

# A multimodal approach for treating post-acute infectious syndrome

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**Long-term complications, such as extensive fatigue and cognitive issues, are known from various infections, including SARS-CoV-2, influenza virus, or *Borrelia burgdorferi*. The pathology is mostly unknown and differs between patients. Unfortunately, there is currently no common and effective treatment. In this perspective, we imply that post-acute infectious syndromes are due to a variety of factors, including among others diminished tissue perfusion, tissue infiltration by viruses, inflammation, and oxidative stress, and that not one specific biomarker can be used to measure these syndromes. Thus, we suggest that a score based on a number of criteria/factors should be used to assess post-acute infectious syndromes. Consequently, probably not one single treatment can be used to treat this group of patients, and we suggest a multimodal treatment regimen comprising a combination of pharmacotherapy, such as metformin and naltrexone with anti-inflammatory effects, alongside physical therapies such as extracorporeal apheresis and transcutaneous neurotherapy. This combined approach aims to reduce biomarker levels and enhance cognitive functions. This implies that a reset of the systems can be achieved by a multimodal approach based on a score for post-acute infectious syndromes.**

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## Introduction

After the COVID-19 pandemic, a number of patients experience persistent symptoms and physiological changes even after recovering from the acute phase of the disease (1). The potential symptoms cover a broad spectrum, including fatigue, breathlessness, headaches, sleep disturbances, difficulty concentrating, cognitive issues, skin rashes, diarrhea, and tinnitus (2–4). SARS-CoV-2 causing COVID-19 is not unique in this ability to cause post-acute sequelae. Various other acute infections, including Ebola, polio, dengue, but also influenza or bacterial infections, such as *Borrelia burgdorferi*, which might give rise to Lyme disease syndrome (5), have been linked to an unexplained chronic disability in a sub-population of patients (6). Post-acute infectious syndromes (PAIS) are not new; they usually come to attention when many people are infected, such as during pandemics, and have been described since the Russian flu (7). The consistent symptom profiles across different PAIS, regardless of the infecting agent, along with the overlapping clinical features with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), indicate the potential contribution of a shared etiopathogenesis (8).

The prevalence of PAIS depends on the pathogen and varies from a few percentages in patients having had influenza (9) to up to 70% of patients with persistent symptoms 2 years after infection with West Nile virus (10). For Long-Covid, the evidence suggests that, before the introduction of the vaccines, about 20% of patients diagnosed with COVID-19 and 5–10% of all infected persons developed long-term complications (11–14), which fell below 5% with the introduction of vaccines and new variants like omicron (15, 16). Interestingly, women seem to have a higher prevalence (6), which might at least partly be explained by the fact that women are generally more susceptible to immune-mediated conditions (17). The recovery period for patients with Long-Covid may vary significantly depending on the severity of the disease, hospitalization, comorbidities, and age (11, 18).

The persistent symptoms experienced by patients with PAIS can result in significant financial losses, affecting individuals, businesses, and economies globally. Furthermore, syndromes following acute infections can greatly diminish quality of life, as chronic symptoms may result in lost productivity, increased healthcare costs, and mental health issues, all of which can interfere with personal, social, and professional life. Health disparities related to PAIS have been shown to particularly affect racial and ethnic minorities. These disparities are driven by factors such as socioeconomic status, discrimination, and limited access to healthcare. They are not confined to specific regions but have global implications (18).

## Factors Responsible for PAIS

The underlying mechanisms for PAIS remain poorly understood but the current hypotheses proposed to elucidate the consequences of chronic fatigue and post-exertional malaise in patients with Long-Covid encompass diminished tissue perfusion (19), viral infiltration of tissues, inflammation in both the brain and peripheral organs (20), the prolonged presence of SARS-CoV-2 spike proteins (21), and the reactivation of other infectious agents such as Epstein–Barr virus, cytomegalovirus (CMV), and various other infectious components (22–26).

