Long COVID: Epidemiology and Proposed Mechanisms

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New York State Department of Health
Commissioner’s Medical Grand Rounds

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Disclosures

• I have no financial interests to disclose
Post-viral Sequelae
**The Backstory: Long COVID causes fatigue, pain. Here’s what long-haulers want you to know.**

Nicole Carroll  USA TODAY
Published 5:01 a.m. ET Sep. 17, 2021

**The road to addressing Long Covid**

By Ed Yong

**Long COVID and kids: scientists race to find answers**

Children get Long COVID too, but researchers are still working to determine how frequently and how severely.

**‘This Is Really Scary’: Kids Struggle With Long Covid**

Lingering physical, mental and neurological symptoms are affecting children as well as adults, including many who had mild reactions to the initial coronavirus infection.

**A Tsunami of Disability Is Coming as a Result of ‘Long COVID’**

We need to plan for a future where millions of survivors are chronically ill.
Post-viral Sequelae

• EBV
  • 23% of college students met criteria for ME/CFS at 6 months.¹

• Post-Ebola Syndrome
  • At year 1: 48% headache, 18% fatigue, 23% muscle pain, 29% memory loss, 48% joint pain.²

• Chikungunya: “chronic chikungunya arthritis”
  • >40% with polyarthralgia lasting >3 months³

• Zika
  • Congenital abnormalities/microcephaly⁴

What is Long COVID?

• Consensus definition is still evolving:
  • “Long COVID”
  • “Long-haulers”

• Convalescent periods
  • >4 weeks: “post-acute COVID-19” or “post-acute sequelae of COVID-19” (PASC) or “post-COVID Conditions”
    • 4-12 weeks: “ongoing symptomatic COVID-19”
    • >12 weeks: “post-COVID syndrome”

A clinical case definition of post COVID-19 condition by a Delphi consensus

6 October 2021

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others (see Table 3 and Annex 2) which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children.
Long COVID Phenotypes

“Expected” post-viral sequelae
- Post-intensive Care Syndrome (PICS)
- Pulmonary fibrosis
- Cardiomyopathy
- Alopecia
- Anxiety, depression, PTSD

“Unexpected” post-viral sequelae
- Cognitive dysfunction
- Brain fog
- ME/CFS
- Post-exertional malaise
- Dysautonomia
- POTS
- Gustatory/olfactory
- Gastrointestinal
- Thromboembolism


Maxime Taquet, Quentin Dercon, Sierra Luciano, John R. Geddes, Masud Husein, Paul J. Harrison

Published: September 28, 2021 • https://doi.org/10.1371/journal.pmed.1003773

- EHR review of 58 HCOs and >270,000 survivors across the US
- 37% reported at least one symptom at 3-6 months
• Risk Factors
  • Gender
    • females more likely to report headache, GI, anxiety/depression
  • Age (range: incidence)
    • Age 10-21: 46%
    • Age 22-44: 55%
    • Age 45-64: 59%
    • Age >65: 61%
  • Acute severity (category: incidence)
    • Outpatient: 55%
    • Inpatient: 64%
    • ICU: 73%
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    • ICU: 73%
Higher incidence with COVID-19 than influenza for all symptoms (HR 1.44-2.04, p<0.001)
• N=1,276 survivors discharged from Jin Yan-tan Hospital in Wuhan, China
• 49% reported at least 1 symptom
  • Fatigue 20%, sleep difficulty 17%, palpitations 9%, joint pain 12%, 26% anxiety or depression
• Women more likely to report:
  • Fatigue or muscle weakness (OR 1.43, CI 1.04-1.96)
  • Anxiety or depression (OR 2.00, CI 1.48-2.69)
  • Diffusion impairment (OR 2.97, CI 1.50-5.88)
• Older age groups more likely to report/have:
  • Anxiety or depression 18% higher (OR 1.18, CI 1.05-1.32)
  • Diffusion impairment 30% higher (OR 1.30, CI 1.01-1.68)
UK Office for National Statistics:

- Estimated >970,000 (1.7%) of population with self-reported long-COVID symptoms
  - 37% with COVID <1 year prior
  - 19% report severe impact on day-to-day activities
- Risk factors: female gender, age 35-69, underserved areas, healthcare or social care employment

Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 7 October 2021

Multinational survey of long-COVID participants conducted by advocacy groups (n=3,762)
- 86% experienced relapses
- 87% with fatigue
- 45% with reduced ability to work
Initial 1,190 patients hospitalized with COVID-19 at NYP/CUIMC during the surge in March and April 2020

