



Clinical practice guideline for long COVID prevention and treatment

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Shareable abstract (@ERSpublications)

This report of the Multidisciplinary Working Group on Long COVID Practice Guidelines (MWG-LCPG) presents clinical guidelines on the prevention and treatment of long COVID <https://bit.ly/3NcykJM>

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Abstract

Background This guideline aims to address key clinical questions of long COVID, and to provide evidence-based recommendations. The target population is adults with long COVID. The primary users of the guideline are clinical physicians, clinical pharmacists, nurses and general practitioners in community healthcare institutions worldwide.

Methods The guideline was registered at the Practice guideline REGistration for transPAREncy platform (PREPARE-2024CN123) and followed a pre-specified protocol. A multidisciplinary working group was established and comprised 60 members from 10 countries and 10 areas of expertise, with a strong background in long COVID research and clinical practice, and methodology of guideline development. Through a two-step process, we determined eight PICO (Population, Intervention, Comparator, Outcome) questions focusing on prevention and treatment of long COVID. After comprehensively searching literature, conducting systematic reviews and investigating patients' values and preferences, three rounds of Delphi survey were conducted among 24 international experts to reach consensus. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach was applied to rate the certainty of evidence and determine the strength of recommendations.

Results The guideline presents 10 specific recommendations, each supported by existing, updated or newly conducted systematic reviews. The key recommendations are pertinent to the following issues: 1) suggestion of vaccination or use of antiviral agents during the acute phase of COVID-19 to prevent long COVID; 2) suggestions against the use of nirmatrelvir/ritonavir and glucocorticoids (patients with persistent respiratory symptoms and olfactory disorders) for long COVID treatment; 3) suggestions supporting the use of multispecies probiotics, cognitive behavioural therapy (patients with fatigue), and personalised rehabilitation (after ruling out post-exertional malaise) for long COVID treatment.

Conclusions This guideline provides evidence-based recommendations for the prevention and treatment of long COVID. Given the limited and often low-methodological-quality evidence, all recommendations are supported by very low to moderate certainty. Further high-quality studies are needed to strengthen the evidence base.

Introduction

SARS-CoV-2 has circulated globally for more than 5 years, resulting in approximately 779 million infections and more than 7 million deaths globally [1]. Although most individuals recover completely from COVID-19, at least 10% of recovered patients continue to experience symptoms such as fatigue, palpitations and dyspnoea 3 months after disease onset [2, 3]. The World Health Organization (WHO) defines post-COVID-19 condition, commonly referred to as long COVID, as the presence of persistent or new symptoms 3 months after initial infection, lasting for at least 2 months and not explained by alternative diagnoses.

The estimated global cumulative incidence of long COVID rose steadily from 2020 to 2023 [4]. Long COVID presents with a wide range of symptoms affecting multiple organ systems. Growing evidence also links SARS-CoV-2 infection with an elevated risk of long-term complications [5–8]. These long-term effects significantly impair patients' quality of life and functional capacity, contributing to increased sick leave and posing substantial economic burdens on individuals, families and society [9].

With advances in the understanding of SARS-CoV-2 and its long-term consequences, increasing attention has been paid to long COVID. Multiple organisations and institutions have issued guidelines or established ongoing task forces (www.ersnet.org/science-and-research/ongoing-task-forces/) on this condition [10–15]. However, these guidelines vary in quality, often lack comprehensiveness, and show significant inconsistency in content. Notably, there is still a lack of recent long COVID guidelines developed using contemporary evidence-based methodologies and shaped by multidisciplinary collaboration.



Given the growing body of evidence, we established an international, multidisciplinary working group to develop a clinical practice guideline for long COVID. This group aims to address key clinical questions of long COVID, mainly including prevention and treatment in adults. During the development of the guideline, the certainty of evidence and strength of recommendations were clearly defined, and patients' values and preferences were incorporated.

Methodology

This international guideline was developed following the WHO guidebook, using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool [16] and adhering to the Reporting Items for practice Guidelines in Healthcare (RIGHT) statement [17]. Methodological support was provided by the Lanzhou University GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Center and WHO Collaborating Centre for Guideline Implementation and Knowledge Translation. The guideline has been registered at the Practice guideline REGistration for transPAREncy platform (<https://guidelines-registry.org/>, registration number PREPARE-2024CN123).

