) should answer.

5.3 The skin — barrier and immune tutor

The skin microbiome is both a barrier component and an immune educator. Healthy commensals (S. epidermidis, S. hominis) secrete strain-specific antimicrobial peptides active against S. aureus, deficient in atopic dermatitis — the cleanest human model of the whole thesis: a weakened barrier permits ingress, a depleted protective microbiome fails to restrain the pathobiont, and chronic inflammation resolves when the barrier and community are restored rather than when the skin is sterilised.

5.4 The gut — the master regulator

The gut is the largest immune organ and the principal site where tolerance is built or lost. Its commensals ferment fibre into SCFAs that induce Tregs and quiet macrophages, and occupy the niche that would otherwise admit pathobionts. Dysbiosis here simultaneously starves the regulatory apparatus and loads the barrier; when the barrier loosens, luminal LPS reaches the circulation[9] as metabolic endotoxaemia.[36] Of the four compartments, the gut is both the most powerful and the most modifiable, which is why it anchors the intervention program.

5.5 The axes between compartments

The compartments form a connected system; a dysbiosis in one raises the load on the others. The best-characterised link is the gut–lung axis (fibre-derived SCFAs shape airway immune tone at a distance); a gut–skin axis and a gut–brain–autonomic axis follow. The practical consequence is twofold: assessment and restoration should be multi-compartment by default, and the gut frequently anchors the others.

Compartment	Health signature	Dysbiotic signature	Innate consequence
Built environment	Diverse, outdoor-influenced community; low pathobiont load	Moisture-driven overgrowth; actinomycetes, molds; high settled-dust PAMP load	Chronic inhaled/contact β-glucan & endotoxin stimulus
Respiratory	Corynebacterium/keystone-rich; protective S. epidermidis	Low diversity; pathobiont & biofilm overgrowth; lost keystones	Persistent mucosal innate activation
Skin	AMP-producing commensals; intact lipid barrier	S. aureus overgrowth; AMP deficiency; barrier breach	Th2 drift; barrier-driven inflammation
Gut	Diverse; SCFA-producers; intact mucus & tight junctions	Low diversity; lost SCFA-producers; pathobiont & LPS overgrowth	Treg starvation; endotoxaemia; systemic danger

Table 3. The four compartments, each read as balance rather than presence. In every case the disease variable is overgrowth and loss of keystone diversity.

PART IV · 6

Environmental and host factors

Why the denominator falls — inputs depleted, barriers damaged, set-points raised.

If tolerance is the denominator, the clinical question is: what lowers it? The factors sort into environmental erosion — which mostly starves or damages the three capacities — and host factors, which set their baseline robustness. Naming them keeps the model from sprawling, because every factor maps onto barrier, regulation/resolution, or set-point.[10]

6.1 Environmental erosion

The dominant mechanism is input depletion: the loss of microbial and dietary signals that build regulation — reduced diversity (the old-friends deficit), a low-fibre diet that starves SCFA and Treg induction, lost early-life exposures, an over-sanitised indoor life. Layered on top are the direct damagers: antibiotics, ultra-processed diets and emulsifiers that thin the mucus layer, air pollutants, and the chemicals and metals that double as barrier and microbiome disruptors.

6.2 Host factors

Host factors set how robust the capacities are to begin with. Genetics comes first but should be weighted with restraint — barrier genes (filaggrin, mucin), innate sensors (NOD2, TLR), HLA, and regulatory genes all modulate the set-point, but most are polygenic and modest. Age raises baseline tone (inflammaging). The neuroendocrine and autonomic set-point is where psychological stress lives on the host side: HPA dysregulation and low vagal tone remove the cholinergic brake — the mechanistic home of "stress makes it worse." Micronutrient status powers the regulatory arm. And the node that closes the loop is mitochondrial and metabolic state, because mitochondria *are* the innate set-point.

