BeyondMold

CLINICAL PRIMER

CDR / ISRMT PHENOTYPE SERIES · NO. B

The Drained Battery

Phenotype B · Drained Battery

Rebuilding the mitochondrial engine — ETC bypass and support, NAD+ and redox restoration, substrate and cofactors, and metabolic-program modulation, on a foundation of strict pacing.

Andrew Heyman, MD, MHSA

Integrative & Metabolic Medicine · Founder, Beyond Mold

ORIENTATION · HOW TO READ THIS PRIMER

Rebuilding an engine that has stalled

This is the Phenotype B companion to the Beyond Mold phenotype series. It assumes the CDR/ISRmt model and the four-phenotype classification, and that the staging baseline has been run. Its job is to lay out the agents that **rebuild mitochondrial output** in a patient whose biology has shifted from alarm into a hypometabolic conservation state and stalled there.

Each agent is presented as mechanism, dosing, cautions, and where it fits, with a conservative evidence grade. Agents are grouped by the lever they pull on the bioenergetic machinery.

THE CARDINAL RULE OF PHENOTYPE B

Do not rebuild the engine while the alarm is still firing, and never out-run the supply. Confirm that CDR1 drivers are controlled (Phenotype A handled) before mitochondrial support — rebuilding into an active danger signal stalls. And because the cardinal feature here is post-exertional malaise, **strict pacing within the energy envelope is itself a therapy**: graded "push-through" exercise is contraindicated. Rule out a co-primary immune component (Phenotype C) before assuming pure B.

01 · THE PHENOTYPE

What CDR2-Mitochondrial actually is

Phenotype B is **established CDR2 arrest with ISRmt as the dominant biology**. The innate-inflammatory phase has given way to a hypometabolic conservation state that will not resolve. ATF4-driven mitokine production elevates GDF15 (often >1,800 pg/mL) and FGF21; the electron transport chain is functionally impaired at Complexes I and III, forcing an aerobic-glycolysis (Warburg-like) shift that conserves resources at the cost of global output.

Immunity is intact (CD3/CD4/NK normal — distinguishing from C); the neuroendocrine system is stressed but not depleted (VIP low-normal — distinguishing from D); VEGF is often low, reflecting capillary hypoperfusion that compounds the energy deficit. The clinical gestalt is **depletion**: flat, non-fluctuating exhaustion ("a phone permanently at 8%"), non-restorative sleep, location-independent symptoms, and — cardinally — **post-exertional malaise**, a delayed (12–48 h) crash lasting days.

Laboratory signature

Domain	Phenotype B pattern
GDF15	Markedly elevated (>1,800 pg/mL) — active ATF4-driven ISRmt; the primary gate.

Domain	Phenotype B pattern
FGF21	Elevated — independent fatty-acid-oxidation-stress confirmation.
MMP-9	Normal — the alarm has handed off (distinguishes from A).
CD3 / CD4 / NK	Normal or borderline — immunity intact (distinguishes from C).
VIP / α-MSH	Low-normal, not critically depleted (distinguishes from D).
HRV	Reduced from metabolic suppression of vagal tone — expected to improve with restoration (not structural collapse as in D).

02 · STRATEGY

The logic of rebuilding the engine

Phenotype B opens to four reinforcing levers, on a foundation of controlled drivers and strict pacing:

- **Bypass & support the ETC** — restore electron flow past the Complex I/III bottleneck and supply the carriers.
- **Restore NAD+ & redox currency** — replenish the repair currency depleted in the danger state and lower the oxidative drive on the ISR.
- **Supply substrate, cofactors & buffers** — the raw materials the rebuild runs on.
- **Modulate the metabolic program & clear damaged mitochondria** — shift away from the Warburg state and use mitophagy so new capacity is healthy capacity; restore hormones and autonomic tone.

03 · PREREQUISITES

The gate you must earn

Entry conditions for Phenotype B treatment

- **CDR1 controlled** — exposure removed, MMP-9 normal, no active danger input (rebuilding into a live alarm stalls).
- **Immune component excluded** — CD3/CD4/NK and viral-reactivation features checked; if depleted, treat as Phenotype C (engine + immunity together).
- **Pacing established** — the patient is working within an energy envelope and not in a boom–bust cycle.

