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Long COVID - Update -2025

This text reviews the main known elements of the chronic Sars-Cov-2 virosis known as Long covid.

Introduction

Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is a newly recognized chronic viral disease. The initial acute COVID-19 infection may go unnoticed, yet the virus can affect nearly every organ system, leading to numerous pathophysiological consequences. Identified mechanisms include viral persistence, autoimmune activation, direct organ damage, cerebral hypoperfusion, endothelial dysfunction, mitochondrial impairment, and coagulation disorders.

No other known virus has exhibited such a widespread multisystemic impact. The resulting destabilization of homeostasis leads to an unprecedented symptom pattern that does not fit into conventional nosological frameworks.

Diagnosis and Imaging

At present, diagnosis is primarily clinical, based on medical history, risk factors, and the recognition of symptoms unfamiliar to both patients and physicians. While conventional diagnostic tests often fail to capture the underlying pathology, advanced imaging techniques, such as:

- Technetium scintigraphy (Brain SPECT-CT) – particularly effective within the first two years of illness,
- 8 FDG PET scans – detecting cerebral hypometabolism,
- Functional MRI and Magnetic Resonance Spectroscopy, may reveal neurological impairments that are not apparent in standard testing.

Cutting-edge molecular biology techniques, including transcriptomics, proteomics, and genomics, are crucial in detecting immunological disruptions that conventional biological analyses cannot identify.

Pathophysiology

Long COVID involves neuroinflammation, endothelial dysfunction (endotheliitis), and the presence of micro-aggregated platelets. Specific organ and systemic manifestations include:

- Cardiac: Pericarditis, myocarditis, arrhythmias.
- Pulmonary: Fibrosis and persistent respiratory issues.
- Gastrointestinal: Colitis and digestive disturbances.
- Neurological: Vision, auditory, olfactory, and gustatory impairments; muscle and nerve damage; mitochondrial dysfunction leading to chronic fatigue.

- Cognitive: Brain fog, aphasia, anomia, working memory deficits, impaired multitasking ability.
- Autonomic Dysregulation: Dysfunction of the vagus nerve leading to respiratory asynchrony, dysautonomia, tachycardia, excessive sweating, and positional vertigo.
- Autoimmune Reactivation: Including conditions such as rheumatoid arthritis.

Recent transcriptomic studies by Professor Van Weyenbergh have confirmed that Long COVID patients continue to harbor viral antisense RNA (a marker of viral persistence) months after acute infection. Additionally, these patients exhibit mast cell activation (worsening allergies and asthma) and platelet activation, potentially responsible for microclot formation.

A fluctuating disease course may be linked to viral reactivation triggered by lipids, possibly explaining post-exertional malaise. This hypothesis is still under investigation.

Psychosocial and Functional Impact

The neurological and cognitive impairments associated with Long COVID profoundly impact daily life. Patients struggle with cognitive overload, diminished working memory, and severe fatigue. Simple activities, such as reading a page of a book or following a television series, become insurmountable challenges. Functional impairments include:

- Loss of multitasking ability
- Difficulty processing multiple conversations at once
- Spatial disorientation

Patients, particularly women (who are affected at a ratio of approximately 3:1 compared to men), experience profound grief over the loss of their former selves. Social, familial, and economic consequences are devastating. Many physicians misinterpret Long COVID as burnout or depression. However, labeling Long COVID as burnout shifts blame from inadequate workplace conditions onto the patient.

Abandoned by healthcare providers and misunderstood by their families, patients often turn to alternative medicine practitioners, who sometimes exploit their financial vulnerabilities. Insurers and medical assessors frequently deny the condition's legitimacy, further exacerbating the crisis.

Fortunately, support organizations recognize the plight of Long COVID patients, such as leressort.be in Wallonia and labraise.org in Brussels.