Furthermore, recent findings demonstrate that heightened lipid levels represent a significant risk factor (27–29). Likewise, Long-Covid induces a substantial elevation in lipids, posing a long-term risk for cardiovascular disease (30). Recently, it was demonstrated that in patients with Long-Covid, a persistent dysregulation and activation of the complement system could be observed (31). Moreover, thromboinflammatory proteins were increased in Long-Covid (31).

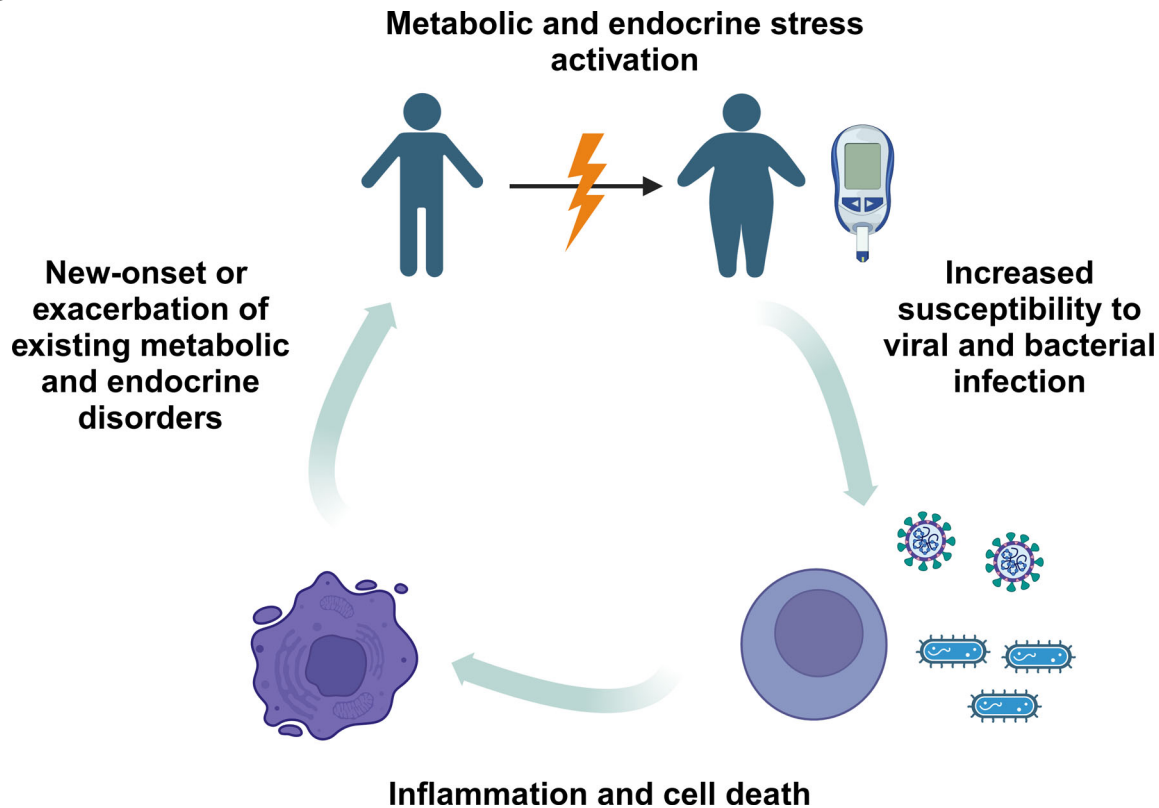
Changes in blood cellular components (32–34) and the rarefaction of vessels (35) have also been proposed as potential factors contributing to the onset of Long-Covid subsequent to SARS-CoV-2 infection. Interestingly, two distinct blood marker profiles during the acute phase of

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**Figure 1.** Metabolic and endocrine stress activation. The endocrine stress axis, which can be triggered by various factors such as psychological stress, physical exhaustion, or metabolic diseases, plays a pivotal role in the body's response mechanisms. When the endocrine stress axis is persistently activated, the body's immune system can become compromised, leading to heightened susceptibility to infections. Chronic or excessive inflammation can lead to tissue damage and cell death, which might aggravate or initiate metabolic and endocrine disorders, thus perpetuating a vicious cycle. Created with [BioRender.com](https://www.biorender.com)

COVID-19 have been associated with cognitive deficits up to 1 year after the acute infection with SARS-CoV-2. One is elevated fibrinogen and the other is elevated D-dimer, both in relation to C-reactive protein (36). Other studies have shown that plasma samples from patients with both acute COVID-19 and Long-Covid contain large anomalous (amyloid) deposits (microclots) that are resistant to fibrinolysis (37).