04 · LEVER 1

Bypass & support the electron transport chain

Methylene blue (low-dose, USP) RX/COMPOUNDED · ETC BYPASS

Mechanism. At low dose, methylene blue acts as an *alternative electron carrier*: it accepts electrons upstream and donates them to cytochrome c, partially bypassing a Complex I/III bottleneck and increasing oxygen consumption and ATP output. It is a hormetic antioxidant at low dose and a monoamine-oxidase inhibitor.

Dosing. Pharmaceutical (USP) grade only. Low/nootropic-mitochondrial dosing ~5–15 mg 1–2×/day (well below the ~1–2 mg/kg used for methemoglobinemia). Start low; titrate cautiously.

Cautions. Serotonin syndrome with SSRIs/SNRIs/MAOIs/triptans/other serotonergics — methylene blue is a potent MAOI; this is the dominant interaction. **G6PD deficiency** — hemolysis risk; screen and avoid. Blue-green urine/sclera; methemoglobinemia at higher doses; avoid in pregnancy; renal caution. Not a casual supplement.

Where it fits. A targeted ETC-bypass tool where the Complex I/III block is the rate-limiter — used with strict attention to the serotonergic and G6PD cautions. Evidence: C

CoQ10 / ubiquinol NATURAL · ETC CARRIER

Mechanism. Coenzyme Q10 shuttles electrons between Complexes I/II and III; ubiquinol is the reduced, better-absorbed form. Directly supports the impaired carriers of this phenotype.

Dosing. 100–300 mg/day ubiquinol with fat; higher in frank deficiency.

Cautions. Very well tolerated; may modestly lower INR (warfarin) and blood pressure.

Where it fits. A foundational ETC-support agent. Evidence: B

PQQ NATURAL · BIOGENESIS

Mechanism. Pyrroloquinoline quinone signals mitochondrial biogenesis (PGC-1α) and is a redox cofactor, supporting growth of new mitochondrial capacity.

Dosing. 10–20 mg/day, often paired with CoQ10.

Cautions. Well tolerated; sleep changes occasionally reported.

Where it fits. A biogenesis-signaling complement to CoQ10. Evidence: C

05 · LEVER 2

Restore NAD+ & redox currency

NAD+ precursors (NR / NMN) NATURAL · NAD+ CAPACITY

Mechanism. Nicotinamide riboside and nicotinamide mononucleotide raise NAD+, the redox and repair currency depleted in the danger state, supporting sirtuins, PARPs, and OXPHOS.

Dosing. NR 250–500 mg/day or NMN 250–500 mg/day; niacinamide is a low-cost alternative precursor.

Cautions. Generally well tolerated; flushing rare with these forms; high-dose data still maturing.

Where it fits. Core to refilling the energy/repair currency. Evidence: C

N-acetylcysteine (NAC) NATURAL · GLUTATHIONE / ISR DRIVE

Mechanism. A glutathione precursor that restores redox headroom and lowers the oxidative drive onto the eIF2α stress kinases (HRI, PKR, PERK arm), easing the ISR brake while supporting mitochondrial glutathione.

Dosing. 600–1200 mg 1–2×/day with food.

Cautions. GI upset; occasional sulfur odor; rare bronchospasm at high doses; very wide safety margin.

Where it fits. A quiet but real ISR-relief and antioxidant contribution. Evidence: B

Alpha-lipoic acid (ALA) NATURAL · COFACTOR / ANTIOXIDANT

Mechanism. A mitochondrial cofactor (pyruvate and α-ketoglutarate dehydrogenase) and amphipathic antioxidant that regenerates other antioxidants and supports glucose handling.

Dosing. 300–600 mg/day (R-lipoic acid better absorbed).

Cautions. Can lower blood glucose (caution with hypoglycemics); may lower biotin; GI upset.

Where it fits. A cofactor/antioxidant adjunct in the NAD+/redox lever. Evidence: C

06 · LEVER 3

Substrate, cofactors & buffers

L-carnitine / acetyl-L-carnitine NATURAL · FATTY-ACID TRANSPORT

Mechanism. Carnitine shuttles long-chain fatty acids into mitochondria for β-oxidation; acetyl-L-carnitine adds a CNS-penetrant, neurotrophic profile.

Dosing. 1–2 g/day in divided doses.

Cautions. GI upset, fishy body odor; theoretical TMAO considerations; caution in seizure history (ALCAR).

