Post-COVID conditions: State of knowledge and the CDC response

CA Infectious Disease Society

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cdc.gov/coronavirus
The views expressed in this presentation are those of the author and do not necessarily represent the opinion of the Centers for Disease Control and Prevention
Post-COVID conditions may **impact millions of people** globally.

~124 million SARS-CoV-2 infections globally

~6-25 million persons impacted by post-COVID conditions

About as many as the population of Los Angeles County

5-20%*

*Estimate of persons infected with SARS-CoV-2 with symptoms lasting >4 weeks. WHO, Policy Brief 39, 2021
There is still a lot we do not know about the human and societal impact of post-COVID conditions.
Objectives

▪ Introduce scientific nomenclature and definitions related to post-COVID conditions

▪ Describe the epidemiology and clinical manifestations of post-COVID conditions

▪ Describe ongoing efforts at CDC to better characterize and respond to post-COVID conditions
Defining post-COVID conditions
The terminology used to describe the longer-term health effects of SARS-CoV-2 infection has not been completely agreed upon or standardized.

- Long COVID
- Long-haul COVID
- Long haulers
- Late sequelae of COVID
- Post-acute COVID syndrome
- Ongoing symptomatic COVID (4-12 weeks)
- Post-COVID syndrome (>12 weeks)
- Post-acute sequelae of SARS-CoV-2 infection (PASC)
- Post-COVID conditions
**Post-COVID condition** is the term used for health effects present ≥4 weeks after SARS-CoV-2 infection.

<table>
<thead>
<tr>
<th>Symptom onset</th>
<th>Week 2</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute infection (COVID-19)</strong></td>
<td><strong>Postacute hyperinflammatory illness</strong></td>
<td><strong>Late sequelae</strong></td>
</tr>
<tr>
<td>Characterization</td>
<td>Dysregulated host response</td>
<td>Pathophysiological pathways proposed but unproven</td>
</tr>
<tr>
<td>Active viral replication and initial host response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Gastrointestinal, cardiovascular, dermatologic/mucocutaneous, respiratory, neurological, musculoskeletal symptoms</td>
<td>Cardiovascular, pulmonary, neurological, psychological manifestations</td>
</tr>
<tr>
<td>Fever, cough, dyspnea, myalgia, headache, sore throat, diarrhea, nausea, vomiting, anosmia, dysgeusia, abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>Viral test (+/-)</td>
<td>Viral test and antibody profile uncharacterized</td>
</tr>
<tr>
<td>Viral test (+)</td>
<td>Antibody (+) after 2 wk</td>
<td></td>
</tr>
<tr>
<td>Antibody (+) after 2 wk</td>
<td></td>
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</tr>
</tbody>
</table>
Post-COVID conditions may overlap with complications not related to SARS-CoV-2 infection making them hard to define.

Post-COVID conditions*

Long COVID

Multiorgan effects

Hospitalization complications

PICS

*Size of circles not proportional to burden
Epidemiology and clinical manifestations of post-COVID conditions
Post-viral syndromes are not unique to SARS-CoV-2 infection.

3 months later there was little improvement. “I am so weak that if I read or write for half an hour I become so tired and faint that I have to lie down,”...

The neurological conditions observed after the Russian influenza were given many names: neuralgia, neurasthenia, neuritis, nerve exhaustion, “grippe catalepsy”, “post-grippal numbness”, psychoses, “prostration”, “inertia”, anxiety, and paranoia.
Post-viral syndromes are not unique to SARS-CoV-2 infection.

- Among 233 SARS survivors 41 months after infection\(^1\)
  - 40% had active psychiatric illness
  - 40% reported a chronic fatigue problem
- Among 52 MERS survivors 18 months after infection\(^2\)
  - 33% reported clinically significant fatigue
- Among 253 patients with Epstein-Barr virus, Q fever, or River Ross virus followed at 6 months\(^3\)
  - 12% had disabling fatigue, musculoskeletal pain, neurocognitive difficulties, and mood disturbance
- A metaanalysis of patients treated for Lyme disease\(^4\)
  - Symptoms were present ≥1 year in 0.5 to 13.1% of patients

Post-COVID symptoms
Three quarters of patients hospitalized with COVID-19 had at least one ongoing symptom 6 months after their acute illness.