The emergence of autoantibodies against G-protein coupled receptors has raised concerns about their potential involvement, given their pathogenic role demonstrated in various autoimmune disorders (38). Particularly noteworthy is the implication of autoantibodies targeting neurotransmitters, such as  $\beta$ -adrenergic receptors, which have been suggested to impact the severity of COVID-19 and contribute to Long-Covid (6, 39). Furthermore, increased levels of autoantibodies against protease-activated receptor-1 (PAR-1), which promotes platelet activation, has been linked to severe COVID-19 (40–42), suggesting that these autoantibodies could also play a role in Long-Covid.

It has been speculated that the activation of interferon (IFN) signaling linked to SARS-CoV-2 could trigger the production of autoantibodies targeting type I IFNs (17) and exacerbate local inflammation (18, 19), thereby possibly contributing to the manifestation of PAIS.

Nonetheless, our research, along with others', suggests that functional autoantibodies against type I IFNs are unlikely to contribute to the pathogenesis of Long-Covid (43, 44). Additionally, we observed no correlation between Long-Covid fatigue scores and IFN-stimulated gene signatures (43).

#### The Effect of Metabolic and Endocrine Diseases on PAIS

Metabolic and endocrine disorders, as well as chronic stress, can trigger activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in dysregulated cortisol release. Moreover, they may impact the

renin-angiotensin-aldosterone and the sympatho-adrenomedullary system (45). Additionally, stimulation of the neuroendocrine stress axis could result in persistent low-grade inflammation throughout the body (45). For instance, both stress and obesity appear to exert comparable effects on brain function, attributed to the presence of neuroinflammation observed in both circumstances (46, 47). Chronic inflammation and imbalance between proinflammatory and anti-inflammatory factors in endocrine and metabolic diseases and in stress increases the susceptibility for additional pathogenic infections, which may lead to an abnormal immune response reaching pathogenic levels (48), which in turn increases the risk of experiencing PAIS. The direct infection of endocrine organs, such as pancreatic islets (49–52), adipose (53–56), or adrenal tissue (57) may lead to new onset of endocrine diseases (58). Moreover, the initial viral entry and replication in cells of metabolic and endocrine organs can induce direct damage, ultimately resulting in cell death, either through the immune system's activation or the initiation of cell-autonomous death signaling pathways (Figure 1). Additionally, immune cells activated to produce antibodies or cytokines, along with infected cells releasing biomolecules, may also affect noninfected cells locally and in distant tissues (59).

In conclusion, PAIS impacts various organ systems and multiple mutually nonexclusive biomedical explanations for the pathogenesis of PAIS can be hypothesized (60), which alone or in combination might be responsible for the development of PAIS. They probably involve unregulated immune response, persistent generation of proinflammatory cytokines (chronic inflammation), autoimmune-like reactions, persistent viral replication, and microclot formation (61). Thus, managing PAIS involves addressing a range of symptoms that include physical, cognitive, and psychological aspects. Consequently, we recommend measuring a panel of biomarkers to obtain a clinical indication for treatment



in patients severely affected by PAIS. Further research involving large groups of patients with and without PAIS is needed to determine exactly which biomarkers should be included in such a score and their respective weights.

### Potential Treatments of PAIS

Several potential treatments for Long-Covid have been explored (62) and recently, a systemic review of all registered clinical trials for treatment of PAIS was conducted (63). This study showed that while most research focuses on monotherapies, a combination of interventions is also being examined. Both pharmacotherapies and rehabilitative approaches but also psychotherapy or complementary and alternative medicine is being tested (63, 64). Most of these studies are still running and because of the heterogeneity among the studies, it is extremely difficult to draw a conclusion at this point. Because of the complexity of symptoms of PAIS, also the treatment is challenging and probably not one single treatment can be used for all patients exhibiting PAIS. Here, we will discuss some of the treatments that have shown a positive effect on Long-Covid. Current or emerging treatments, such as nutritional supplements or restoration of the gut microbiota, will not be discussed here as they have been recently described elsewhere (62).