Where it fits. Substrate-delivery support for fat-based energy. Evidence: B

Riboflavin (B2), thiamine (B1) & B-complex NATURAL · ETC COFACTORS

Mechanism. Riboflavin is the FAD precursor for Complexes I and II; high-dose thiamine supports the TCA cycle and pyruvate dehydrogenase; the broader B-complex supplies one-carbon and TCA cofactors the rebuild runs on.

Dosing. Riboflavin 100–400 mg/day; thiamine (or benfotiamine) higher where indicated; a methylated B-complex base.

Cautions. Generally benign; bright-yellow urine (B2); niacin flushing if included.

Where it fits. The cofactor floor beneath every other lever. Evidence: C

D-ribose NATURAL · ATP SUBSTRATE

Mechanism. A pentose that feeds the purine-salvage pathway to regenerate adenine nucleotides (ATP/ADP), addressing the depleted nucleotide pool of stressed mitochondria.

Dosing. 5 g 2–3×/day, often peri-activity.

Cautions. Mild hypoglycemia and GI at higher doses; take with food.

Where it fits. Substrate support, particularly around exertion. Evidence: C

Creatine monohydrate NATURAL · PHOSPHATE BUFFER

Mechanism. Expands the phosphocreatine buffer that rapidly re-phosphorylates ADP to ATP, smoothing energy delivery in muscle and brain.

Dosing. 3–5 g/day; no loading needed.

Cautions. Well tolerated; mild water retention; ensure hydration; renal caution if impaired.

Where it fits. An energy-buffering staple. Evidence: B

Magnesium NATURAL · ATP COFACTOR

Mechanism. ATP is biologically active as Mg-ATP; magnesium is cofactor to hundreds of enzymatic steps and is commonly depleted.

Dosing. 200–400 mg/day elemental (glycinate/malate/threonate by goal).

Cautions. Loose stools (oxide/citrate); caution in renal impairment.

Where it fits. A foundational cofactor; magnesium malate suits fatigue. Evidence: B

07 · LEVER 4

Modulate the program & clear damaged mitochondria

Fermented wheat germ extract (FWGE / Avemar) NATURAL · METABOLIC MODULATOR

Mechanism. A standardized fermented wheat-germ extract that modulates glucose metabolism — inhibiting glucose-6-phosphate dehydrogenase and transketolase to restrain the pentose-phosphate/Warburg-like glycolytic shift — with anti-inflammatory and immune-modulating effects. Mechanistically it pushes metabolism back toward oxidative phosphorylation, the core problem in CDR2.

Dosing. ~9 g/day (one standardized sachet, e.g., Avemar), with food.

Cautions. Contains wheat/gluten — avoid in celiac disease; GI upset; fructose-malabsorption caution; pregnancy/lactation data limited.

Where it fits. A metabolic-program modulator layered onto ETC and cofactor support; most evidence is oncologic/immune, extrapolated here. Evidence: C

Urolithin A NATURAL · MITOPHAGY

Mechanism. Induces mitophagy, clearing damaged mitochondria so that new biogenesis yields healthy capacity rather than dysfunctional units.

Dosing. 500 mg/day.

Cautions. Well tolerated; limited long-term data.

Where it fits. Quality-control complement to NAD+/biogenesis support. Evidence: C

Mitochondrial-derived & ETC-targeted peptides PEPTIDE · EXPERIMENTAL

Mechanism. MOTS-c (a mitochondrial-derived peptide influencing metabolic homeostasis) and elamipretide/SS-31 (a cardiolipin-binding peptide stabilizing the inner membrane and ETC) target the bioenergetic lesion directly but remain investigational/compounded.

Dosing. Per compounded protocols; clinician-directed.

Cautions. Limited human data; off-label/compounded; injection-site effects.

Where it fits. Optional, experimental adjuncts once the foundational stack is in place. Evidence: D

Hormonal & autonomic restoration (Phase 4)

Rebuild is anabolic and trophic. Restore the cortisol rhythm, thyroid/free-T3, DHEA, sex steroids, and vitamin D as indicated, and rehabilitate autonomic tone with HRV resonance breathing, vagal toning, and *sub-threshold* graded movement — never push-crash exposure. Rising HRV is an accessible readout that vagal capacity is returning.