Capacity	Environmental erosion	Host vulnerability
Barrier	Antibiotics, emulsifiers, alcohol, NSAIDs, pollutants, dysbiosis, low fiber	Filaggrin/mucin variants; low zinc/ vitamin A; age
Regulation & resolution	Low diversity & fiber → low SCFA; omega-3 deficiency; chronic stress	Regulatory-gene variants; low vitamin D/ A; low vagal tone; female hormonal axis
Innate set-point	Repeated PAMP/DAMP load; over-sanitised early life; metabolic stressors	Innate-sensor & HLA variants; mitochondrial dysfunction; inflammaging

Table 4. Environmental and host erosion mapped onto the three capacities. Susceptibility is not mysterious; it is a low tolerance reserve, and each contributing factor acts on a nameable capacity.

PART IV · 7

The feed-forward loop

How the alarm manufactures its own perpetuation — loss of tolerance is both cause and consequence.

The element that turns this from a list into a theory of chronicity is that sustained CDR1 actively degrades the very tolerance that would let it resolve. The alarm disassembles the barrier — neutrophil proteases such as MMP-9 and the tight-junction disruption of inflammatory cytokines[11] — which raises the antigen and LPS load. It suppresses the regulatory and resolution programs, shifting away from Tregs and pro-resolving mediators. And the mitochondrial danger-metabolism that powers the alarm holds the innate set-point low, keeping myeloid cells primed. The response erodes the denominator; the falling denominator amplifies the response; the cycle becomes self-sustaining — exactly what a stuck alarm requires and what a single-trigger model cannot supply. The therapeutic corollary is hopeful: because the loop is driven by erodible, rebuildable capacities, interrupting it at any node can begin to reverse it.

PART V · 8

Measuring a capacity, not a molecule

CDR1 is an inflammatory state from summed loads; no single marker captures it.

Honesty requires beginning with the limitation. CDR1 is not a discrete analyte; it is an inflammatory state produced by the summation of many loads against an eroded, multi-part tolerance, and tolerance itself is a latent capacity read only through imperfect proxies. There is, at present, no validated composite that reports "tolerance reserve," and any clinician who claims a single number for it is overreaching in exactly the way this series has criticised elsewhere. What can be done is to triangulate: measure each capacity and each compartment through several converging markers, and judge the model by whether those markers move together, and before symptoms, under intervention. That convergence — not any one assay — is the unit of evidence.

Convergence is the rule, but selective *divergence* can be equally informative when it maps onto a compartment. A marker that moves with one reservoir while the others stay flat localises the signal rather than weakening it: the selective association of α-MSH — but not VIP or MMP-9 — with nasal MARCoNS clearance (§5.2) is a worked example, pointing to the respiratory reservoir specifically rather than to global inflammatory tone[56] [56]. The discipline is to predict, in advance, which markers should track which compartment, and then to read both convergence and patterned divergence against that prediction.

For the **barrier**, circulating markers of microbial translocation and epithelial damage are most useful: LBP and soluble CD14 (endotoxin exposure), I-FABP (enterocyte damage), and the lactulose-mannitol dual-sugar permeability test. A specific caution: the widely sold serum "zonulin" assays do not reliably measure zonulin — independent work shows the common ELISAs detect other proteins and correlate poorly with functional permeability. For the **regulatory/resolution** capacity: Treg phenotyping, IL-10/TGF-β, SPM lipidomics and the omega-3 index, and HRV. For the **innate set-point**: ex-vivo whole-blood cytokine production on standardised re-stimulation, hsCRP, and — connecting to CDR — GDF15, FGF21, and lactate. For the **compartments**: 16S or shotgun sequencing of home dust, nasal, skin, and stool, reported as diversity, keystone abundance, and pathobiont load rather than presence/absence.[12]

Tier	Markers	Reads	Caveat
Tier 1 — accessible	hsCRP; CBC/ferritin; omega-3 index; HRV; vitamin D; basic stool panel; symptom indices	Baseline inflammatory tone, resolution substrate, vagal tone	Non-specific individually; useful in combination
Tier 2 — specialised	LBP, sCD14, I-FABP; calprotectin; Treg %/IL-10; shotgun microbiome (gut/nasal/skin); GDF15/FGF21	Barrier translocation, regulatory capacity, compartment dysbiosis, mitokine stress	Reference ranges immature; lab-dependent
Tier 3 — research	SPM lipidomics; ex-vivo trained-immunity cytokine assays; dual-sugar permeability; home-dust metagenomics	Resolution capacity, innate set-point, functional barrier, built-environment load	Research-grade; not yet standardised for clinic

Tier	Markers	Reads	Caveat
Use with caution	Commercial serum "zonulin" ELISA	Marketed as gut permeability	Does not reliably measure zonulin; poor functional correlation

Table 5. A tiered, multi-compartment measurement framework, with caveats made explicit. No single marker reports tolerance; the evidentiary unit is convergence across markers and their movement ahead of symptoms under intervention.