A multidisciplinary working group was established in December 2023 and comprised 60 members from 10 areas of expertise and 10 countries, with a strong background in long COVID research and clinical practice, and methodology of guideline development. Candidate PICO (Population, Intervention, Comparator, Outcome) questions were developed through a two-step process involving clinicians and guideline methodologists, followed by review and prioritisation by the steering and consensus group, resulting in eight clinical questions (table 1). The working group then conducted systematic evidence searches, assessed risk of bias with validated tools, and applied the GRADE approach to rate certainty and develop recommendations. Three rounds of Delphi surveys conducted among 24 international experts were used to reach consensus, and patient partners contributed to values and preferences. A total of 10 recommendations were formulated after the Delphi survey, considering the certainty of the evidence, balance of benefits and harms, patient values and preferences, acceptability, and cost considerations (table 2) [18]. Plans for dissemination, evaluation and future updates were also defined. Detailed methodological procedures are provided in appendix 1, methods supplement.

Respiratory manifestations of long COVID

Evidence summary

A summary of evidence for the prevention and treatment of respiratory manifestations of long COVID can be found in table 3.

Explanation

Pulmonary involvement is a common and clinically significant component of long COVID, closely related to the severity and extent of pulmonary involvement during the acute phase of SARS-CoV-2 infection [34]. Long-term abnormalities in lung imaging and pulmonary function, particularly impaired diffusing capacity, have been reported to persist for years after acute infection [35, 36]. These findings suggest sustained lung parenchymal injury and microvascular dysfunction, which are considered key pathophysiological substrates underlying pulmonary long COVID [15].

Prevention of pulmonary long COVID

Current preventive strategies for long COVID, including vaccination and acute-phase pharmacological treatments, may reduce the overall risk of long COVID [37–40]; however, evidence specifically addressing the prevention of pulmonary long COVID remains limited. Available data suggest that the potential protective effects of vaccination and antiviral therapy on respiratory sequelae are largely indirect and mediated through attenuation of acute disease severity, rather than targeted prevention of chronic lung injury [41]. In our current guideline, an evidence synthesis evaluating the association between acute-phase antiviral treatment and long COVID-related dyspnoea did not demonstrate a significant protective effect, and evidence for other pulmonary symptoms is also lacking. Greater attention is still needed to investigate preventive strategies for other clinical phenotypes of pulmonary long COVID.

Pharmacological treatment of pulmonary long COVID

Pharmacological treatment options for established pulmonary long COVID are also limited. The findings based on limited evidence suggest that antiviral therapy has not demonstrated clear benefit for respiratory symptoms in patients with long-standing disease and negative markers of viral persistence [19], although they do not exclude a potential effect in other long COVID populations. Multiple ongoing clinical studies are evaluating antiviral drugs (nirmatrelvir/ritonavir (NMV/r), amantadine, ensitrelvir, *etc.*) for long COVID [42–48]. Future studies should focus on identifying patients most likely to benefit through biomarker-based risk stratification for viral persistence, earlier treatment initiation and longer treatment

TABLE 1 Eight PICO questions for prevention and treatment of long COVID

PICO questions	Population	Intervention	Comparison	Main outcomes
PICO question 1: What vaccines or treatments (antiviral drugs, anti-inflammatories, monoclonal antibodies, metformin, etc.) can prevent long COVID?	Adult patients with long COVID	Vaccines or pharmacological interventions (antiviral drugs, anti-inflammatories, monoclonal antibodies, metformin, etc.)	No vaccines or no pharmacological interventions	Risk of developing long COVID and related symptoms
PICO question 2: In patients with long COVID, should antiviral drugs be used <i>versus</i> no antiviral drugs?	Adult patients with long COVID	Antiviral drug	No antiviral drug	Long COVID symptoms
PICO question 3: In patients with long COVID, should monoclonal antibody be used <i>versus</i> no monoclonal antibody?	Adult patients with long COVID	Monoclonal antibodies	No monoclonal antibodies	Long COVID symptoms, time to symptom resolution, safety
PICO question 4: In patients with long COVID, should probiotics be used <i>versus</i> no probiotics?	Adult patients with long COVID	Probiotics (multispecies)	No probiotics/placebo	Long COVID symptoms, quality of life, safety
PICO question 5: In patients with long COVID, should glucocorticoids be used <i>versus</i> no glucocorticoids?	Adult patients with long COVID	Glucocorticoids (systemic or local administration)	No glucocorticoids	Cardiopulmonary function, olfactory recovery, safety
PICO question 6: In patients with long COVID, should immunomodulators be used <i>versus</i> no immunomodulators?	Adult patients with long COVID	Immunomodulators including MMF, JAK inhibitors, tacrolimus, etc.	No immunomodulators	Pulmonary function, systemic symptoms, safety
PICO question 7: In patients with long COVID, should cognitive behavioural therapy be used <i>versus</i> no cognitive behavioural therapy?	Adult patients with long COVID	Cognitive behavioural therapy	No cognitive behavioural therapy/usual care	Fatigue, anxiety, depression, social functioning, stress, self-efficacy
PICO question 8: In patients with long COVID, should rehabilitation exercise be used <i>versus</i> no rehabilitation exercise?	Adult patients with long COVID	Rehabilitation exercise (e.g. breathing, resistance, aerobic, strengthening or combined interventions; delivered face-to-face or <i>via</i> telerehabilitation)	No rehabilitation exercise/usual care	Exercise capacity, dyspnoea, quality of life, safety
JAK: Janus kinase; MMF: mycophenolate mofetil.				

