Long COVID Syndrome

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CDC long COVID definition

- Although most people with COVID-19 get better within weeks of illness, some people experience post-COVID conditions.

- **Post-COVID conditions** are a wide range of new, returning, or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes COVID-19.
Definition

- Even people who did not have COVID-19 symptoms in the days or weeks after they were infected can have post-COVID conditions.
- These conditions can present as different types and combinations of health problems for different lengths of time.
- These post-COVID conditions may also be known as long COVID, long-haul COVID, post-acute COVID-19, long-term effects of COVID, or chronic COVID.
Types of Post-COVID Conditions

- New or Ongoing Symptoms
- Multiorgan Effects of COVID-19
- Effects of COVID-19 Illness or Hospitalization
New or Ongoing Symptoms

- New or ongoing symptoms that can last weeks or months after first being infected with the virus that causes COVID-19.

- These symptoms can happen to anyone who has had COVID-19, even if the illness was mild, or if they had no initial symptoms.
- Difficulty breathing or shortness of breath
- Tiredness or fatigue
- Symptoms that get worse after physical or mental activities (also known as post-exertional malaise)
- Difficulty thinking or concentrating (sometimes referred to as “brain fog”)
- Cough
- Chest or stomach pain
- Headache
- Fast-beating or pounding heart (also known as heart palpitations)
- Joint or muscle pain
- Pins-and-needles feeling
- Diarrhea
- Sleep problems
- Fever
- Dizziness on standing (lightheadedness)
- Rash
- Mood changes
- Change in smell or taste
- Changes in menstrual period cycles
Multiorgan Effects of COVID-19

- Multiorgan effects or autoimmune conditions can affect many, if not all, body systems, including heart, lung, kidney, skin, and brain functions.

- Multisystem inflammatory syndrome (MIS)
Effects of COVID-19 Illness or Hospitalization

- Hospitalizations and severe illnesses for lung-related diseases, including COVID-19, can cause health effects like severe weakness and exhaustion during the recovery period.
- post-intensive care syndrome (PICS)
- post-traumatic stress disorder (PTSD)
- It can be difficult to know whether they are caused by the effects of hospitalization, the long-term effects of the virus, or a combination of both.
WHO definition

- **WHO** defines long Covid in the following way:

  “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 and that **last for at least 2 months** and cannot be explained by an alternative diagnosis.”
A wide range of long-term symptoms are reported, among others:

- Fatigue
- Headache
- Chest pain
- Muscle pain
- Pins and needles
- Forgetfulness
- Depression
- Loss of smell
- Persistent cough
- Shortness of breath
- Palpitations
- Diarrhoea
- Abdominal pain
- Rash
- Recurrent fever
More serious long-term complications appear to be less common but have also been reported, especially in patients with severe COVID-19 who were hospitalized. These have been noted to affect different organ systems in the body and include:

- Cardiovascular: inflammation of the heart muscle
- Respiratory: lung function abnormalities
- Dermatologic: rash
- Neurologic: loss of taste & smell, sleep disturbance
- Psychiatric: depression, anxiety, changes in mood
Classification

(1) **Residual symptoms** that persist after recovery from acute infection;
(2) **Organ dysfunction** that persists after initial recovery;
(3) **New** symptoms or syndromes that develop after initial asymptomatic or mild infection
PERSISTENT SYMPTOMS IN SEVERE COVID-19

- All symptoms are more common in ICU admitted patients than ward:
  - New fatigue
  - New or worsened breathlessness
  - PTSD
  - New or worsened concentration problems
  - Sleep disorders
PERSISTENT SYMPTOMS IN MILD COVID-19

- Cough
- Fatigue
- Dyspnea
- anosmia, agnosia, sleep disorders

35% of patients reported **not having returned to their baseline state of health**: risk factors
underlying chronic medical conditions

Obesity
underlying psychiatric condition
• Fatigue 55%
• Difficulty breathing 42%
• Memory loss 34%
• Sleep disorder 32%
• Attention disorder 27%
• Significant hair loss 20%
• Cough 17%
• Loss of smell 13%
• Chest pain 11%
• Loss of taste 11%
PROLONGED ORGAN DYSFUNCTION

- Pulmonary Sequelae
- Cardiac Sequelae
- Thromboembolic Sequelae
- Neurologic Sequelae
- Renal Sequelae
- Potential Rehabilitation Requirements
Cardiac Involvement in COVID-19

Direct viral infection leading to myocardial injury

Potential for cardiac fibrosis and decrease cardiac function in the long term
COVID-19 related risk factors for venous thromboembolism

- ICU admission
- Cytokine storm
- Inflammation
- Lung injury
- Comorbidities
- Cancer
- Obesity
- Age
- Male sex
Body systems and organs that can be affected:

- **Heart:** Damage to heart muscle, heart failure
- **Lungs**
  Damage to lung tissue and restrictive lung failure
- **Brain and the nervous system**
  - Loss of sense of smell (anosmia)
  - Consequences of thrombo-embolic events such as pulmonary embolism, heart attack, stroke
  - Cognitive impairment (e.g. memory and concentration)
- **Mental health**
  - Anxiety, depression, post-traumatic stress disorder and sleep disturbance
- **Musculoskeletal and others**
  - Pain in joint and muscles
  - Fatigue
Cross-talk among injured organs might explain post-acute COVID syndrome

Microbial metabolites
Cytokines
Other circulating factors
Immune system dysfunction
NICE, the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP) have published a joint guideline covering diagnosis, management and monitoring of long COVID
The guideline clinically defines three phases following COVID-19 infection, as follows:

- **Acute COVID-19**: Signs and symptoms of COVID-19 for up to 4 weeks
- **Ongoing symptomatic COVID-19**: Signs and symptoms occurring from 4 weeks up to 12 weeks
- **Post-COVID-19 syndrome**: Signs and symptoms that develop during or after infection, continue for more than 12 weeks and are not explained by an alternative diagnosis.
Acute infection (acute COVID-19)
- Active viral replication and initial host response

On going symptomatic COVID
- Postacute hyperinflammatory illness
- Immune-mediated response
- Persistent viral replication
- Organ dysfunction

Post-COVID-19 syndromes
- The pathophysiology is not known, nor have the viral or immunological responses been defined in this phase

PROLONGED COVID-19
- Low vision - 17%
- Red eyes - 10%
- Vertigo - 6%
- Fatigue - 53%
- Muscle pain - 6%
- Lack of appetite - 8%
- Diarrhoea - 3%
- Skin lesions - 7%
- Joint pain - 27%
- Headache - 9%
- Rhinitis - 13%
- Loss of/changed sense of smell - 15%
- Sjögren's syndrome - 14%
- Loss of/changed sense of taste - 10%
- Sore throat - 7%
- Cough - 16%
- Chest pain - 22%
- Shortness of breath - 43%
POSTACUTE COVID-19-RELATED CLINICAL SYNDROMES

- multisytem inflammatory syndrome (MIS):
  Initially described in children and adolescents: MIS-C
- MIS-C is an inflammatory condition with overlap with Kawasaki Disease that most often occurs in the postinfectious period
- Then, a detailed report from the CDC described MIS occurring in adult patients: MIS-A
MIS-C

(1) age < 21 years with fever, laboratory findings of inflammation, and severe illness affecting multiple organ systems;

(2) no alternative diagnosis;

(3) evidence of SARS-CoV-2 infection as demonstrated by molecular, serological, or antigen testing (or exposure to a suspected or confirmed COVID-19 case within the 4 weeks before presentation)
● Fever, usually persistent (median duration four to six days) – 100 percent
● Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) – 60 to 100 percent
● Rash – 45 to 76 percent
● Conjunctivitis – 30 to 81 percent
● Mucous membrane involvement (red or swollen lips, strawberry tongue) – 27 to 76 percent
• Neurocognitive symptoms (headache, lethargy, confusion) – 29 to 58 percent
• Respiratory symptoms – 21 to 65 percent
• Sore throat – 10 to 16 percent
• Myalgia – 8 to 17 percent
• Swollen hands/feet – 9 to 16 percent
• Lymphadenopathy – 6 to 16 percent
Multisystem Inflammatory Syndrome in Children (MIS-C)
A Delayed Immune Response Related to COVID-19

Children, adolescents, or young adults who develop certain symptoms after having COVID-19 might have MIS-C. They should see a doctor if they had COVID-19, or have been in close contact with someone who had COVID-19, within the past 6 weeks and now have the following:

Ongoing Fever

PLUS more than one of the following:

- Stomach Pain
- Diarrhea
- Vomiting
- Skin Rash
- Blood Shot Eyes
- Dizziness or Lightheadedness
PATHOPHYSIOLOGY

- Preliminary studies suggest that patients with severe MIS-C have persistent immunoglobulin G (IgG) antibodies with enhanced ability to activate monocytes, persistent cytopenias (particularly T cell lymphopenia) and greater activation of CD8+ T cells that differ from findings in acute COVID-19 infection.
MIS-A

- Adults develop rare but severe COVID-related MIS syndrome

- The patients were not severely ill with COVID-19 but had **cardiovascular**, **gastrointestinal**, **dermatologic**, and **neurologic** signs and symptoms and elevated biomarkers of inflammation and abnormal blood clotting

- Markedly elevated laboratory markers of coagulopathy and inflammation and evidence of cardiac dysfunction are typical,
A patient aged $\geq 21$ years hospitalized for $\geq 24$ hours, or with an illness resulting in death, who meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness.
**Clinical Criteria**