PART VI · 9

Principles of restoration

Lower the load below threshold; rebuild the three capacities — manage, do not sterilise; sequence; individualise.

Therapeutics follow directly from the governing ratio. There are only two levers: lower the numerator (trigger load) enough to fall below the patient's current threshold, and raise the denominator (tolerance reserve) by rebuilding the three capacities. Because the surfaces are never sterile, the first lever has a floor — get the load below threshold, not to zero — and the durable work is in the second. The program is sequenced: relieve the most provocative loads and stabilise the barrier first, because a leaking barrier defeats everything downstream; then rebuild regulation and resolution; then, cautiously, address the innate set-point, which is the slowest to move and the easiest to inflame. Throughout, the operative verb is *immunomodulation, not stimulation*.

PART VI · 10

Reducing the load and sealing the barriers

Take the pressure off, then close the gates — environmental load reduction; gut, airway, and skin barrier repair.

Reducing trigger load means competent environmental remediation aimed at lowering the microbial and PAMP load of the home (moisture control, source removal, ventilation, and probiotic/biodiversity approaches) rather than at an unattainable sterility; reducing chemical and metal exposures; treating genuine infections; and, where a food-antigen load drives mucosal activation, a temporary, targeted reduction of the offending antigens while the barrier heals. Sealing the barriers is the first rebuilding step because barrier failure feeds every other problem.

The intestinal barrier

GUT

SEAL THE TIGHT JUNCTIONS, RESTORE THE MUCUS

L-glutamine (enterocyte fuel, tight-junction support); zinc (notably zinc-carnosine); vitamins A and D (epithelial integrity and tolerogenic mucosal immunity); butyrate and fibre (enterocyte fuel and Treg-inducing metabolite — simultaneously barrier and regulatory therapy); polyphenols, mucin support, and immunoglobulins/colostrum; and avoidance of barrier-thinning emulsifiers, excess alcohol, and unnecessary NSAIDs.

The respiratory mucosa

AIRWAY

RESTORE THE LINING, LOWER THE NASAL LOAD

Nasal hygiene to reduce biofilm and pathobiont load, humidification and barrier-supportive sprays to maintain the mucosal lining, and niche-modifying nasal probiotics. The aim is a lower, better-balanced nasal reservoir and an intact mucosa, not a sterilised sinus.

The cutaneous barrier

SKIN

REPLACE THE LIPIDS, SUPPORT THE DEFENCES

Ceramide- and physiologic-lipid-based emollients to rebuild the stratum-corneum barrier, gentle non-stripping cleansing, and support for the commensal antimicrobial defences depleted in barrier disease. The atopic-dermatitis evidence shows barrier repair and microbiome restoration outperform sterilising approaches.[14]

PART VI · 11

Membranes, lipids, and nutrients

Comprehensive lipid replacement and the regulatory micronutrients — rebuild the membranes the alarm degrades; resupply the resolution substrate.

Sustained inflammation and oxidative stress damage cellular and mitochondrial membranes, which both impair mitochondrial function (raising the metabolic alarm) and distort the lipid signalling on which resolution depends. Membrane (glycerophospholipid) replacement — orally delivered phosphatidylcholine and mixed membrane phospholipids — restores membrane and mitochondrial function and is mechanistically apt because the innate set-point is mitochondrial. Cardiolipin, the signature inner-mitochondrial-membrane lipid, is a particular casualty of oxidative stress and a particular target of repair.