#### Metformin

One of the pharmaceutical therapies that shows a positive effect on Long-Covid is the treatment with metformin. Worldwide, metformin is the first-line drug in the treatment of type 2 diabetes mellitus (65) due to its effectiveness, safety, and affordability (66).

Apart from its ability to inhibit gluconeogenesis and enhance insulin sensitivity, metformin has been recognized as a powerful suppressor of the chronic inflammatory response in macrophages. In acute inflammation, metformin reduces the transcription of interleukin (*Il*) *1b* and *Il10* by activating AMP-activated protein kinase (AMPK) (67), whereas in chronic inflammation, it reduces the production of reactive oxygen species (ROS) by mitochondria, which leads to a reduction in the levels of HIF1- $\alpha$  and results in decreased expression of *Il1b*, whereas expression of *Il10* is enhanced (68). Recent studies demonstrated that the SARS-CoV-2 spike protein 1 induces  $\alpha$ -synucleinopathy through microglia-mediated inflammation and mitochondrial ROS, which can be suppressed by metformin (69). This ability of metformin to reduce the levels of inflammatory markers has led to the hypothesis that metformin could be used for the treatment of Long-Covid. Furthermore, targeted machine learning analysis indicated that metformin use is associated with a reduced risk of post-infection mortality in COVID-19-positive patients (70). Indeed, in a double-blind trial, adults with overweight or obesity and SARS-CoV-2 infection who took metformin for 2 weeks were less likely than those who took a placebo to later report a diagnosis of Long-Covid (71). Similar findings were observed in a study assessing the 3-month and 6-month risk of PAIS in patients with type 2 diabetes mellitus. This study compared metformin users with those using sulfonylureas or dipeptidyl peptidase-4 inhibitors and found that metformin users had a lower risk of PAIS (72). These results suggest that additional interventions aimed at reducing mitochondrial ROS production should be identified and subjected to further investigation.

#### Low-dose Naltrexone

Another promising therapy is low-dose naltrexone (LDN) (73). Naltrexone is an oral  $\mu$ -opioid receptor antagonist. It is FDA approved for the treatment of opioid and alcohol dependence standardly in high doses of 50–150 mg/day. In low doses of 1–5 mg/day, opioid receptor signaling is not completely blocked, which leads to endogenous production of opioids and opioid receptors. These endogenous opioids modulate the immune system by inhibiting the proliferation of B and T cells (74). Furthermore, on immune cells, LDN is a specific antagonist for Toll-like receptor 4, thereby inhibiting the production of proinflammatory cytokines (75).

The anti-inflammatory effects of LDN have been widely used off-label for the treatment of autoimmune diseases and pain in diseases such as multiple sclerosis, Crohn's disease, and fibromyalgia (73, 76–78). In addition, LDN has been applied for the treatment of ME/CFS (79, 80). Recently, LDN was tested for treatment of Long-Covid, where it demonstrated to

have a positive effect on clinical symptoms and self-reported measures of fatigue (81–84).

#### Extracorporeal Apheresis

Apheresis involves the extracorporeal extraction of targeted blood constituents, such as particular cells or specific plasma components. Originally devised for eliminating lipids to address severe dyslipidemias and autoantibodies, methods for removing various pathogenic molecules from plasma have yielded surprising additional benefits. Subsequent research revealed the capacity to enhance blood viscosity by eliminating high molecular weight proteins, reduce oxidative stress by removing oxLDL, mitigate inflammation by extracting cytokines and inflammatory lipids and eliminate autoantibodies (85–88).