Symptoms among 1,733 patients after hospitalization for COVID-19, China

- Any symptoms: 76%
- Fatigue or muscle weakness: 63%
- Dyspnea: 26%
- Sleeping difficulties: 26%
- Anxiety or depression: 23%
- Hair loss: 22%
- Smell disorder: 11%
- Palpitations: 9%
- Joint pain: 9%

Huang et al., Lancet. 2021
Prolonged symptoms are common among patients with mild COVID-19 not requiring hospitalization.

- Survey of patients in post-COVID 19 clinic in France\(^1\) and surveys in the Faroe islands\(^2\) and Switzerland\(^3\)
  - 35-54% of patients with mild acute COVID-19 had **persistent symptoms after 2-4 months**
  - 50-76% of patients **reported new symptoms** not present in their acute COVID-19 illness or **symptoms that resolved and reappeared**\(^1\)
  - 9% reported prolonged symptoms as **severe**\(^2\)

More than one quarter of patients developed new neurological symptoms after acute COVID-19.

COVID-19 symptoms among 70 non-hospitalized patients, France

- Fatigue or muscle weakness
- Sensory disturbances
- Chest pressure or pain
- Dyspnea
- Palpitations/tachycardia
- Headaches
- Cognitive neurological disorders
- Problems with taste or smell
- Other neurological signs

Salmon-Ceron et al., J Infect. 2020
1 in 5 persons may have symptoms for ≥5 weeks and 1 in 10 may have symptoms for ≥12 weeks.

<table>
<thead>
<tr>
<th>Symptomatic Period post infection</th>
<th>Prevalence</th>
<th>Lower 95% confidence interval limit</th>
<th>Upper 95% confidence interval limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 weeks post-infection</td>
<td>21.0</td>
<td>17.8</td>
<td>24.8</td>
</tr>
<tr>
<td>12 weeks post-infection</td>
<td>13.7</td>
<td>10.8</td>
<td>17.4</td>
</tr>
<tr>
<td>Median duration of symptoms after infection (days)</td>
<td>35.5</td>
<td>20.5</td>
<td>76.5</td>
</tr>
</tbody>
</table>

Source: ONS Coronavirus (COVID-19) Infection Survey
Post-COVID symptoms continue to be described.
Post-COVID multiorgan effects
Objective clinical findings in multiple organ systems have been reported among patients with post-COVID conditions.
One in five patients not requiring supplemental oxygen during hospitalization had decreased lung function after 6 months.

Pulmonary function and 6-minute walk test distance results among COVID-19 hospitalized patients, China

6 minute walk test distance <LLN
- Not requiring supplemental oxygen: 23%
- Requiring supplemental oxygen: 24%
- Requiring HFNC, NIV, or IMV: 29%

DLCO <80% predicted
- Not requiring supplemental oxygen: 22%
- Requiring supplemental oxygen: 29%
- Requiring HFNC, NIV, or IMV: 56%

LLN = lower limit of normal; DLCO = diffusion capacity for carbon monoxide

Huang et al., Lancet. 2021
Young adults with mild/moderate COVID-19 had lower cognitive scores than healthy controls.

*\( p < 0.05 \)  **\( p < 0.01 \)  

A: N = 10  N = 18

B: Healthy  COVID-19

E: Number of patients

Woo et al., Brain Communications. 2020
COVID-19 was associated with increased incidence of a first psychiatric diagnosis compared to influenza and other respiratory viruses.

Taquet et al., Lancet Psychiatry. 2021

HR = 2.1 (1.8-2.5)

HR = 1.8 (1.4-2.3)

HR = 2.3 (1.9-2.7)
6 months after acute COVID-19, 33% of adults had received any neuropsychiatric diagnosis and in 12% diagnoses were new.

Neuropsychiatric diagnoses among 236,379 patients diagnosed with COVID-19, U.S.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any outcome</td>
<td>33%</td>
</tr>
<tr>
<td>Mood, anxiety, or psychotic disorder</td>
<td>10%</td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>5%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2%</td>
</tr>
<tr>
<td>Nerve, nerve root, or plexus disorders</td>
<td>1%</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1%</td>
</tr>
<tr>
<td>Dementia</td>
<td>1%</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>1%</td>
</tr>
<tr>
<td>Myoneural junction or muscle disease</td>
<td>1%</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>1%</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>1%</td>
</tr>
<tr>
<td>Guillain-Barre syndrome</td>
<td>1%</td>
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</tbody>
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6 months after acute COVID-19, 33% of adults had received any neuropsychiatric diagnosis and in 12% diagnoses were new.