TABLE 2 Working group recommendations for PICO questions on the prevention and treatment of long COVID

Recommendations	Strength of recommendation	Certainty of evidence	Remarks
Prevention			
PICO question 1: What vaccines or treatments (antiviral drugs, anti-inflammatories, monoclonal antibodies, metformin, etc.) can prevent long COVID?			
Irrespective of prior SARS-CoV-2 infection, vaccination against COVID-19 is suggested to prevent the development of long COVID. The specific vaccination dosage and timing should be determined by taking into account the availability, requirements of the local department and patient's condition, while closely monitoring any potential adverse events.	Conditional	Very low	
We suggest using antiviral drugs during the acute phase of COVID-19 to prevent the development of long COVID, especially in patients who are at higher risk.	Conditional	Low	Currently, COVID-19 antivirals are primarily indicated for treating acute SARS-CoV-2 infection, with indications varying by drug. The recommendation should not be interpreted as superseding or contradicting current clinical guidelines for antiviral use during the acute phase. Use of antivirals to prevent long COVID should involve shared decision-making, considering the patient's clinical condition, risk factors, and the specific indications and availability of each agent.
Treatment			
PICO question 2: In patients with long COVID, should antiviral drugs be used <i>versus</i> no antiviral drugs?			
We suggest against the use of nirmatrelvir/ritonavir for the treatment of long COVID in adult patients.	Conditional	Low	Given the lack of evidence for other antiviral drugs in long COVID treatment, this recommendation primarily pertains to nirmatrelvir/ritonavir.
PICO question 3: In patients with long COVID, should monoclonal antibody be used <i>versus</i> no monoclonal antibody?			
We have no recommendation for or against the use of neutralising monoclonal antibodies in adult patients with long COVID.	NA	Very low	
PICO question 4: In patients with long COVID, should probiotics be used <i>versus</i> no probiotics?			
We suggest using the multispecies probiotics to alleviate symptoms for adult patients with long COVID.	Conditional	Moderate	The availability of standardised preparations varies across settings. The recommendation should be interpreted in the context of local availability.
PICO question 5: In patients with long COVID, should glucocorticoids be used <i>versus</i> no glucocorticoids?			
We suggest against the use of glucocorticoids for improving cardiopulmonary function in adult patients with long COVID with persistent respiratory symptoms.	Conditional	Very low	
We suggest against the use of glucocorticoids for the treatment of olfactory disorders in adult patients with long COVID.	Conditional	Low	
PICO question 6: In patients with long COVID, should immunomodulators be used <i>versus</i> no immunomodulators?			
We have no recommendation for or against the use of immunomodulators (MMF, JAK inhibitors, tacrolimus) for adult patients with long COVID who have interstitial lung disease.	NA	Very low	
PICO question 7: In patients with long COVID, should cognitive behavioural therapy be used <i>versus</i> no cognitive behavioural therapy?			
We suggest using cognitive behavioural therapy in adult patients with long COVID to alleviate fatigue symptoms.	Conditional	Low	The recommendation of cognitive behavioural therapy does not imply psychological causation of fatigue among patients with long COVID.
PICO question 8: In patients with long COVID, should rehabilitation exercise be used <i>versus</i> no rehabilitation exercise?			
We suggest personalised rehabilitation training for adult patients with long COVID, following appropriate screening to exclude those with post-exertional malaise, and under the guidance and supervision of healthcare professionals.	Conditional	Low	
JAK: Janus kinase; MMF: mycophenolate mofetil; NA: not applicable.			