Symptoms

Symptoms fluctuate over time and affect multiple organ systems. (more than 60 related symptoms)
Common manifestations include:

- Fatigue
- Cognitive impairment ("brain fog")
- memory loss, word finding difficulties, dysphasia
- Dyspnea (shortness of breath)
- Post-exertional malaise
- Palpitations
- Chest pain

- Muscle or joint pain
- Sleep disturbances
- Depression or anxiety
- Persistent cough
- Dysautonomia symptoms (e.g., postural orthostatic tachycardia syndrome, or POTS)
- Loss of smell or taste

Pathophysiological Mechanisms

Although research is ongoing, key mechanisms include:

- Immune dysregulation and persistent inflammation
- Viral persistence
- Microvascular and endothelial dysfunction
- Coagulation disorders
- Autonomic nervous system disruption
- Post-viral syndromes resembling ME/CFS (likely due to mitochondrial impairment)

Impact on Patient-Physician Relationships

A profound gap exists between clinical symptoms and standard laboratory imaging results, severely straining the doctor-patient relationship. Physicians often struggle with symptoms that defy standard classifications, while patients feel invalidated and abandoned. This disconnect creates tension, mirroring a broader divide between clinicians and scientific researchers.

Scientific Interest and Medical Awareness

The scientific community, particularly researchers specializing in HIV, has shown great interest in Long COVID. The rapid proliferation of publications reflects the urgency of the issue. However, many physicians remain unaware of or fail to integrate emerging evidence into clinical practice. In Belgium, Long COVID remains largely unrecognized by many doctors, academic institutions, and policymakers.

Socioeconomic Repercussions

The impact on work capacity is severe, often leading to legal and financial difficulties. Many patients, mistakenly diagnosed with burnout or depression, receive inadequate support. The gender disparity (affecting two women for every man) is significant, and children and adolescents also experience Long COVID, though often diagnosed late.

Long COVID affects between 5% to 30% of individuals who have had acute COVID-19, posing major challenges to workforce sustainability and social welfare systems.

Prognosis

The duration and severity of Long COVID vary:

- One-third of patients recover within a few months.
- One-third remain symptomatic but adapt to daily life.

- One-third face prolonged disability, potentially lasting years.

All patients experience profound trauma—not just from the illness but from the distress of being dismissed by healthcare professionals.

Treatment and Management

Management is complex and must address biological, psychological, social, and economic factors. Essential aspects of care include:

- Recognition and validation of suffering
- Patient and family education
- Defense against medical dismissal and denial of benefits

While no definitive pharmacological treatment exists, ongoing clinical trials (e.g., antivirals, monoclonal antibodies) offer hope. Meanwhile, symptomatic treatments and vigilant monitoring for coagulation, metabolic, and autoimmune complications are necessary. Long COVID patients remain at high biological, psychological, and social risk.

Sources and Further Reading

This document is based on a substantial body of research. A comprehensive bibliographic repository, Long COVID Open Library, has been created on Zotero, covering nearly all ICPC (International Classification of Primary Care) categories.

Jamoulle, M. (2025). *Structuring knowledge on Long Covid: a bibliographic approach based on 3CGP (Core Content Classification in General Practice)*. <https://hdl.handle.net/2268/327758>

Supporting text and presentation

Jamoulle, M. (2023). *Exploring Long COVID: An Unexpected Research Journey in Family Medicine Leading to Translational Research*. Medical Research Archives, 11(11). <https://esmed.org/MRA/mra/article/view/4673>

Jamoulle, M. (22 September 2024). *Long COVID: The Invisible Disease* [Paper presentation]. WONCA International Classification Committee Annual Meeting, Newcastle upon Tyne, United Kingdom. <https://orbi.uliege.be/handle/2268/322246>

About the Author

Dr. Marc Jamoulle has practiced family medicine for 50 years. He holds a PhD in Medical Sciences and is a member of WONCA's International Classification Committee and scientific collaborator at CAMG-UCL and HEC Information system Uliege (Belgium) . Since July 2021, he has been monitoring a cohort of Long COVID patients. He collaborates with the COVID Human Genetic Effort network (<https://www.covidhge.com/>) and together with Prof van Weyenbergh (KUL) and Prof Charles Nicaise (Unamur) coordinates a Long COVID Research Network in Belgium.