The resolution arm depends on a specific lipid substrate. Omega-3 fatty acids (EPA and DHA) are the precursors of the specialised pro-resolving mediators that actively terminate inflammation; deficiency leaves the

alarm without an off-switch, and repletion restores resolution capacity. This is membrane medicine in two senses at once: rebuilding the structural membranes the alarm has degraded, and resupplying the signalling lipids that end the alarm. The regulatory micronutrients complete the picture, each tied to a capacity — vitamin D and A to Treg induction and mucosal tolerance, zinc to barrier integrity, magnesium to mitochondrial function, and the fibre/SCFA axis as among the most powerful regulatory inputs available.

Agent	Mechanism / capacity served	Notes & cautions
Membrane phospholipids (PC, mixed)	Membrane & mitochondrial repair → innate set-point	Protected oral delivery; evidence strongest for fatigue/mitochondrial endpoints
Omega-3 (EPA/DHA)	SPM precursor → resolution capacity	Dose to an omega-3 index target; quality and oxidation matter
Specialised pro-resolving mediators	Direct resolution signalling	Research frontier; promising but not yet standard
Vitamin D	Treg induction; mucosal tolerance → regulation	Repletion to sufficiency; avoid megadosing
Vitamin A	Mucosal tolerance & barrier	Watch cumulative dose; pregnancy caution
Zinc (± carnosine)	Tight-junction & innate balance → barrier	Balance with copper on long-term use
Fibre / butyrate	SCFA → Treg induction & enterocyte fuel	Titrate up to avoid fermentative flare in dysbiosis

Table 6. Lipid replacement and regulatory nutrients, each mapped to a tolerance capacity. The logic is repair-and-resupply.

PART VI · 12

Peptides, special compounds, and probiotics

Calm and rebalance — without training the alarm upward.

12.1 Plant sterolins

The β-sitosterol / β-sitosterol-glucoside complex (the basis of Moducare) is the best-known phytosterol immunomodulator. The proposed action fits this model unusually well: rather than stimulating, it is reported to normalise the Th1/Th2 balance, dampen over-active cytokine responses, and normalise the DHEA:cortisol ratio — to push a dysregulated immune system toward equilibrium. Honesty requires the counterweight: the evidence base is older, largely from one group, and a European regulatory review (EFSA) declined to authorise

an immune-balance health claim. Sterolins are a reasonable, low-risk immunomodulator used with realistic expectations.

β-glucans train the alarm

CAVEAT

RIGHT FAMILY, WRONG DIRECTION — USUALLY

β-glucans are the prototypical inducers of trained immunity: through Dectin-1 they drive an mTOR/HIF-1α metabolic shift and epigenetic reprogramming that *potentiate* innate responses. In a host whose core problem is a hyper-reactive, trained-up innate set-point, an agent whose defining action is to train innate immunity upward is mechanistically the wrong tool, and the reflexive use of "immune-boosting" β-glucan in inflammatory patients deserves scrutiny. The picture is not absolute — outcomes are ligand-, dose-, and context-dependent — but the default in a stuck-alarm patient should be caution, not enthusiasm. This is the clearest example of why "modulate, don't boost" is a safety rule.

12.3 Peptides and other special compounds

Several peptides target barrier and regulation rather than innate stimulation — the right direction. BPC-157 (largely preclinical) for epithelial and connective-tissue barrier healing; KPV, the C-terminal tripeptide of α-MSH, carrying anti-inflammatory and barrier-protective activity, of particular interest for mucosal inflammation; thymic peptides for T-cell regulation; colostrum and lactoferrin for the gut barrier. The unifying principle is selection for barrier repair and regulatory support and against innate stimulation.[16]

12.4 Probiotics across the four compartments

Live-organism and biodiversity strategies operationalise the overgrowth-not-presence principle directly — restoring competitive balance and keystone diversity rather than sterilising. They differ by compartment, and the honest framing is that this is a fast-moving field with real promise and uneven proof; strain, dose, and host context determine the result.

Built-environment probiotics

HOME

DISPLACE PATHOBIONTS, DON'T STERILISE

Probiotic (Bacillus-spore) cleaning systems have, in hospital studies, lowered pathogen load, resistance genes, and infection incidence by competitive exclusion. For the home, the same principle — plus moisture control, ventilation, and outdoor/biodiversity exposure — aims to shift the building microbiome toward a lower-inflammation balance.