TABLE 3 Summary of evidence for the prevention and treatment of respiratory manifestations of long COVID

Studies included	Study participants	Summary
PICO question 1: What vaccines or treatments (antiviral drugs, anti-inflammatories, monoclonal antibodies, metformin, etc.) can prevent long COVID?		
Acute-phase drugs (within 4 weeks post-infection)		
Updated meta-analysis	Updated meta-analysis including 50 studies (six RCTs, two non-randomised trials, 40 cohort studies, and two case-control studies) (appendix 2)	
Updated meta-analysis	7 060 422 participants	Antivirals had no significant effect on dyspnoea (OR 0.94, 95% CI 0.72–1.23) (seven studies, 828 949 participants).
PICO question 2: In patients with long COVID, should antiviral drugs be used <i>versus</i> no antiviral drugs?		
One RCT	155 adults with history of COVID-19 and long COVID (no SARS-CoV-2 RNA detected in baseline stool samples)	At 10 weeks, there was no statistically significant difference between the nirmatrelvir/ritonavir group and the placebo-ritonavir group in the severity of shortness of breath of long COVID (change of severity score from baseline: –20.60 <i>versus</i> –24.50) [19].
PICO question 3: In patients with long COVID, should monoclonal antibody be used <i>versus</i> no monoclonal antibody?		
One case report	One immunocompromised adult with long COVID (thymoma with pleural metastasis) who had cough	The patient who received casirivimab/imdevimab (dosage not reported) experienced complete resolution of cough, suggesting potential benefit in immunocompromised individuals [20].
PICO question 4: In patients with long COVID, should probiotics be used <i>versus</i> no probiotics?		
One RCT	463 adults with long COVID (285 patients had shortness of breath and 249 patients had cough)	Compared with placebo, probiotics (e.g. SIM01, an oral synbiotic containing three bacterial strains) alleviated shortness of breath (OR 1.87, 95% CI 1.16–3.03) and cough (OR 1.85, 95% CI 1.04–3.29) [21].
PICO question 5: In patients with long COVID, should glucocorticoids be used <i>versus</i> no glucocorticoids?		
Six studies (one RCT, five observational studies)	3189 adults with long COVID with respiratory symptoms	Results were inconsistent from observational studies: some reported modest improvements in 6MWD [22, 23], FEV ₁ [24], FVC [22–24] and D _{LCO} [24, 25], while others found no significant effect [26]. However, caution is warranted in application considering the inconsistency. One RCT [27] comparing high-dose <i>versus</i> low-dose prednisone found no significant difference in lung function or radiological outcomes. Overall, findings were heterogeneous, with limited and inconsistent benefits. Note: Oral glucocorticoids dosages for the treatment of persistent respiratory symptoms in long COVID are shown in appendix 1: table S1.
PICO question 6: In patients with long COVID, should immunomodulators be used <i>versus</i> no immunomodulators?		
One cohort study, one case-control study, two case reports [28–31]		
One cohort study	48 adults with long COVID	MMF: patients with interstitial lung disease receiving immunosuppressive therapy (glucocorticoid alone or MMF combined with corticosteroids) showed improvements in lung function and oxygenation over 6 months, with good tolerability. However, the study did not include patients who did not receive immunosuppressive therapy as control [28].
One case-control study	41 adults with long COVID	JAK inhibitors: in patients with hypoxia, active inflammation and lung involvement, adding JAK inhibitors (baricitinib or tofacitinib) to glucocorticoid steroids allowed more rapid corticosteroid tapering and fewer adverse events, though no difference in oxygen support requirements was observed [29].
Two case reports	2 adults with long COVID	Tacrolimus: improved pulmonary function and successful withdrawal from oxygen therapy with a combination of corticosteroid and tacrolimus [30, 31].
PICO question 7: In patients with long COVID, should cognitive behavioural therapy be used <i>versus</i> no cognitive behavioural therapy?		
None		

