Challenges to delivering evidence-based management for long COVID

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Early on in the COVID-19 pandemic, scientists forewarned of a potential medium to long-term post-acute sequelae in patients infected with SARS-CoV-2, similar to that documented in bacterial, protozoan and viral infections including Epstein-Barr virus, Ebola virus, dengue virus, Chikungunya virus, going far back to the influenza pandemic in 1918. These varied symptoms following acute SARS-CoV-2 infection is now termed as long COVID and is also known as long-haulers syndrome, post COVID-19 condition (PCC), post-acute sequelae of SARS-CoV-2 infection (PASC), chronic COVID and many other terms. The Department of Health and Human Services in collaboration with the US Centers for Disease Control and Prevention broadly defines long COVID as ‘signs, symptoms, and conditions that continue or develop after initial COVID-19 infection’. Through a global consensus, the WHO, in October 2021, defined post COVID-19 condition as ‘the presence of symptoms 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’. In February 2023, the WHO issued a new definition for post COVID-19 in children and adolescents. Endorsing the definition by WHO, the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) was developed and classified this condition as ‘Diagnosis Code U09.9 (Post COVID-19 condition, unspecified)’.

The heterogeneity of long COVID results in a single or complex presentation of ailments with over 200 symptoms reported, affecting every organ system in the body, irrespective of the viral variant and vaccination status. Patients with long COVID may have residual symptoms, worsening of existing symptoms or the development of new symptoms at any time following acute infection, unrelated to initial disease severity. Zhang et al’s study identified four reproducible PASC subphenotypes, dominated by cardiac and renal; respiratory, sleep and anxiety; musculoskeletal and nervous system; and digestive and respiratory system sequelae. These subphenotypes were associated with distinct patient demographics, underlying conditions before SARS-CoV-2 infection and acute infection phase severity. These constellation of symptoms are also seen in chronic disease, in patients with severe illness following critical care, known as post-intensive care syndrome or as a delayed complication such as multisystem inflammatory syndrome in children. Longitudinal studies have shown that patients feel better through time, but some studies have documented an impairment of daily activities for longer than 1–2 years. Among this heterogeneous presentation, distinct subtypes have been identified to support the integration of individuals into specific care pathways.

There is still an open debate as to what entails long COVID, including confusion over appropriate terminology, due to the heterogeneous phenotypes, multiple case definitions, lack of a specific diagnostic, exacerbation of existing conditions (eg, diabetes mellitus), and because there is a significant overlap with other chronic conditions such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS) and mast cell activation syndrome.

Both POTS and small fibre neuropathy are commonly seen in long COVID, where POTS often occurs following a viral infection and is most often comorbid with ME/CFS. There is evidence that autonomic dysfunction may contribute to long COVID as it does in ME/CFS. There is also evidence that, as in ME/CFS, autoantibodies may be contributing to long COVID. When various factors (eg, infection, injury, cold temperatures, lack of sufficient nutrients) threaten the viability of a cell or of an organism, it may give rise to ME/CFS. Although many patients with ME/CFS report a prorome consistent with infection, no single agent is consistently implicated. A diagnosis of ME/CFS is based on symptoms as there is no specific diagnostic test with adequate sensitivity and specificity.

What is the current evidence for the management of long COVID?

Government, non-government organisations and academe have taken steps to support, fund and conduct research on repurposed drugs, newly developed medications and non-pharmacological interventions that may alleviate symptoms and optimise function and quality of life for patients with post COVID-19 condition; as well as disseminate research findings to raise awareness and understanding among the public and health professionals of post COVID-19 symptoms. Patient networks are also influencing the research agenda and accelerating progress in research.
Most trials recruited patients with persistent symptoms after a specific time range (usually 3 or more months since acute infection) and focused on fatigue, asthenia and respiratory symptoms. Most frequently reported outcomes included symptom improvement (30 days for which a baseline response rate was determined or important improvement in patients assigned to the control arm). Thirty-five percent (n=42) reported improvement in more than 30% of the patients despite not being treated with the intervention shown promise in treating olfactory and/or gustatory dysfunction. High certainty. Other interventions showed promising results but with low certainty evidence, for example, Actovegin potentially addresses asthenia/fatigue and respiratory symptoms, anticoagulant regimens are a promising way to address abnormal clotting, and palmitoylethanolamide with luteolin supplements have shown promise in treating olfactory and/or gustatory dysfunction. These interventions deserve further study.

Many of the RCTs have shown complete symptom resolution or important improvement in patients assigned to the control arm. Of the 72 outcomes assessed in 28 RCTs with a median follow-up of 30 days for which a baseline response rate was determined (proportion of patients assigned to control arm with important improvement), 42 (58%) reported improvement in more than 30% of the patients despite not being treated with the intervention assessed in that trial.

