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LONG COVID AND POST-ACUTE SEQUELAE: PATHOPHYSIOLOGY, BIOMARKERS, AND POTENTIAL REPURPOSED DRUG THERAPIES

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ABSTRACT

Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection, affects a substantial proportion of individuals following acute COVID-19, with symptoms persisting for weeks to months. Common manifestations include fatigue, cognitive impairment, dyspnea, chest pain, and autonomic dysfunction. The pathophysiology is multifactorial, involving persistent viral reservoirs, immune dysregulation, endothelial dysfunction, microclot formation, and tissue damage. Identifying reliable biomarkers has been challenging, but studies have reported alterations in inflammatory cytokines, autoantibodies, markers of coagulation, and metabolomic profiles. No approved therapies exist for long COVID, but several repurposed drugs are being investigated, including antivirals (nirmatrelvir/ritonavir, molnupiravir), anti-inflammatory agents (colchicine, corticosteroids), anticoagulants/antiplatelets, metformin, and drugs targeting autonomic or neurological symptoms. This review critically examines the current understanding of long COVID pathophysiology, the state of biomarker discovery, and the evidence for repurposed drug therapies, focusing on literature through early 2025. The heterogeneity of long COVID phenotypes complicates clinical trial design, and many early trials have been small or inconclusive. Future directions include better phenotyping, adaptive platform trials, and mechanistic biomarker-guided therapy. Until effective treatments are established, multidisciplinary supportive care remains central.

Keywords: Long COVID; Post-Acute Sequelae; SARS-Cov-2; Biomarkers; Drug Repurposing; Pathophysiology Introduction

1 INTRODUCTION

The COVID-19 pandemic has left a large population with persistent symptoms following acute infection, a condition commonly called long COVID. The World Health Organization defines post-COVID-19 condition as symptoms occurring at least three months after infection, lasting at least two months, and not explained by alternative diagnoses. Estimates suggest that 10–30% of infected individuals experience prolonged symptoms, with a higher burden among those with severe acute illness, though even mild cases can be affected. Long COVID encompasses diverse symptoms affecting multiple organ systems, including fatigue, brain fog, breathlessness, palpitations, and gastrointestinal disturbances.

The pathophysiology of long COVID is not fully understood, but several mechanisms have been proposed. These include persistence of viral antigen or RNA, immune dysregulation with chronic inflammation, autoimmunity, endothelial dysfunction and microthrombosis, and tissue damage from acute infection. Biomarkers that reliably diagnose or predict

long COVID are lacking, which hampers clinical management and research. Repurposing existing drugs offers a faster route to therapy, but evidence remains limited. This review summarizes current knowledge on pathophysiology, biomarkers, and repurposed drug therapies, drawing on literature through early 2025.

2 PATHOPHYSIOLOGY

Multiple overlapping mechanisms likely contribute to long COVID. Persistent viral reservoirs have been hypothesized based on detection of SARS-CoV-2 RNA or protein in tissues months after infection. Immune dysregulation includes elevated cytokines (e.g., IL-6, TNF-α), exhausted T cells, and autoantibodies targeting G-protein coupled receptors or interferons. Endothelial dysfunction and coagulation abnormalities, including microclot formation and platelet hyperreactivity, may explain cardiovascular and neurological symptoms. Reactivation of latent herpesviruses (e.g., Epstein-Barr virus) has also been reported. The relative contribution of each mechanism may vary across patient subgroups.

3 BIOMARKERS

Efforts to identify biomarkers for long COVID have yielded inconsistent results due to heterogeneity and small sample sizes. Some studies report elevated markers of inflammation (C-reactive protein, IL-6), coagulation (D-dimer), and endothelial activation (von Willebrand factor). Autoantibodies, particularly against autonomic receptors, have been associated with postural orthostatic tachycardia syndrome. Metabolomic and proteomic profiling have identified distinct signatures, but none have been validated for clinical use. Machine learning models combining clinical and laboratory data show promise but require prospective validation. Biomarkers for specific phenotypes, such as cognitive impairment or post-exertional malaise, are urgently needed.

4 POTENTIAL REPURPOSED DRUG THERAPIES

4.1 Antivirals

Some hypothesize that persistent virus contributes to long COVID, supporting trials of antivirals. Nirmatrelvir/ritonavir and molnupiravir have been evaluated in small studies with mixed results. A randomized trial of nirmatrelvir/ritonavir in long COVID did not show significant benefit overall, though some subgroups may respond. Larger trials are ongoing.

4.2 Anti-inflammatory and Immunomodulatory Agents

Colchicine and corticosteroids have been tested. Colchicine showed some benefit in acute COVID but data for long COVID are limited. Low-dose naltrexone, an immunomodulator, has anecdotal support for fatigue and pain, but controlled evidence is lacking. Intravenous immunoglobulin and plasmapheresis are being explored for autoimmune phenotypes.

4.3 Anticoagulants and Antiplatelets

Given endothelial dysfunction and microclot formation, anticoagulants such as apixaban have been studied. Early results suggest possible improvement in some patients, but bleeding risk and lack of biomarker-guided selection limit use. Ongoing trials are evaluating antiplatelet and anticoagulant combinations.

4.4 Metformin

Metformin, an antidiabetic drug with anti-inflammatory and antiviral properties, showed a reduction in long COVID incidence when given during acute infection in a large randomized trial. Its role in established long COVID is uncertain, but it may have preventive benefit.

4.5 4.5 Symptom-Specific Therapies

Beta-blockers, ivabradine, and fludrocortisone are used for autonomic dysfunction. Cognitive rehabilitation, graded exercise therapy (controversial for post-exertional malaise), and neuromodulation are being evaluated. Antihistamines and mast cell stabilizers may help some patients with histamine-mediated symptoms.

5 CHALLENGES AND RESEARCH GAPS

Long COVID is heterogeneous, with overlapping phenotypes and variable natural history. Many trials are small, lack control groups, and use heterogeneous endpoints. Standardized outcome measures, including patient-reported outcomes and functional assessments, are needed. Biomarker-guided patient stratification may improve trial efficiency. The lack of a clear mechanism for many patients complicates drug selection. Long-term follow-up studies are essential.

6 FUTURE PERSPECTIVES

Adaptive platform trials, such as the RECOVER initiative, are testing multiple repurposed agents simultaneously. Deep phenotyping combined with multi-omics may identify endotypes. Newer antivirals, monoclonal antibodies, and immunomodulators may be repurposed. Preventive strategies, including vaccination and early antiviral treatment, are important. Public health systems must develop long COVID clinics and support services.

7 CONCLUSION

Long COVID is a complex, multi-system condition with significant individual and societal burden. Pathophysiology involves viral persistence, immune dysregulation, endothelial dysfunction, and autoimmunity. Biomarkers are emerging but require validation. Repurposed drugs show promise, but no definitive therapy exists. Multidisciplinary care and continued research are priorities.

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