Nasal & skin probiotics

NOSE / SKIN

RE-SEED THE PROTECTIVE COMMUNITY

Niche-modifying nasal approaches aim to restore keystone and protective strains (Corynebacterium, protective S. epidermidis) and disrupt biofilm. Topical application of AMP-producing skin commensals (S. hominis/epidermidis, Roseomonas mucosa) has reduced S. aureus and improved atopic dermatitis in early trials.

Gut probiotics, prebiotics, fermented foods

GUT

REBUILD DIVERSITY AND SCFA OUTPUT

The highest-yield compartment: multi-strain and spore-based probiotics, SCFA-producing and Treg-inducing organisms, prebiotic fibre, and fermented foods (shown to increase diversity and lower inflammatory markers); FMT is the research frontier. Effects are strain- and host-specific, so this is titrated and monitored, not prescribed generically.

PART VI · 13

Regulation, resolution, and the autonomic brake

Restoring the active off-switch — the capacities that end inflammation rather than prevent it.

Two capacities are restored as much by physiology as by pills, and they are easy to neglect because they are not products. The resolution program is rebuilt by supplying its omega-3 substrate, by treating the metabolic stress that depletes SPMs, and — at the frontier — by SPMs themselves. The autonomic brake — the vagal cholinergic anti-inflammatory pathway[17] — is trainable: HRV biofeedback, paced breathing, regular sleep, circadian alignment, and genuine stress regulation all raise vagal tone, which both reflects and lowers inflammatory status, and notably enhances endogenous pro-resolving-mediator production. None of this is glamorous; all of it raises the denominator, and because it is low-risk it can run in parallel from the start.

Capacity / lever	First-line interventions	Adjuncts & special compounds
Lower the load	Remediation (moisture/source/ventilation); reduce chemical & metal exposure; treat true infection; targeted, temporary antigen reduction	Binders where indicated; air filtration
Barrier	Glutamine, zinc(-carnosine), vitamin A/D, butyrate/fibre; ceramide lipids (skin); nasal hygiene	BPC-157, KPV, colostrum/lactoferrin; polyphenols, mucin support
Regulation & resolution	Omega-3 to index target; vitamin D/A; fibre/SCFA; stress & sleep	SPMs (frontier); plant sterolins (modest evidence)

Capacity / lever	First-line interventions	Adjuncts & special compounds
Innate set-point	Membrane/lipid replacement; mitochondrial support; treat metabolic stress	Re-tolerising strategies; avoid innate-training agents (β-glucan caution)
Microbiome rebalance	Diet diversity, fermented foods, prebiotic fibre; multi-strain/spore probiotics	Nasal & skin probiotics; built-environment probiotic cleaning; FMT (frontier)
Autonomic brake	HRV biofeedback, paced breathing, sleep/circadian, stress regulation	Vagal-tone practices; treat OSA

Table 7. The restoration program, consolidated by capacity. The columns move from broadly-evidenced first-line measures to adjunctive or frontier options; the logic is to lower load below threshold and rebuild each capacity, sequenced barrier-first.

PART VII · 14

Reading and sequencing the individual

From the ratio to a Monday-morning workflow — a model is only useful if it changes what the clinician does.

The governing ratio translates into a concrete, repeatable workflow — not a protocol, but a sequence of questions that orders an otherwise overwhelming problem.

- **Step 1 — Map the load.** Inventory the numerator across the trigger classes of Table 1; the aim is not to find the one cause but to total the pressure and identify which loads are large and removable.
- **Step 2 — Find the rate-limiting capacity.** Using the tiered panel, ask which of the three capacities is most eroded; most patients have a dominant deficit. That is where the program starts.
- **Step 3 — Sequence the program.** Lower the most provocative loads first; seal the barrier next; then rebuild regulation and resolution; then, cautiously and last, address the innate set-point. The low-risk foundation runs from day one.
- **Step 4 — Locate the patient on the CDR map.** The tolerance lens complements the four-phenotype reading: set-point-dominant near Stuck Alarm, metabolic near Drained Battery, unresolved remodelling near Worn-Out Defender, failed reconnection near Closed Gate.
- **Step 5 — Monitor by convergence.** Under an effective program the capacity markers should move together and lead the symptoms. If they do not move, the program is aimed at the wrong capacity; if symptoms improve while markers stay fixed, the account is wrong for that patient.

