OUTPOST

APPRISE
AUSTRALIAN PARTNERSHIP FOR PREPAREDNESS RESEARCH ON INFECTIOUS DISEASE EMERGENCIES

A research definition for Long COVID

Background

Long COVID is characterised by a wide range of post-acute and long-term symptoms which are difficult to categorise in a single definition. Long COVID is a post-viral syndrome (PVS). Similar post-viral syndromes can also occur after other infections such as Influenza and Respiratory Syncytial Virus (RSV).

Clinical definitions for Long COVID, such as the consensus definition developed by the WHO, are broad and inclusive, but not suitable for research purposes:

> *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**. Common symptoms include fatigue, shortness of breath, cognitive dysfunction **but also others** and **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.*[1]

Particularly challenging for research purposes are the (highlighted items): ambiguity around confirmation of, and timeframe from, initial infection; plus the need to systematically exclude alternative explanatory medical and psychiatric diagnoses. The ambiguity regarding the functional impact of symptoms which allows inclusion of illness manifestations of minor significance. Further, the allowance for a complete gap between the initial infection and symptom onset are also problematic when considering the premise of truly COVID-19-induced illness. The APPRISE Long COVID research definition is therefore more restrictive to enable a better characterised and less ambiguous cohort and to facilitate analysis. The implementation of this research case definition is undertaken with validated, public-domain, self-report questionnaires and protocolised further assessments which have been outlined.

Research definition of post-viral syndrome

This is a three-part definition that can be used to characterise both new onset and previously identified cases of post-viral syndrome.

1. Confirm an acute respiratory viral infection:

Designate an acute respiratory viral infection at symptom onset, either as:

a. Confirmed by molecular or antigen detection at time of acute infection, or serological confirmation (anti-Nucleocapsid IgG seroconversion between acute and convalescent samples)

   OR

b. Probable acute viral infection based on an influenza-like illness (ILI) within a high risk, epidemiological context (e.g., a family cluster with at least one confirmed acute respiratory virus case)

Primary case designation

2. Application of a modified WHO Long COVID research case definition at 12 weeks post infection:

a. New onset of ongoing symptoms - including ***at least one*** of fatigue, shortness of breath, cognitive disturbance, and sleep disturbance - which ***substantially impact*** on everyday functioning.

b. ***No symptom-free interval*** from acute infection.

c. Additional symptoms such as myalgia, disturbed taste and smell, and others may co-occur.

d. Symptoms may fluctuate over time.

3. Rule out other known causes of the symptoms by clinical evaluation and investigation

a. The clinical evaluation should include a thorough history and physical examination, as well as a mental status examination;

b. A minimum set of laboratory screening tests should be completed (as stipulated for the diagnosis of chronic fatigue syndrome[2]) including:

- full blood count with leucocyte differential;
- erythrocyte sedimentation rate or C-reactive protein;
- serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose;
- blood urea nitrogen, electrolytes, and creatinine

- thyroid-stimulating hormone;
- urinalysis;

c. Additional investigations could also be undertaken if needed to reliably identify alternative medical explanations for specific symptoms. Examples include:

- Lung function tests including spirometry when shortness of breath is reported; or exercise oximetry and measurement of the diffusion capacity for carbon monoxide (DLCO) to identify suspected interstitial lung injury;
- CT pulmonary angiography (CTPA) to consider pulmonary emboli;
- ECG and echocardiography when a cardiac cause is suspected.

Secondary case designations

Syndromal designation of one or more of concurrent or overlapping conditions: chronic fatigue syndrome (CFS), fibromyalgia (FM), or postural orthostatic tachycardia syndrome (POTS), and major depression may be made according to the published diagnostic criteria with the following modifications:

a. In subjects with confirmed or probable acute COVID-19 infection, and who met the modified WHO case definition for Long COVID (see above), and who remain unwell at 24 weeks post-infection an additional secondary case designation may be made, *if*

b. The symptom complex continues to be associated with disability – that is, it results in a substantial reduction in previous levels of occupational, educational, social, or personal activities (as specified in the CFS and major depression case definitions, but added to the FM and POTS definitions);

c. The symptom complex must have been present without symptom-free interval from the time of the acute respiratory virus infection;

d. The symptom complex must not have been present prior to the acute respiratory virus infection.

Instrumentation

A. Questionnaires (validated for each symptom domain with 'clinically-significant' thresholds):

- Somatic and Psychological Health Report (SPHERE)[3] – SOMA (*fatigue*) & PSYCH (*mood disturbance*) subscales[4, 5]
- Modified MRC Dyspnoea scale[6] – *shortness of breath*
- Patient's Assessment of Own Functioning (PAOFI)[7] – *cognitive disturbance*
- Pittsburgh Sleep Quality Index[8] – *sleep disturbance*
- WHODAS 12[9] – *assessment of disability*
- McGill Pain questionnaire - short form[10] – *musculo-skeletal pain*
- Kessler Psychological Distress Scale -10 (K10)[11] – *psychological distress reflecting anxiety and depression*
- COMPASS 31[12] – *autonomic disturbance*

B. Interview – Structured Clinical Interview for Neurasthenia (SCIN) [13]

C. Physical examination and protocolised investigations (as previously listed)

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