Continued

TABLE 3 Continued

Studies included	Study participants	Summary
PICO question 8: In patients with long COVID, should rehabilitation exercise be used <i>versus</i> no rehabilitation exercise?		
Two SRs	14 RCTs, 1244 adults with long COVID	Compared with usual care, rehabilitation interventions (breathing exercises, breathing exercises in combination with resistance and/or aerobic training, strengthening and aerobic exercises and aerobic exercises alone) may improve: - dyspnoea (SMD -1.00, 95% CI -1.94 to -0.10) (eight RCTs, 573 adults with long COVID). Compared with usual care or sham exercise, rehabilitation interventions (breathing exercises, breathing exercises in combination with resistance and/or aerobic training, and strengthening and aerobic exercise) showed no significant effect on: - FEV₁ (SMD -0.16, 95% CI -0.42 to 0.11) - FVC (SMD -0.13, 95% CI -0.38 to 0.12) (six RCTs, 363 adults with long COVID) [32].
	Eight RCTs, 985 adults with long COVID	Compared with usual care, inspiratory muscle training may improve dyspnoea (MD 1.10 , 95% CI 0.44 to 1.76), but have no significant effect on breathlessness and activities (MD 2.40 , 95% CI -2.66 to 7.46) (one RCT, 148 adults with long COVID) [33]. Compared with standard physiotherapy, multicomponent exercise of progressively increasing intensity may improve: - dyspnoea (mMRC dyspnoea scale: MD -0.76, 95% CI -1.20 to -0.32; multidimensional dyspnoea profile: MD -18.61, 95% CI -27.40 to -9.82) - breathing discomfort (MD -1.74, 95% CI -2.79 to -0.69) - emotional response to dyspnoea (MD -6.95, 95% CI -12.44 to -1.46) - sensory dimension of dyspnoea (MD -9.93, 95% CI -14.56 to -5.30) (one RCT, 60 adults with long COVID) [33].
6MWD: 6-min walking distance; CI: confidence interval; D_{LCO} : diffusing capacity of the lung for carbon monoxide; FEV ₁ : forced expiratory volume in 1 s; FVC: forced vital capacity; JAK: Janus kinase; MD: mean difference; MMF: mycophenolate mofetil; mMRC: modified Medical Research Council; OR: odds ratio; RCT: randomised controlled trial; SMD: standardised mean difference; SR: systematic review.		

duration [49]. Similarly, evidence supporting the use of monoclonal antibodies, which are highly specific proteins produced through B-cell cloning that bind to distinct epitopes on pathogens, is extremely sparse and confined to isolated reports in immunocompromised patients [15].

Anti-inflammatory and immunomodulatory therapies have either mainly been evaluated in small, uncontrolled studies or show inconsistent effect. No meta-analysis was performed for adult patients with long COVID and persistent respiratory impairment owing to substantial heterogeneity across studies. Although available evidence suggests that glucocorticoids may improve certain lung imaging and function outcomes (e.g. 6-min walking distance, forced expiratory volume in 1 s, forced vital capacity and diffusing capacity of the lung for carbon monoxide), results are inconsistent, and the magnitude of improvement is generally limited. Thus, the clinical benefit of glucocorticoids in this population remains uncertain. Additionally, while no serious adverse events were reported during follow-up periods, other non-serious adverse events were not systematically assessed. The potential long-term risks of glucocorticoid therapy, including infections, osteoporosis, gastrointestinal bleeding and mental health disorders, remain a concern. The recent identification of neutrophil-driven small airway inflammation and epithelial barrier dysfunction through single-cell sequencing also raises the possibility that anti-inflammatory strategies, including small-molecule inhaled corticosteroids, may have therapeutic potential for dyspnoea and chronic cough in pulmonary long COVID. However, this hypothesis requires validation in well-designed clinical trials [50]. Therefore, based on current evidence, we suggest against the use of glucocorticoids for improving cardiopulmonary function in adult patients with long COVID and persistent respiratory symptoms.

Among the agents studied, mycophenolate mofetil (MMF) has shown potential effectiveness in improving peripheral oxygen saturation and pulmonary function test performance in patients with long COVID and interstitial lung disease, but MMF was used in combination with corticosteroids and the study lacked proper control without immunosuppressive therapy [28]. Janus kinase (JAK) inhibitors have demonstrated benefit in reducing inflammatory biomarker levels and reducing time to liberation from oxygen support in patients with long COVID in addition to steroids [29]. Tacrolimus has also been reported to improve pulmonary symptoms, although supporting evidence is limited to two case reports [30, 31], and steroids were administered as basic treatment. After removing disease definition restrictions for long COVID, a living systematic review (SR) published in 2024 in *The BMJ* [33] described similar symptom improvement among patients receiving an 8-week course of subcutaneous leronlimab compared with patients in the placebo group.

Non-pharmacological treatment of pulmonary long COVID

Non-pharmacological interventions currently play a central role in the management of pulmonary long COVID. Among these, rehabilitation exercise programmes (including breathing exercises, resistance training, strength training, aerobic exercise and stretching) demonstrate the most consistent evidence for improving dyspnoea among patients with long COVID without post-exertional malaise (PEM), although the magnitude of benefit is generally modest and the certainty of evidence ranks low to very low [32, 33, 51]. Specifically, the effects of inspiratory muscle training in improving dyspnoea make it an optional intervention for patients with pulmonary long COVID, although high-quality evidence is still needed. Rehabilitation programmes should be supervised, individualised and adapted to specific symptom severity. The type and intensity of rehabilitation should be adapted to the patient's condition. For example, older adult patients or individuals who have been in intensive care for severe COVID-19 should receive a more cautious and personalised rehabilitation plan developed in consultation with rehabilitation specialists, to avoid unnecessary or redundant interventions [12]. In contrast to exercise programmes, evidence supporting cognitive behavioural therapy (CBT) for pulmonary outcomes is lacking, because available studies primarily address fatigue and psychological symptoms rather than respiratory end-points [52–54].