Dominant deficit	Signature	First-line emphasis
Barrier-dominant	Translocation markers (LBP/sCD14/I-FABP) up; gut symptoms; food reactivity	Load reduction + barrier sealing (gut/skin/airway) before all else
Regulation/resolution-dominant	Low omega-3 index & HRV; poor resolution; autoimmune drift	Omega-3/SPM substrate, vitamin D/A, fibre/SCFA, vagal & sleep work
Set-point-dominant	High baseline tone; GDF15/FGF21 up; hyper-reactivity to small exposures	Membrane/lipid replacement, mitochondrial support; avoid innate-training agents
Microbiome-dominant	Marked dysbiosis across compartments; recurrent infection/colonisation	Multi-compartment rebalancing; gut anchors; remediate the home reservoir

Table 8. Dominant-deficit phenotypes and where to begin. Most patients show one rate-limiting capacity even when all are involved; identifying it sets the sequence.

PART VIII · 15

Holding the model to its own standard

What would prove it right, and what would prove it wrong — a unified trigger theory must specify, bound, and test, or become a universal solvent.

This series has criticised a prior construct for over-unifying — for a frame so accommodating it explained everything and predicted nothing. The integrity of the present model depends on not repeating that error. Three commitments do that.

- **It is one trigger theory among several.** Dysbiosis and loss of tolerance are a major and often-neglected route into CDR1 — not the only one. The model unifies the effector (innate alarm)[19] and the governing ratio (load over reserve), not the aetiology. That hedge is what keeps it falsifiable.
- **It makes convergent, falsifiable predictions.** Across a defined group the dysbiosis indices of the four compartments should correlate with one another and with the innate/CDR readouts; the markers should track the clinical state; and under intervention they should move together and ahead of symptoms. If symptoms improve while markers stay fixed, or if eradication without rebalancing reliably helps, the model is wrong.
- **It demands the studies it implies.** Multi-compartment sampling paired with the tiered panel in cases versus matched controls; longitudinal tracking to test "markers lead symptoms"; and randomised trials of capacity-directed programs. n-of-1 designs suit the individuality of the dysbiosis.

Held this way, the loss-of-tolerance account is a research program rather than a story: bounded, mechanistic, addressed to modifiable targets, and continuous with the CDR/ISRmt framework it serves. Its central claim is modest and, I think, closer to the truth of these illnesses than any single-cause alternative — that in a world we

can never sterilise, health is not the absence of microbes or chemicals but the restored capacity to tolerate them.[16]

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Conclusion: the threshold, not the trigger

The stuck alarm of CDR1 has resisted single-cause explanation because it does not have a single cause. Many distinct insults converge on one innate effector, and the variable that decides who becomes and stays inflamed is the host's tolerance reserve — a reserve built from a lifetime of microbial dialogue and decomposable into the barrier that keeps signals out, the regulatory and resolution apparatus that stands them down, and the metabolic, mitochondrial set-point that decides how readily the alarm fires. Loss of tolerance is the erosion of those capacities, driven by environmental depletion and host vulnerability, and amplified by the alarm itself in a feed-forward loop that explains chronicity.

Because our living spaces and bodies are never sterile, the work is not eradication but the patient restoration of the threshold: lowering load below it, sealing barriers, replacing membranes and the substrate of resolution, rebalancing the four microbial compartments, and retraining the autonomic and metabolic set-point — while measuring honestly enough to know whether the capacities are truly moving.

The model's promise is that tolerance, unlike a toxin, is something a body can be helped to relearn.

REFERENCES

References & Notes

1. Naviaux RK. Metabolic features of the cell danger response. *Mitochondrion.* 2014;16:7–17.

2. Naviaux RK. Metabolic features and regulation of the healing cycle. *Mitochondrion.* 2019;46:278–297.

3. Naviaux RK. Incomplete healing as a cause of aging: the role of mitochondria and the cell danger response. *Biology (Basel).* 2019;8(2):27.

4. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell.* 2014;157(1):121–141.