Neuropsychiatric diagnoses among 236,379 patients diagnosed with COVID-19, U.S.

- Any outcome
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- Encephalitis
- Guillain-Barre syndrome

Total and new diagnoses by disease severity:
- Non-hospitalized: 32% and 12%
- Hospitalized: 39% and 15%
- Intensive care unit: 46% and 26%

Taquet et al., Lancet Psychiatry. 2021
COVID-19 was associated with increased incidence of a neurologic diagnosis compared to influenza and other respiratory viruses.

HR = 1.3 (1.1-1.4)

HR = 1.5 (1.4-1.6)

HR = hazard ratio

Taquet et al., Lancet Psychiatry. 2021
COVID-19 was associated with **increased incidence of a neurologic diagnosis** compared to influenza and other respiratory viruses.

HR = 4.5 (3.7-5.6)  
HR = 1.3 (1.2-1.4)
SARS-CoV-2 infection may be associated with new or worsening of chronic conditions.

- Among patients hospitalized at 6-month follow-up\(^1\):
  - 35% with acute kidney injury had decreased eGFR
  - 13% without kidney injury had decreased eGFR
SARS-CoV-2 infection may be associated with new or worsening of chronic conditions.

- Among patients hospitalized at 6-month follow-up\(^1\):
  - 35% with acute kidney injury had decreased eGFR
  - 13% without kidney injury had decreased eGFR
- Among patients at 2-month follow-up\(^2\):
  - ↓ left and right ventricular ejection fraction compared to healthy controls
  - 78% had abnormal cardiac MRI findings and 60% had myocardial inflammation

SARS-CoV-2 infection may be associated with new or worsening of chronic conditions.

- Among patients hospitalized at 6-month follow-up\(^1\):
  - 35% with acute kidney injury had decreased eGFR
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- Among patients at 2-month follow-up\(^2\):
  - left and right ventricular ejection fraction compared to healthy controls
  - 78% had abnormal cardiac MRI findings and 60% had myocardial inflammation

- Among patients hospitalized at 6-month follow-up\(^1,3\):
  - 58 were diagnosed with new-onset diabetes mellitus
  - Reports of diabetic ketoacidosis and subacute thyroiditis

Retrospective cohort study of post-COVID syndrome among adults hospitalized with COVID-19

- 47,780 adults hospitalized with COVID-19 between January and September 2021
  - 4,745 (10%) admitted to intensive care unit
  - Mean follow-up 140 days (standard deviation 50 days)
- Matched 1:1 with controls from previous 10 years
  - Age, sex, ethnicity
  - Geography, deprivation index
  - Smoking status, body mass index
  - Pre-existing conditions
- Outcomes: death, readmission, respiratory disease, MACE, diabetes, chronic kidney disease, chronic liver disease

MACE = major adverse cardiovascular event

Ayoubkhani et al. BMJ. 2021.
Adverse events were more common among hospitalized patients with COVID-19 compared to controls.

Rates of adverse events among critical care COVID-19 patients compared with controls patients, England: January–September 2020

MACE = major adverse cardiovascular event; RR = rate ratio

Ayoubkhani et al. BMJ. 2021.
New-onset adverse events were more common among hospitalized patients with COVID-19 compared to controls.

Rates of new-onset adverse events among hospitalized COVID-19 patients compared with controls patients, England: January–September 2020

MACE = major adverse cardiovascular event; RR = rate ratio

Ayoubkhani et al. BMJ. 2021.
Key points

▪ New or persistent symptoms (lasting >4-6 months) may occur among patients with COVID-19 regardless of acute illness severity or age.

▪ In addition to respiratory symptoms, patients may present with fatigue, sleeping difficulties, depression, anxiety, and neurological dysfunction.

▪ Objective clinical findings in multiple organ systems have been reported among patients with COVID including the development of new chronic conditions.