Studies have indicated that probiotics can inhibit various respiratory viruses and reduce viral load *in vivo* [55] while modulating both the innate and adaptive immune response [56] and regulating the dynamic balance between pro-inflammatory and immunoregulatory cytokines [57], thereby attenuating respiratory infection severity. An *in vivo* study reported that fecal microbiota transplantation from individuals with long COVID into germ-free mice induced lung inflammation in the absence of SARS-CoV-2 [58]. In patients with long COVID, probiotics have shown potential benefits for respiratory symptoms in small studies, including shortness of breath and cough, two manifestations that remain of particular concern to pulmonologists given their high prevalence and clinical relevance. However, substantial heterogeneity in formulations and limited availability of standardised preparations preclude clinical recommendation [21, 59].

Despite increasing recognition of pulmonary long COVID, substantial evidence gaps remain. Respiratory end-points such as dyspnoea, pulmonary function and imaging abnormalities are infrequently prioritised as

primary outcomes in clinical trials. Given the marked heterogeneity in pulmonary long COVID phenotypes, further refinement and validation of distinct subtypes are needed. Notably, the identification of xenon-129 magnetic resonance imaging-defined clusters reflecting abnormalities in ventilation, membrane diffusion and red blood cell gas transfer highlights the potential value of advanced imaging-based phenotyping in refining the diagnostic approach to pulmonary long COVID and enabling more mechanism-oriented clinical evaluation [60]. Data on high-risk populations, including older adults, critically ill survivors and patients with fibrotic or vascular lung sequelae, are particularly limited. Future research should prioritise standardised pulmonary outcome measures, phenotype-driven trial designs and biomarker-informed patient stratification to advance targeted prevention and treatment strategies for pulmonary long COVID.

Extra-respiratory manifestations of long COVID

PICO question 1: What vaccines or treatments (antiviral drugs, anti-inflammatories, monoclonal antibodies, metformin, etc.) can prevent long COVID?

Evidence summary

A summary of evidence on vaccination and acute-phase pharmacological interventions for the prevention of extrapulmonary long COVID can be found in table 4.

Explanation

Preventing long COVID is of considerable clinical importance, and current research primarily focuses on vaccination and pharmacological interventions administered during the acute phase of SARS-CoV-2 infection (within 4 weeks of infection). Several SRs have suggested that vaccination, whether administered before or after SARS-CoV-2 infection, may reduce the risk or odds of long COVID [37–40]. However, high heterogeneity across studies and the lack of large-scale randomised controlled trials (RCTs) result in very low certainty of evidence. Vaccine effectiveness is influenced by age, comorbidities, individual immune responses and viral variants [65], and the optimal timing and dosing remain unclear. Therefore, vaccination decisions should follow local public health recommendations and individual clinical assessments.

Pharmacological treatment during the acute phase may also reduce the risk of long COVID [66, 67]. Our updated SR supports a potential benefit of selected antiviral agents, although the certainty of evidence remains low to very low, and varies by drug type, target symptoms and patient risk profiles. Evidence does not support routine use of non-antiviral agents for long COVID prevention. Clinical decision-making should integrate individual risk profiles, drug–drug interactions and practical contextual factors. Several clinical trials are currently underway and are expected to provide further insights into preventive strategies for long COVID [68–70].

PICO question 2: In patients with long COVID, should antiviral drugs be used versus no antiviral drugs?

Evidence summary

A summary of evidence on antiviral drugs for the treatment of extrapulmonary long COVID can be found in table 5.

Explanation

Persistent viral presence has been proposed as one potential mechanism for long COVID [2]. NMV/r, an inhibitor of SARS-CoV-2 main protease, is approved for the treatment of COVID-19 in adult patients at risk of progression to severe COVID-19 [71]. Case series and reports [72–75] have suggested that antiviral agents, including NMV/r, may alleviate symptoms in some patients with long COVID; however, high-quality evidence remains limited. The included RCT demonstrated that NMV/r was safe but did not result in significant symptomatic improvement in patients with long COVID who had symptoms nearly 1.5 years after their acute infection and negative stool viral RNA at baseline.

PICO question 3: In patients with long COVID, should monoclonal antibody be used versus no monoclonal antibody?