5. Rook GAW. Regulation of the immune system by biodiversity from the natural environment. *Proc Natl Acad Sci USA.* 2013;110(46):18360–18367.

6. Strachan DP. Hay fever, hygiene, and household size. *BMJ.* 1989;299(6710):1259–1260.

7. Stiemsma LT, Reynolds LA, Turvey SE, Finlay BB. The hygiene hypothesis: current perspectives and future therapies. *Immunotargets Ther.* 2015;4:143–157.

8. Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol.* 2020;20(6):375–388.

9. Cheng SC, Quintin J, Cramer RA, et al. mTOR- and HIF-1α–mediated aerobic glycolysis as metabolic basis for trained immunity. *Science.* 2014;345(6204):1250684.

10. Saeed S, Quintin J, Kerstens HHD, et al. Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. *Science.* 2014;345(6204):1251086.

11. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature.* 2014;510(7503):92–101.

12. Tracey KJ. The inflammatory reflex. *Nature.* 2002;420(6917):853–859.

13. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature.* 2013;504(7480):446–450.

14. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature.* 2013;504(7480):451–455.

15. Atarashi K, Tanoue T, Oshima K, et al. Treg induction by a rationally selected mixture of Clostridia strains. *Nature.* 2013;500(7461):232–236.

16. Trompette A, Gollwitzer ES, Yadava K, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med.* 2014;20(2):159–166.

17. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science.* 2013;341(6145):569–573.

18. National Academies of Sciences, Engineering, and Medicine. *Microbiomes of the Built Environment.* National Academies Press; 2017.

19. Gilbert JA, Stephens B. Microbiology of the built environment. *Nat Rev Microbiol.* 2018;16(11):661–670.

20. Caselli E, Brusaferro S, Coccagna M, et al. Reducing healthcare-associated infections incidence by a probiotic-based sanitation system. *PLoS One.* 2018;13(7):e0199616.

21. Caselli E, D'Accolti M, Soffritti I, et al. Impact of a probiotic-based hospital sanitation on antimicrobial resistance. *Infect Drug Resist.* 2019;12:501–510.

22. Tarricone R, Rognoni C, Arnoldo L, Mazzacane S, Caselli E. A probiotic-based sanitation system: a budget impact analysis. *Pathogens.* 2020;9(6):502.

23. Paramasivan S, Bassiouni A, Shiffer A, et al. The international sinonasal microbiome study (ISMS). *Allergy.* 2020;75(8):2037–2049.

24. Lee JT, Frank DN, Ramakrishnan V, et al. Unraveling the role of the microbiome in chronic rhinosinusitis. *J Allergy Clin Immunol.* 2022;149(5):1449–1461.

25. Abreu NA, Nagalingam NA, Song Y, et al. Sinus microbiome diversity depletion and Corynebacterium tuberculostearicum enrichment. *Sci Transl Med.* 2012;4(151):151ra124.

26. Iwase T, Uehara Y, Shinji H, et al. Staphylococcus epidermidis Esp inhibits S. aureus biofilm formation and nasal colonization. *Nature.* 2010;465(7296):346–349.

27. Liu Q, Liu Q, Meng H, et al. Staphylococcus epidermidis contributes to healthy maturation of the nasal microbiome. *Cell Host Microbe.* 2020;27(1):68–78.

28. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. *Nat Rev Microbiol.* 2018;16(3):143–155.

29. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal bacteria protect against S. aureus. *Sci Transl Med.* 2017;9(378):eaah4680.

30. Naik S, Bouladoux N, Wilhelm C, et al. Compartmentalized control of skin immunity by resident commensals. *Science.* 2012;337(6098):1115–1119.