▪ There is still a lot we do not understand, and empathy toward patients experiencing longer term COVID-19 health effects is fundamental.
Many questions remain about post-COVID conditions

- Previous studies are limited by:
  - Absence of general population controls to assess differences in symptom prevalence and incidence
  - Selection of optimal controls to assess differences in incidence of post-COVID conditions
  - Limited assessment of pre-COVID medical conditions
  - Convenience sampling at post-COVID clinics or social media/internet COVID-19 support groups
  - Dependent on clinician use of ICD-10 codes
  - Limited assessment of return to work and quality of life assessments
CDC efforts to better characterize and respond to post-COVID conditions
Overview of CDC's work to understand Post-COVID conditions

CDC has invested $46 million to understand the long-term health effects of COVID-19

Examples of CDC’s current work include:

1. Partnering with clinicians to understand:
   • Clinical needs for patients after acute infection
   • Type and frequency of late symptoms
   • Characteristics of persons most likely to experience late symptoms

2. Analyzing electronic health data including medical records, laboratory data and administrative claims data
   • To rapidly describe health outcomes several months after COVID-19 diagnosis

3. Establishing studies with external partners
   • To understand the duration of COVID-19 illness, and risks for complications.
Priority Research Questions

- What are the clinical symptoms or signs associated with prolonged illness or new persistent symptoms following SARS-CoV-2 infection?
- In patients with persistent symptoms and without other medical explanations, do the symptom profiles match ME/CFS symptom profiles?
- What factors increase the risk of long-term symptoms?
- What is the prevalence/incidence of long-term symptoms in the population?
- What are the mechanisms of viral infection leading to symptoms of potential long term organ damage?
Communication and Outreach

Late Sequelae of COVID-19

The identification of the novel coronavirus SARS-CoV-2 in December 2019 has led to a growing and continually evolving body of knowledge about the virus and the disease it causes, COVID-19.

Long-Term Effects of COVID-19

CDC is actively working to learn more about the whole range of short- and long-term health effects associated with COVID-19. As the pandemic unfolds, we are learning that many organs besides the lungs are affected by COVID-19 and there are many ways the infection can affect someone’s health.

While most persons with COVID-19 recover and return to normal health, some patients can have symptoms that can last for weeks or even months after recovery from acute illness. Even people who are not hospitalized and who have mild illness can experience persistent or late symptoms. Multiyear studies are underway to further investigate. CDC continues to work to identify how common these symptoms are, who is most likely to get them, and whether these symptoms eventually resolve.

Treating Long COVID: Clinician Experience with Post-Acute COVID-19 Care

CDC/IDSA COVID-19 Clinician Call - Long COVID (with extended time for a Vaccine Q&A)

January 16, 2021

1/16/2021
Short term approach: characterizing Post-COVID conditions

• **Medical record abstraction**
  • Goal: obtain detailed clinical data of patients cared for at post-COVID clinics to better characterize post COVID symptoms, identify risk factors, and describe the management of patients cared for at post-COVID clinic
  • Piloting at one site → expand to 3 post-COVID clinics

• **Multi-state post-COVID symptom survey**
  • Goal: obtain estimates of symptom characteristics, frequency, and impact on physical and mental health
Population-level measures of post-COVID conditions

- Provide estimates of extent of long-term impact
  - Incidence and prevalence of post COVID conditions
  - ME/CFS diagnosis and association with COVID-19 illness

- Understand the distribution in the population
  - Overall
  - By demographic characteristics including age, sex, race/ethnicity
  - By geographic differences
  - By socio-economic differences
  - By risk factors
Methods to measure post-COVID conditions at the population-level

Use of federal health surveys to measure self-report of COVID-19 illness and ME/CFS

- National Health Interview Survey
  - Nationally representative of the noninstitutionalized U.S. population
- Behavioral Risk Factor Surveillance System
  - Provides state-based estimates

Sentinel surveillance

- Establish detailed surveillance at specific sites throughout the country

Electronic health records

- Analysis of diagnosis and health care utilization
Long term approach: cohort studies

- Enroll cohorts of patients with and without SARS-CoV-2 infection
- Assess baseline health of the participants
- Monitor participants over time and for multiple years
- Assess risk factors and outcomes of interest including:
  - Symptom profiles
  - Long-term immunologic response
  - Cardiovascular, respiratory, renal, neurological outcomes
  - Mental and physical functioning
Post COVID Conditions Unit can be contacted at eocevent513@cdc.gov
Resources

▪ CDC webpages on post COVID conditions:

▪ NIH Workshop on Post-Acute Sequelae of COVID-19
  – Day 1: https://videocast.nih.gov/watch=38878
  – Day 2: https://videocast.nih.gov/watch=38879

▪ CDC webpage for Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS): https://www.cdc.gov/me-cfs/index.html
References

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