

Post-Infectious Illness as a Failure of Biological Resolution

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Abstract. Postinfectious syndromes expose the gap between pathogen control and return of normal regulation. The paper compares residual infection, immune memory, tissue injury and autonomic disruption as distinct processes, using the language of resolution without collapsing them into a universal explanation.

The infection ends on one timeline; recovery follows another

Pathogen clearance, tissue repair and restoration of normal sleep, activity and autonomic function do not always occur together. Some acute illnesses create discrete organ injury, while others appear to trigger persistent immune or neurological consequences. In postinfectious illness, the central error is often to demand one explanation for a population that may contain biologically different subgroups.

Multiple maintaining pathways

One person may have residual pulmonary or cardiac injury; another may have postural tachycardia or altered exercise tolerance; another may retain viral antigen or ongoing immune activation; others may have multiple interacting problems. Research on long COVID has explored these possibilities without establishing a singular universal mechanism. Microvascular abnormalities and tissue-level inflammation are plausible in some settings, yet they should be investigated rather than presumed.

A resolution framework

We propose distinguishing four states: persistent provoking signal, prolonged immune response after signal reduction, structural consequence of previous injury, and secondary behavioral or physiological feedback. These categories are not mutually exclusive. The value is that they generate different tests and treatment hypotheses. A patient with ongoing myocarditis cannot be assessed as though the problem were identical to isolated postinfectious fatigue.

The danger of a neat mechanistic story

Attractive explanations involving 'viral debris,' clotting, autoantibodies or hidden tissue reservoirs may each contain truth in specified subgroups. Population-level association cannot establish that any one mechanism causes every individual case. Lack

of a simple laboratory test is not evidence that no disease exists, but diagnostic uncertainty must not be filled with a marketed test lacking demonstrated validity.

Clinical implications

Careful evaluation for recognized organ damage and treatable alternate disorders remains necessary. Rehabilitation and activity advice must be individualized; symptoms worsened by exertion require particular caution against rigid exercise escalation. Experimental therapies should be described with their actual evidence, uncertainty and risks.

Conclusion

Biological resolution can be incomplete even after an infection is no longer detectable. That principle is important, but it becomes clinically useful only when a specific maintaining process is supported by evidence in the patient group under discussion.

Compartment and persistence must be specified

Evidence of viral material in a tissue, evidence of replicating infectious virus and evidence of an immune response to a previous infection are three different findings. They should not be treated as interchangeable proof of a reservoir. Similarly, circulating fibrin fragments and vascular microthrombi represent different measurement objects. The scientific legitimacy of postinfectious research depends on maintaining those distinctions.

Physiological state may worsen symptoms without explaining origin

Insomnia, inactivity and altered autonomic tone may amplify fatigue or cognitive symptoms, but their presence does not demonstrate that the patient has a psychological disorder or that the original infection was irrelevant. Secondary loops can be causally important even if they did not start the illness. A respectful mechanistic model recognizes this temporal distinction and avoids assigning blame for persistent symptoms.

Critical outcome standards

A successful intervention must improve function or other clinically meaningful outcomes, not merely change a research biomarker. Longitudinal measurement is necessary because many postinfectious illnesses fluctuate and spontaneous improvement may occur. Adverse events and worsening after exertion should be recorded rather than reclassified as beneficial 'healing crises.' Proper causal uncertainty protects patients and makes the underlying ideas more scientifically credible.

Selected scientific reading

1. [Proal AD et al. SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 \(PASC\). Nat Immunol. 2023;24:1616–1627.](#)
2. [Netea MG et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol. 2020;20:375–388.](#)

3. [Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature. 2014;510:92–101.](#)

Editorial status: Conceptual scientific essay, not peer reviewed. Not original clinical data, a treatment protocol or medical advice. Selected readings are not a systematic review. Evidence and interpretation should be assessed independently.