

28. Post-Infectious Illness as a Failure of Biological Resolution

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Abstract

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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.

Post-infectious is a temporal description, not one diagnosis

Persistent illness after infection can reflect residual tissue destruction, ongoing pathogen activity, immune-mediated injury, autonomic dysregulation, medication effects or a mixture of factors. The phrase 'post-infectious syndrome' does not specify which one. A patient with chronic breathlessness after severe pneumonia may have lung fibrosis or cardiac consequences; another patient with dizziness and palpitations may show orthostatic intolerance; another may have a defined inflammatory complication. These examples require different evaluations and may respond to different interventions.

The resolution framework asks whether the tissue has disengaged successfully from the acute defense response. That is a promising question, but the evidence must distinguish persistent activation from ongoing damage. A raised cytokine level can reflect a cause, a consequence, an intercurrent infection or unrelated inflammatory disease. Even a characteristic immune profile may represent only one subgroup of a heterogeneous clinical population.

Identifying mechanisms without overfitting

Investigators could follow patients from acute illness through recovery, tracking infection severity, medications, functional capacity, autonomic tests, organ imaging and immune or metabolic markers. A model should specify which early findings predict later symptoms beyond baseline health and disease severity. Retrospective recruitment of only highly symptomatic patients can distort the prevalence of candidate mechanisms and cannot establish temporal order. Comparisons with both fully recovered people and patients with similar disability from other causes are needed.

It is also important not to interpret all persistent symptoms as psychological or all symptoms as evidence of an invisible pathogen. The appropriate position is that symptoms are real clinical data whose mechanisms require assessment. Some patients will have treatable neurological, cardiopulmonary or endocrine conditions. Other mechanisms remain under investigation. A strong theoretical essay should make room for both without pretending that uncertainty is an explanation.

Resolution as an endpoint

A therapy that improves sleep, autonomic tolerance or functional capacity may help patients even if it does not directly alter an inflammatory pathway. Conversely, reducing a candidate biomarker without symptom or organ improvement would challenge the claim that the biomarker reflects a maintaining cause. Longitudinal research should prioritize validated functional outcomes and harms, because a treatment can change physiology without producing meaningful recovery.

The most defensible formulation is that some post-infectious illnesses may involve failed or incomplete transitions from defense to restoration. Demonstrating which transitions fail—and in whom—requires better phenotyping and disease-specific studies. No single theory currently resolves the full range of syndromes, and effective standard care for identifiable complications remains essential.

Subgroups are a scientific obligation, not an inconvenience

When a cohort contains people with persistent lung injury, dysautonomia, sleep disruption and distinct immune abnormalities, an average biomarker comparison may conceal the relationships researchers most need to understand. The answer is not unlimited subgroup searching after the results are known; it is prespecified phenotyping informed by clinical examination and reproducible measures. Exploratory discoveries can then be tested in independent populations. Without replication, a cluster generated by a statistical algorithm may reflect sampling differences rather than a biological subtype.

The proposed incomplete-resolution model should also allow full recovery without normalization of every biomarker. Some biological signals remain altered after an infection for reasons unrelated to symptoms. The strongest causal support would be a mediator whose trajectory distinguishes recovering from persistently ill patients and whose selective modification changes function. Finding a different abnormality in each patient does not establish a universal terrain syndrome; it may instead argue for several independent conditions sharing a temporal relationship with infection.

Safety before mechanistic experimentation

Research studies should not subject severely symptomatic participants to indiscriminate exertion or prolonged challenge protocols without regard to established risk and individual response. Functional outcomes can often be assessed with less provocative measures, symptom diaries and carefully selected physiological testing. Before classifying a patient as having incomplete immune resolution, clinicians must evaluate evident treatable complications and warning signs. The concept is useful precisely when it prompts more discriminating investigation of recovery pathways; it becomes harmful if it leads practitioners to postpone diagnosis or replace evidence-based care with a speculative restorative regimen.

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 and evidentiary note

This is an expanded conceptual synthesis, not original clinical research or a clinical treatment protocol. It preserves selected references from the original edition, whose bibliographic metadata have not all been independently reverified. Claims about specific diagnoses and treatments require appropriate primary evidence and professional assessment. Mechanistic plausibility does not establish therapeutic efficacy.