**Challenges and limitations**

We found an overall high risk of bias due to suboptimal randomisation, allocation concealment and blinding (as well as other methodological and reporting concerns). Most RCTs were also very small in size and had small event numbers. The methods were very poor overall, and the reporting was suboptimal, making the quality of evidence weak. In general, follow-up periods were too short to provide solid evidence. Definitions for post COVID-19, long COVID remain obscure, resulting in studies having methodological and analytical limitations, especially when defining patient cohorts. It is also challenging to draw definitive broad conclusions and generalisability on therapeutic based on the data across different studies.

Designing clinical trials for long COVID remains a challenge with many symptoms that differ between patients and within the same patient (waxing and waning or new symptoms), no specific diagnostic and overlap with similar chronic diseases. There is evidence that chronic conditions such as diabetes mellitus and renal failure may occur with COVID-19 and the elderly population is likely to experience a varied and complicated post-acute sequelae. Further research is needed to examine long COVID and the incidence of chronic diseases.

Although the PAHO living rapid review is focused on pharmacological and non-pharmacological interventions, this is only one aspect of the holistic management for long COVID. Future research
should be directed towards establishing standardised diagnostic biomarkers for long COVID among others. A multidisciplinary and comprehensive approach will be crucial in improving outcomes of these patients.

Better evidence for better care

Although we are still at the stage of symptom-driven treatment, there are sufficient therapeutics to address long COVID. Adequately designed and implemented clinical trials with greater transparency are essential for the practice of evidence-based medicine. In May 2022, the Seventy-fifth World Health Assembly approved a new resolution (WHA75.8) on 'Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination'. The communication of scientific results in a timely and clear manner is also fundamental for clinical management and for the organisation of the response of health systems for long COVID.

The PAHO technical team on post COVID-19 condition will continuously monitor the rapidly evolving literature, particularly if it applies to any special population subgroups such as children, pregnant women, those with immune condition, those with comorbidities, ethnic and minority groups and those affected by contextual factors. As new evidence emerges, studies will be assessed and updated in the living review, complemented through an interactive online version that will facilitate the use of the review’s results through interactive tables and figures. This living review will support countries, organisations and regional collaborations in the development of guidelines and policies for the management of patients with long COVID. PAHO continues to support Latin American and Caribbean countries in developing or adapting guidelines to specific contexts based on this evidence.

Table 2  Summary of findings by affected organ/system

<table>
<thead>
<tr>
<th>Organ/system affected</th>
<th>Important benefits</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>CoE</td>
</tr>
<tr>
<td>Asthenia or fatigue</td>
<td>Actovegin</td>
<td>Low ⨁⨁◯◯</td>
</tr>
<tr>
<td></td>
<td>Enzymes+probiotics</td>
<td>Low ⨁⨁◯◯</td>
</tr>
<tr>
<td></td>
<td>tDCS</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td></td>
<td>Physical training</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td></td>
<td>Telerehabilitation</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td></td>
<td>AXA1125</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td></td>
<td>Cognitive behavioural training</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td>Respiratory symptoms (ie, dyspnoea)</td>
<td>Respiratory training</td>
<td>Moderate ⨁◯◯◯</td>
</tr>
<tr>
<td></td>
<td>Treamid</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td>Neurocognitive symptoms</td>
<td>Actovegin</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td></td>
<td>Hyperbaric oxygen</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td></td>
<td>Physical training</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td>Olfactory and/or gustatory dysfunction</td>
<td>Pal+Lut</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td>Psychological distress</td>
<td>VR info video</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td>PIMS-TS</td>
<td>Steroids</td>
<td>Low ⨁◯◯◯</td>
</tr>
<tr>
<td>Thromboembolic risk</td>
<td>Balance between benefits and harms favours the intervention with moderate to high certainty</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td></td>
<td>Balance between benefits and harms favours the intervention with low certainty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Balance between benefits and harms does not favour the intervention with low certainty</td>
<td></td>
</tr>
</tbody>
</table>

CoE, certainty of the evidence; Pal+Lut, palmitoylethanolamide+luteolin; PIMS-TS, paediatric inflammatory multisystem syndrome associated with SARS-CoV-2; tDCS, transcranial direct current stimulation; VR info video, virtual reality informational video.
to support a research agenda, as well as to support clinicians to improve diagnosis and management of people living with long COVID.

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Contributors LR conceptualised and conducted the study. LR, SP and AI planned the study. SP and AI extracted the data, analysed the data and wrote the manuscript. LR, SP, AI, SA, SL, CM and PO edited the subsequent drafts and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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