Evidence summary

A summary of evidence on monoclonal antibody for the treatment of extrapulmonary long COVID can be found in table 6.

Explanation

In the context of long COVID, most therapeutic monoclonal antibodies are neutralising agents that target specific viral epitopes to inhibit viral entry and replication. Evidence supporting their use in long COVID

TABLE 4 Summary of evidence on extrapulmonary long COVID for PICO question 1: What vaccines or treatments (antiviral drugs, anti-inflammatories, monoclonal antibodies, metformin, etc.) can prevent long COVID

Studies included	Study participants	Summary
Vaccination		
Three high-quality SRs including 44 observational studies [37–39]		
Risk/odds of long COVID		
Three SRs	14 842 052 participants	- Before infection: two doses significantly reduced odds of long COVID (OR 0.76, 95% CI 0.65–0.89, $I^2=93.4\%$); one or three doses showed no significant effect [39]. The point estimated ORs of long COVID with one dose of vaccine were 0.22–1.03; with two doses, ORs were 0.25–1.02; with three doses, 0.16; with any dose, 0.48–1.01 [38]. Another SR suggested that the prevalence of post-COVID-19 syndrome symptoms was lower in vaccinated individuals (9.5%) than unvaccinated (14.6%), with a notable decrease in activity-limiting symptoms (adjusted OR 0.59, 95% CI 0.48–0.73) [37]. - After infection: one dose post-infection reduced odds of long COVID (OR 0.85, 95% CI 0.73–0.98, $I^2=77.9\%$); two doses showed no significant effect [39]. Another SR showed that the point estimated OR of long COVID with vaccine after infection ranged from 0.38 to 0.91 [38]. - Vaccine types: both mRNA (BNT162b2) and adenoviral vector vaccines (ChAdOx1 nCoV-19) reduced risk of long COVID, regardless of the timing of administration [39].
Acute-phase drugs (within 4 weeks post-infection)		
Updated meta-analysis including 50 studies (six RCTs, two non-randomised trials, 40 cohort studies and two case–control studies) (appendix 2)		
Risk/odds of long COVID		
Updated meta-analysis	7 060 422 participants [#]	- Antivirals: overall, antiviral use was associated with reduced odds of long COVID (21 studies, OR 0.69, 95% CI 0.64–0.74, $I^2=98.0\%$). Nirmatrelvir/ritonavir, molnupiravir and favipiravir showed significant benefit, whereas remdesivir, ensitrelvir and azvudine did not. - Monoclonal antibodies: no significant effect on long COVID or individual symptoms. - Corticosteroids: no significant preventive effect on long COVID. - Metformin: one RCT showed reduced risk (HR 0.59, 95% CI 0.39–0.89) of long COVID, two large retrospective studies also supported the benefit [61–63].
Neuropsychological system		
Updated meta-analysis	7 060 422 participants [#]	Antivirals reduced odds of cognitive impairment (OR 0.83, 95% CI 0.74–0.94) and sleep disorders (OR 0.94, 95% CI 0.89–0.98).
Musculoskeletal system		
Updated meta-analysis	7 060 422 participants	Antivirals had no significant effect on myalgia (OR 0.88, 95% CI 0.70–1.10) (six studies, 3809 participants).
Systemic symptoms		
Updated meta-analysis	7 060 422 participants [#]	Antivirals reduced odds of fatigue (OR 0.90, 95% CI 0.84–0.97).
Safety: No significant adverse events were reported in any of the included RCTs, despite the use of different vaccinations. For monoclonal antibodies, one study suggested potential pulmonary fibrosis risk with rituximab [64].		
CI: confidence interval; HR: hazard ratio; OR: odds ratio; RCT: randomised controlled trial; SR: systematic review. [#] : the numbers of participants for the specific outcome were not adequately reported in the included studies; therefore, the data presented here reflect the total number of participants included in each study.		

is extremely limited. Our SR found no robust evidence demonstrating clinical benefit in the general long COVID population. One case report suggested possible symptomatic improvement, including pulmonary symptoms, in immunocompromised patients. The status of immunocompromise can potentially indicate viral reactivation or re-infection [15], providing a biological rationale for why exogenous neutralising antibodies may facilitate symptom improvement in this population. Given the lack of efficacy and safety data, high cost, and uncertainty regarding optimal patient selection, current evidence does not support a recommendation for their routine use in long COVID. Several clinical trials investigating monoclonal antibodies, including AER002 and casirivimab-imdevimab, are currently ongoing [76–79].

PICO question 4: In patients with long COVID, should probiotics be used versus no probiotics?

Evidence summary

A summary of evidence on probiotics for the treatment of extrapulmonary long COVID can be found in table 7.