Up to 70% of patients with ME/CFS, including patients with Long-Covid, reported a significant improvement in their symptoms after extracorporeal apheresis (89). We demonstrated that patients who reported significant improvement after two cycles of therapeutic apheresis showed a substantial reduction in neurotransmitter autoantibodies, lipids, and inflammatory markers. Additionally, we observed a 70% decrease in fibrinogen levels, and dark field microscopy revealed that erythrocyte rouleaux formation and fibrin fibers largely disappeared post-apheresis (90). However, randomized, sham-controlled trials that are sufficiently powered and include psychological and physiological outcomes are still lacking.

#### Transcutaneous Electrical Nerve Stimulation

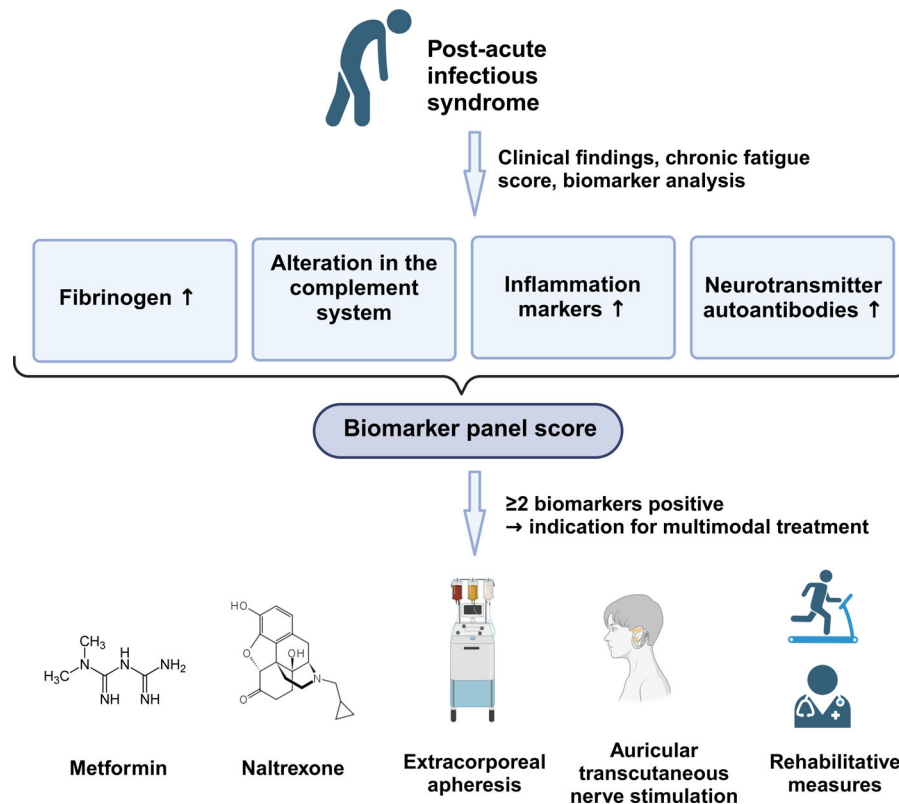
For nonresponders of pharmacotherapy, alternative strategies are important. As mentioned above, PAIS is a complex condition containing a neurological dimension but also cognitive and affective symptoms that might not be pharmacologically treated. For treatment of these patients, noninvasive brain stimulation, and in particular auricular transcutaneous nerve stimulation (atVNS) has been suggested (91). atVNS is a brain stimulation technique primarily used as a treatment for epilepsy and depression, but it is also being explored for other conditions like migraines and Alzheimer's disease (92).

The exact mechanism of how VNS works is not fully understood, but it's thought to modulate brain activity and the release of the neurotransmitters gamma-aminobutyric acid and noradrenaline (93). Furthermore, HPA axis activation is inhibited (94–96). In addition, anti-inflammatory effects of atVNS are mediated via the  $\alpha 7$  nicotinic acetylcholine receptor (97), which leads to modulation of cholinergic anti-inflammatory pathways thereby inhibiting the release of cytokines, such as TNF- $\alpha$  in the prefrontal cortex, hippocampus, and hypothalamus, thus suppressing neurological inflammation (98).