Persistent symptoms reported at 6-months
- 26% cardiac and pulmonary symptoms
- 24% neuropsychiatric symptoms
- 21% gastrointestinal symptoms

Patients with more severe COVID at the time of hospitalization were more likely to have reduced mobility, reduced independence, and need for dialysis
CUIMC COVID-19 Persistence ID Cohort (C-PIC)

• Collaboration between CUIMC ID Division and the Aaron Diamond AIDS Research Center

• Aims:
  • Characterize phenotypes of Long COVID
  • Evaluate the host-immune response and viral persistence

• 11 study visits over 2 years

• Study measures
  • Survey data
    • Baseline survey: demographics, acute illness
    • Symptom survey: broad organ system-based questions
    • Mental health surveys: PHQ9, GAD7, PCL-C, ISS
  • Biorepository: PBMC, plasma, saliva, stool, semen

• Current Enrollment: >300 participants
## Table 1. Organ System

<table>
<thead>
<tr>
<th>Sequelae phenotypes reported at study visits conducted within weekly ranges post-symptom onset</th>
<th>≤6 weeks (N=196)</th>
<th>7-18 weeks (N=135)</th>
<th>19-30 weeks (N=116)</th>
<th>31-42 weeks (N=58)</th>
<th>43-54 weeks (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic PASC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>31(58%)</td>
<td>37(27%)</td>
<td>38(33%)</td>
<td>22(39%)</td>
<td>17(41%)</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>10(5%)</td>
<td>16(12%)</td>
<td>17(15%)</td>
<td>7(12%)</td>
<td>13(31%)</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>74(38%)</td>
<td>52(39%)</td>
<td>50(43%)</td>
<td>24(41%)</td>
<td>19(45%)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>63(32%)</td>
<td>49(36%)</td>
<td>47(41%)</td>
<td>27(47%)</td>
<td>18(43%)</td>
</tr>
<tr>
<td>Any symptom</td>
<td>102(52%)</td>
<td>72(53%)</td>
<td>68(59%)</td>
<td>36(62%)</td>
<td>25(60%)</td>
</tr>
<tr>
<td>Non-Neurologic PASC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>7(37%)</td>
<td>50(37%)</td>
<td>43(37%)</td>
<td>19(33%)</td>
<td>13(31%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>90(46%)</td>
<td>50(37%)</td>
<td>37(32%)</td>
<td>16(28%)</td>
<td>18(43%)</td>
</tr>
<tr>
<td>GI</td>
<td>64(33%)</td>
<td>40(30%)</td>
<td>24(21%)</td>
<td>13(22%)</td>
<td>15(36%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>63(32%)</td>
<td>5(40%)</td>
<td>37(32%)</td>
<td>18(31%)</td>
<td>16(38%)</td>
</tr>
</tbody>
</table>
Short Communication

Anxiety, depression, insomnia, and trauma-related symptoms following COVID-19 infection at long-term follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6-12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9</td>
<td>8/52 (15%)</td>
<td>8/52 (15%)</td>
</tr>
<tr>
<td>GAD-7</td>
<td>2/51 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>ISS</td>
<td>13/52 (25%)</td>
<td>17/52 (33%)</td>
</tr>
<tr>
<td>PCL-C</td>
<td>6/50 (12%)</td>
<td>11/50 (22%)</td>
</tr>
</tbody>
</table>
Proposed Long COVID Mechanisms

- Autoimmune
- Immune Dysregulation
- Organ Damage
- Viral Persistence

Host
Viral
Proposed Long COVID Mechanisms

Autoimmune

Host

Immune Dysregulation

Organ Damage

Viral Persistence

Viral
Autoantibodies in Acute COVID-19

• Acute autoantibodies
  • Anti-SSA/Ro, ANA\textsuperscript{1}
  • Anti-type 1 interferon\textsuperscript{2}
  • Autoantibodies against immunomodulatory proteins (cytokines, chemokines, complement, cell-surface proteins)\textsuperscript{3}

\textsuperscript{2}Bastard, et al. Science. October 2020. PMCID 7857397
Long COVID: Autoantibodies

• **G-protein coupled receptor (GPCR) autoantibodies**
  • **ME/CFS:**
    • Elevations in beta adrenergic and muscarinic acetylcholine autoantibodies in chronic fatigue syndrome\(^1\)
  • **COVID-19:**
    • All 31 with PASC enrolled had 2 to 7 GPCR-autoantibodies detected\(^2\)