08 · THE ROADMAP

A sequenced approach

Stage	Do	Exit gate
0 · Earn it	Confirm CDR1 controlled and pacing established; exclude an immune (C) component.	MMP-9 normal; CD3/CD4/NK intact; patient pacing within envelope.
1 · Foundation	CoQ10/ubiquinol, B-complex/riboflavin, magnesium, NAC; begin HRV/pacing discipline.	Basic cofactors repleted; tolerating the stack; no exertional crashes from the regimen.
2 · Rebuild	Add NAD+ precursor, carnitine, ALA, D-ribose, creatine, PQQ.	Energy floor lifting; PEM threshold rising modestly.
3 · Modulate	Layer FWGE and, where the ETC block dominates, low-dose methylene blue (with serotonergic/G6PD screening); urolithin A for mitophagy.	GDF15/FGF21 trending down; tolerance maintained.
4 · Restore & re-phenotype	Hormone and autonomic restoration; reassess at ~12 weeks. If GDF15/FGF21 normalize but recovery stalls with low VIP/α-MSH and collapsed HRV, transition to Phenotype D.	Rising spare respiratory capacity; mitokines receding; or a clear re-phenotyping decision.

> **Pace as therapy.** Throughout, the energy envelope is non-negotiable. A stage that triggers PEM means step back, recover, and re-advance more slowly — the rebuild proceeds on consistency, not intensity.

09 · AT A GLANCE

Master summary

Agent	Lever	Mechanism (one line)	Dosing	Ev.
Methylene blue	ETC bypass	Alternative electron carrier to cytochrome c; ↑OXPHOS	~5–15 mg 1–2×/d (USP)	C
CoQ10/ubi-quinol	ETC carrier	Electron shuttle I/II→III	100–300 mg/d	B
PQQ	biogenesis	PGC-1α biogenesis signal	10–20 mg/d	C
NR / NMN	NAD+	Restores NAD+ repair currency	250–500 mg/d	C
NAC	redox/ISR	Glutathione; lowers oxidative kinase drive	600–1200 mg 1–2×/d	B
ALA	cofactor	PDH/α-KGDH cofactor; antioxidant	300–600 mg/d	C
Carnitine	FA transport	Long-chain fatty-acid import	1–2 g/d	B
B2/B1/B-cplx	cofactors	FAD/TCA/one-carbon cofactors	B2 100–400 mg/d	C
D-ribose	substrate	Purine-salvage ATP substrate	5 g 2–3×/d	C
Creatine	buffer	Phosphocreatine ATP buffer	3–5 g/d	B
Magnesium	cofactor	Mg-ATP; enzymatic cofactor	200–400 mg/d	B
FWGE (Ave-mar)	metabolic	↓G6PD/transketolase; anti-Warburg; immune	~9 g/d	C
Urolithin A	mitophagy	Clears damaged mitochondria	500 mg/d	C

10 · EVIDENCE, SAFETY & SOURCING

Honest framing

The bioenergetic mechanisms are well grounded; their application to CDR2 biotoxin illness is mechanistically reasoned. CoQ10, creatine, magnesium, NAC, and carnitine reach good human data; methylene blue, FWGE, NAD+ precursors, PQQ, ALA, D-ribose, and urolithin A rest more on mechanism and adjacent-population data.

- **Monitor** GDF15/FGF21 trend, lactate/L:P and acylcarnitines where available, HRV trend, and — objectively — spare respiratory capacity on a Seahorse assay as the reserve climbs. Direction matters more than any single value.

- **Methylene blue specifically** — screen for G6PD deficiency and serotonergic medications before use; pharmaceutical USP grade only; this is the one agent here that demands a formal interaction check.
- **Pace as a prescription** — PEM is a contraindication to graded push-through exercise; all movement stays sub-threshold.

*This document supports clinician decision-making and education within the Beyond Mold CDR/ISRmt framework. It is a clinical synthesis, not a guideline: it is not individualized medical advice, does not establish a standard of care, and does not replace prescriber judgement, informed consent, or appropriate monitoring for the individual patient. Many agents are used off-label and several peptides are compounded; source from reputable compounding pharmacies with potency and sterility documentation, and apply standard monitoring. Evidence grades are deliberately conservative: **A** RCT-level in this or a closely adjacent indication · **B** good human data, extrapolated here · **C** mechanistic + preclinical, limited human · **D** mechanistic / experimental only. Not a substitute for clinical judgement.*