31. Myles IA, Earland NJ, Anderson ED, et al. First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis. *JCI Insight.* 2018;3(9):e120608.
32. Fasano A. Zonulin and its regulation of intestinal barrier function. *Physiol Rev.* 2011;91(1):151–175.
33. Scheffler L, Crane A, Heyne H, et al. Widely used commercial ELISA does not detect precursor of haptoglobin2... *Front Endocrinol.* 2018;9:22.
34. Massier L, Chakaroun R, Kovacs P, Heiker JT. Blurring the picture in leaky gut research. *Gut.* 2021;70(8):1801–1802.
35. Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. *Gut.* 2019;68(8):1516–1526.
36. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes.* 2007;56(7):1761–1772.
37. Bouic PJD, Lamprecht JH. Plant sterols and sterolins: a review of their immune-modulating properties. *Altern Med Rev.* 1999;4(3):170–177.
38. Bouic PJD. The role of phytosterols and phytosterolins in immune modulation. *Curr Opin Clin Nutr Metab Care.* 2001;4(6):471–475.
39. EFSA Panel on Nutrition, Novel Foods and Food Allergens. A combination of β-sitosterol and β-sitosterol glucoside... *EFSA J.* 2019;17(6):5776.
40. Nicolson GL, Ash ME. Lipid Replacement Therapy. *Biochim Biophys Acta.* 2014;1838(6):1657–1679.
41. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans.* 2017;45(5):1105–1115.
42. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol.* 2008;8(9):685–698.
43. Cantorna MT, Snyder L, Lin YD, Yang L. Vitamin D and 1,25(OH)2D regulation of T cells. *Nutrients.* 2015;7(4):3011–3021.
44. Prasad AS. Zinc in human health: effect of zinc on immune cells. *Mol Med.* 2008;14(5-6):353–357.
45. Rao R, Samak G. Role of glutamine in protection of intestinal epithelial tight junctions. *J Epithel Biol Pharmacol.* 2012;5(Suppl 1-M7):47–54.
46. Sturniolo GC, Di Leo V, Ferronato A, et al. Zinc supplementation tightens "leaky gut" in Crohn's disease. *Inflamm Bowel Dis.* 2001;7(2):94–98.
47. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. *Nat Med.* 2019;25(5):716–729.
48. Wastyk HC, Fragiadakis GK, Perelman D, et al. Gut-microbiota-targeted diets modulate human immune status. *Cell.* 2021;184(16):4137–4153.
49. Suomalainen A, Battersby BJ. Mitochondrial diseases: the contribution of organelle stress responses to pathology. *Nat Rev Mol Cell Biol.* 2018;19(2):77–92.
50. Williams DP, Koenig J, Carnevali L, et al. Heart rate variability and inflammation: a meta-analysis. *Brain Behav Immun.* 2019;80:219–226.
51. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol.* 2016;14(8):e1002533.
52. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. *Nature.* 2016;535(7610):65–74.
53. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. *Nat Rev Immunol.* 2017;17(4):219–232.
54. Roduit C, Frei R, Ferstl R, et al. (PASTURE/farm-effect studies on early-life exposure and tolerance). *J Allergy Clin Immunol.*
55. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ.* 2015;351:h5527.

56. DiTulio M, Navarro-Torres CA. Clearance of multiple antibiotic-resistant coagulase-negative staphylococci is selectively associated with higher circulating α-melanocyte stimulating hormone in patients evaluated for chronic inflammatory response syndrome. *Front Endocrinol.* 2026;17:1728408.

Note on sources and evidence grading. The immunological foundations (tolerance, trained immunity, SCFA–Treg induction, pro-resolving mediators, the cholinergic anti-inflammatory pathway, mucosal and skin immunity) and the microbiome-compartment science are drawn from primary and review literature at the level of established consensus. Intervention evidence is graded in-text: some pillars are well supported (omega-3/SPM biology, SCFA/fiber, barrier nutrients), several are mechanistically reasoned but clinically immature (membrane lipid replacement, compartment probiotics, peptides), and at least one (plant sterolins) rests on older, single-group data that EFSA found insufficient for a health claim. The β-glucan caution reflects mainstream trained-immunity science; the commercial serum "zonulin" assay is named as unreliable on the basis of independent validation studies. Reference 56 (DiTulio & Navarro-Torres, 2026) is newly integrated at §5.2 and §8 and is graded in-text as a retrospective, associational cohort whose grouping on a post-treatment outcome precludes causal attribution. A number of citation details should be confirmed against the originals before formal submission. This monograph presents a mechanistic, testable framework for clinical reasoning and research design; it does not assert that any single supplement, organism, or test is proven therapy. © Beyond Mold · Andrew Heyman, MD, MHSA.