• **Anti-ACE2 autoantibody\(^3\)**
  • 26/32 (81%) of convalescent inpatients
  • 14/15 (93%) of acute inpatients
  • 1/20 (5%) of outpatients
  • 0/13 controls

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\(^1\)Loebel, et al. Brain Behav Immun. 2016. PMID 26399744
\(^3\)Arthur et al. PLOS One. Sept, 2021. DOI: 10.1371/journal.pone.0257016
Proposed Long COVID Mechanisms

- Autoimmune
- Immune Dysregulation
- Organ Damage
- Viral Persistence

Host

Viral
PASC: General Immune Dysregulation

• Compared with healthy controls, Long COVID patients had¹:
  • Monocyte activation: CD14, CD16, and CCR5
  • Decreased PD-1 expressing T cells: CD4 and CD8
  • Cytokine elevation: CCL5/RANTES, IL-2, IL-4, CCL3, IL-6, IL-10, IFN-gamma, VEGF
  • Cytokine decrease: GM-CSF, CCL4

• Neurologic Long COVID²
  • Cytokine elevation: IL-4 and IL-6
  • Neuronal dysfunction: amyloid beta, neurofilament light, neurogranin, p-T181-tau

Proposed Long COVID Mechanisms

Autoimmune

Immune Dysregulation

Organ Damage

Viral Persistence

Viral
Proposed Long COVID Mechanisms

Autoimmune

Immune Dysregulation

Host

Organ Damage

Viral Persistence

Viral
NYP-CUIMC Care

- Neurology/ID/Primary Care
  - ME/CFS\(^1\):
    - Pacing: identify mental and physical activity limits
    - Pharmacologic therapy
    - Diet modification
  - Insomnia:
    - Sleep optimization
    - Pharmacologic therapy

- Neurology/cardiology
  - Dysautonomia:
    - Compression stalkings, hydration, salt intake
    - Pharmacologic therapy

- Rehabilitation services
  - Pulmonary
  - Cardiovascular
  - Physical Medicine and Rehabilitation

- Mental health services

\(^1\)https://www.cdc.gov/me-cfs/treatment/index.html
Long COVID & Stigma

Long Covid Doubles Burden of Mystery Illness Few Doctors Treat
Oct. 14, 2021, 5:36 AM

- No lab test for chronic fatigue syndrome
- Condition is often misdiagnosed, doctors say

Lydia Wheeler  Senior Reporter

SONYA CHOWDHURY

Long Covid and ME patients deserve a better approach
Sonya Chowdhury  Monday October 18, 2021, 9.00pm BST, The Times

Don’t give Covid-19 long-haulers the silent treatment
By E. Wesley Ely  Oct. 22, 2021

Needed for long Covid: a less authoritarian approach to understanding, treatment
By Diane O’Leary  April 22, 2021

THE WALL STREET JOURNAL.

World
Coronavirus Stigma Lingers Long After Disease Fades
Some people have recovered from Covid-19 only to find friends and colleagues shunning them, which can make it harder to fight outbreaks
Recent PASC updates

Guidance on “Long COVID” as a Disability Under the ADA, Section 504, and Section 1557

A clinical case definition of post COVID-19 condition by a Delphi consensus

6 October 2021

ICD-10-CM Official Guidelines for Coding and Reporting
FY 2022
(October 1, 2021 - September 30, 2022)

(m) Post COVID-19 Condition
For sequelae of COVID-19, or associated symptoms or conditions that develop following a previous COVID-19 infection, assign a code(s) for the specific symptom(s) or condition(s) related to the previous COVID-19 infection, if known, and code U09.9, Post COVID-19 condition, unspecified.

Code U09.9 should not be assigned for manifestations of an active (current) COVID-19 infection.
PASC Resources

- Clinical resources
  - AMA: https://www.ama-assn.org/topics/covid-19-long-haulers
  - UpToDate: COVID-19: Evaluation and management of adults following acute viral illness

- Long-COVID advocacy groups
  - Body Politic COVID-19 support group
  - Survivor Corps
  - Patient-led Research for COVID-19
  - Long COVID Alliance
  - Long COVID Support Group
  - Long Haul COVID Fighters
Thank you

**CUMC COVID-19 ID Persistence Cohort**
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Nicola Medrano
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Michelle Chang
Anthony Bowen
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Lara Karaaslan

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Medini Annavajhala
Heekuk Park
Alexander Chong

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