A pilot randomized controlled trial of atVNS showed a trend suggesting that atVNS may have mild to moderate effect in reducing mental symptoms in a subset of patients with Long-Covid (99). Another pilot study involving 24 female patients with Long-Covid showed significant improvements in various cognitive functions, anxiety, depression, and sleep immediately post-intervention, with benefits persisting or increasing at the 1-month follow-up. Improvements in fatigue were delayed, achieving statistical significance at the 1-month follow-up compared with baseline (100). These findings support allocating resources to conduct further trials and advance the understanding of atVNS as a potential treatment for Long-Covid.

#### Multimodal Treatment

Given the absence of a single definitive biomarker for PAIS, and recognizing the significant heterogeneity among patients with PAIS, we propose a pragmatic treatment approach. Our recommendation involves a multimodal treatment regimen comprising a combination of pharmacotherapy, such as metformin and naltrexone with anti-inflammatory effects, alongside physical therapies such as rehabilitative measures, extracorporeal apheresis and transcutaneous neurotherapy. This combined approach aims to reduce biomarker levels and enhance cognitive functions. Selection criteria for this treatment should be based on presenting symptoms and a biomarker panel score (Figure 2). As mentioned above, additional research is necessary to identify the specific biomarkers that should be measured and to establish the threshold scores for diagnosing Long-Covid or other PAIS.



**Figure 2.** Multimodal strategy for treating PAIS. As PAIS appears to be multifactorial in nature with a wide variety of symptoms, we propose an approach involving the measurement of a panel of biomarkers such as different blood parameters, complement factors, inflammation markers, or neurotransmitter autoantibodies. If two or more of these biomarkers test positive, we recommend implementing a combined approach comprising both pharmaceutical (e.g., metformin or naltrexone) and physical interventions (e.g., extracorporeal apheresis or auricular transcutaneous nerve stimulation). Furthermore, rehabilitative measures addressing both physical and psychological needs should be considered. Created with [BioRender.com](https://BioRender.com)

Ideally, the suggested multimodal treatment should be accessible to everyone. Since both metformin and naltrexone are relatively inexpensive, providing the pharmaceutical component should be feasible. However, access to specialists offering extracorporeal apheresis or atVNS is limited, making these components challenging to implement. This underscores the need for inclusive healthcare strategies and support for all communities worldwide.

### Conclusion

Long-term complications are known from various infections. The pathology is mostly unknown and differs between patients. Unfortunately, currently there is no common and effective treatment. Limited data on the prevalence and outcomes of unexplained PAIS make interpretation difficult. The absence of comprehensive, prospective studies with long-term follow-ups, objective measures, and appropriate control groups, along with small sample sizes, obscures case outcomes. Methodological differences and varied symptom criteria further hinder comparison across studies, making it challenging to draw definitive conclusions about prevalence accuracy and long-term prognosis. This data gap undermines foundational knowledge for designing clinical studies and assessing interventions' impact on post-infectious chronic disease and disability management.

To develop a clinical scoring system for PAIS, multicenter studies involving a larger patient cohort, inclusive of those who have not responded to treatment, will be imperative. These studies will aim to correlate individual biomarkers with treatment outcomes. Specifically, multivariable analysis will be essential for establishing a practical clinical scoring system to monitor both short-term and long-term treatment efficacy. Moreover, a more comprehensive exploration of disease mechanisms underlying Long-Covid and other PAIS could enhance or supplement the existing panel of clinical biomarkers. Furthermore, in the future, modern artificial

intelligence-based technologies, particularly those employing machine learning, will be ideally suited to tailor and define individualized treatment protocols based on specific markers for various patient subgroups afflicted with post-infectious syndromes.

In conclusion, a comprehensive approach is needed to address global health disparities while also encouraging specialists to combine well-established treatments with potentially lesser-known therapies to achieve optimal results.

### Author Contributions

CS and SRB wrote the initial draft of the paper. NT, YPK, PM, HB, AB, JK, HH, and MP wrote smaller sections of the perspective. CS prepared the figures. All authors reviewed successive drafts of the Review. All authors approved the final submitted version and had final responsibility for the decision to submit for publication.

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