- Subjective fever or documented fever ($\geq 38.0^\circ C$) for $\geq 24$ hours prior to hospitalization or within the first THREE days of hospitalization and
- At least THREE of the following clinical criteria occurring prior to hospitalization or within the first THREE days of hospitalization.
- At least ONE must be a primary clinical criterion.
• Primary clinical criteria
  • Severe cardiac illness Includes myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF<50%), 2nd/3rd degree A-V block, or ventricular tachycardia. (Note: cardiac arrest alone does not meet this criterion)
  • Rash AND non-purulent conjunctivitis

• Secondary clinical criteria
  • New-onset neurologic signs and symptoms Includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome)
  • Shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy)
  • Abdominal pain, vomiting, or diarrhea
  • Thrombocytopenia (platelet count <150,000/ microliter)
• Laboratory evidence
  The presence of laboratory evidence of inflammation AND SARS-CoV-2 infection.
  • Elevated levels of at least TWO of the following:
    C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin
  • A positive SARS-CoV-2 test for current or recent infection by RT-PCR, serology, or antigen detection
Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

LR Feldstein, S Li et al., for the Overcoming COVID-19 Investigators, and the CDC COVID-19 Response Team

- 186 patients in 26 states, median age 8.3 years
- 80% required ICU care, 20% required mechanical ventilation
- 71% with involvement of at least 4 organ systems
- 73% with no underlying conditions
POTENTIAL MECHANISMS OF long COVID

Multifactorial:

- Virus’s potential for direct neuro-invasion was thought to lead to persistent neuropsychiatric sequelae

- Virus-induced “cytokine storm” and dysregulated immune response
POTENTIAL MECHANISMS OF long COVID

• **Replication-competent** virus is rarely recovered beyond 20 days after symptom onset.
  Lingering virus continues to be present in immunologically privileged sites within the body, where it can be difficult for the immune system to eradicate.

• Severe **endothelial injury** along with diffuse thrombosis with microangiopathy.

• Post-ICU syndrome.
Pathogenesis of long COVID Syndrome

- The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor. Once these cells have been invaded, the virus can cause a multitude of damage ultimately leading to numerous persistent symptoms.
• Chronic fatigue following viral infection may be the result of miscommunication in the inflammatory response pathways
• however, a cross-sectional analytical study found no association between pro-inflammatory markers and long term fatigue in covid-19 patients with persisting fatigue.
• It is likely that a range of central, peripheral, and psychological factors play a role in the development of post-covid-19 fatigue
• An increased resistance to cerebrospinal fluid drainage through the cribriform plate as a result of olfactory neuron damage, may contribute to post-covid-19 fatigue.

• Hypometabolism in the frontal lobe and cerebellum has also been implicated in covid-19 patients with fatigue and is likely caused by systemic inflammation and cell mediated immune mechanisms, rather than direct viral neuro-invasion.
• Negative psychological and social factors associated with the covid-19 pandemic have also been linked to chronic fatigue

• Lastly, peripheral factors such as direct SARS-CoV-2 infection of skeletal muscle, resulting in damage, weakness, and inflammation to muscle fibers and neuromuscular junctions may contribute to fatigue
Chronic Fatigue Syndrome (CFS)

CFS triggering: superposition of humoral and cellular responses

- Chronic viral infection, lung inflammation, exposure to toxicants, etc.
- Acute viral, bacterial, parasite infection, microbiome dysregulation, etc.

Genetic differences & environmental changes

Dysregulation/polarization of the immune system & Low-Grade Inflammation
The role of the immune system is to monitor the proper functioning of tissues and organs and intervene/repair as required. In CFS, it is found constantly activated at low grade, while polarized in pro-inflammatory mode, thus causing muscular, cognitive and energy depletion disorders.

**Polarized Immune System**
In pro-inflammatory mode

**Low-Grade Inflammation**
Maintains the immune system activated: flu-like symptoms

**Muscles**
Weakness & muscle pain

**Brain**
Brain fog & memory loss

**Energy**
Energy depletion & exhaustion
Treating fatigue, cognitive, and neuropsychiatric symptoms

- Self-management and support are important in managing fatigue.
- Cognitive behavioral therapy (CBT) and graded exercise therapy (GET).
- Another management strategy for fatigue is pacing, whereby patients manage tasks and activities to avoid over-exertion and exacerbating fatigue.
- Concerns over the potential negative effects of GET, including postexertional malaise.
• Cognitive impairment in long covid, sometimes called “brain fog,” has been compared to “chemobrain.”
• The Mayo clinic recommendations suggest strategies to manage chemobrain including repeating exercises, tracking what influences deficits, and using stress relief and coping strategies.
• Furthermore, medications include in methylphenidate, donepezil, modafinil, and memantine may be considered
• Sleep disturbances may be managed by following relevant guidelines on insomnia, and a range of treatment strategies can be considered.

• Patients with mental health problems alongside or as a result of long covid can be managed following the relevant guidelines: depression, anxiety, PTSD, obsessive-compulsive disorder, and other mental health problems.
Thank You!