Explanation

Probiotics may influence host immunity and inflammation through modulation of the gut microbiota [81], and have shown potential protective effects in respiratory diseases, mainly through direct antiviral activity

TABLE 5 Summary of evidence on extrapulmonary long COVID for PICO question 2: In patients with long COVID, should antiviral drugs be used *versus* no antiviral drugs?

Studies included	Study participants	Summary
One RCT [19]		
Gastrointestinal system		
One RCT	155 adults with history of COVID-19 and long COVID (no SARS-CoV-2 RNA detected in baseline stool samples)	At 10 weeks, there was no statistically significant difference between the nirmatrelvir/ritonavir group and the placebo-ritonavir group in the severity of gastrointestinal symptom of long COVID (change of severity score from baseline: -19.60 <i>versus</i> -11.30) [19].
Neuropsychological system		
One RCT	155 adults with history of COVID-19 and long COVID (no SARS-CoV-2 RNA detected in baseline stool samples)	At 10 weeks, there was no statistically significant difference between the nirmatrelvir/ritonavir group and the placebo-ritonavir group in the severity of brain fog of long COVID (change of severity score from baseline: -28.40 <i>versus</i> -47.20) [19].
Musculoskeletal system		
One RCT	155 adults with history of COVID-19 and long COVID (no SARS-CoV-2 RNA detected in baseline stool samples)	At 10 weeks, there was no statistically significant difference between the nirmatrelvir/ritonavir group and the placebo-ritonavir group in the severity of body aches of long COVID (change of severity score from baseline: -22.50 <i>versus</i> -20.80) [19].
Cardiovascular system		
One RCT	155 adults with history of COVID-19 and long COVID (no SARS-CoV-2 RNA detected in baseline stool samples)	At 10 weeks, there was no statistically significant difference between the nirmatrelvir/ritonavir group and the placebo-ritonavir group in the severity of cardiovascular of long COVID (change of severity score from baseline: -23.50 <i>versus</i> -20.80) [19].
Systemic symptoms		
One RCT	155 adults with history of COVID-19 and long COVID (no SARS-CoV-2 RNA detected in baseline stool samples)	At 10 weeks, there was no statistically significant difference between the nirmatrelvir/ritonavir group and the placebo-ritonavir group in the severity of fatigue of long COVID (change of severity score from baseline: -23.50 <i>versus</i> -43.40) [19].
Safety: The incidence of adverse events was similar between the nirmatrelvir/ritonavir and placebo/ritonavir groups.		
RCT: randomised controlled trial.		

and immune modulation. For patients with long COVID, some studies [21, 59, 80] suggest that probiotics might help alleviate persistent symptoms [82]. However, these studies differ significantly in terms of probiotic strains, dosages and treatment duration, and individual responses may vary based on baseline microbiome composition and other host factors. Moreover, most probiotic formulations are not readily available as pharmaceutical preparations. As a result, evidence remains insufficient to support routine probiotic use in long COVID.

PICO question 5: In patients with long COVID, should glucocorticoids be used *versus* no glucocorticoids?

Evidence summary

A summary of evidence on glucocorticoids for the treatment of extrapulmonary long COVID can be found in table 8.

Explanation

Glucocorticoids, as a class of steroid hormones, regulate multiple physiological processes and are widely used during acute COVID-19, but recommendations for their use in long COVID are limited. Regarding olfactory disorders, both local and systemic glucocorticoid therapy have been shown to improve olfactory scores in adult patients with long COVID. However, no significant differences were observed in patients' self-reported olfactory recovery. Furthermore, the magnitude of score improvement does not meet the threshold for clinical significance (defined as an increase of >2 points on a 10-point scale). A recent small-scale trial suggested that endoscopic topical therapy is feasible and safe for treating olfactory dysfunction post SARS-CoV-2 infection, supporting future larger trials [87]. Two SRs [88, 89] on inhaled glucocorticoids for persistent post-COVID olfactory dysfunction were identified; although their definitions of long COVID differed from the WHO definitions adopted in this guideline, their findings are largely consistent with ours.

TABLE 6 Summary of evidence on extrapulmonary long COVID for PICO question 3: In patients with long COVID, should monoclonal antibody be used *versus* no monoclonal antibody?

Studies included	Study participants	Summary
One case report [20]		
Systemic symptoms		
One case report	One immunocompromised adult with long COVID (thymoma with pleural metastasis) who had fever and malaise	The patient received casirivimab-imdevimab (dosage not reported) and experienced complete resolution of fever and malaise, suggesting potential benefit in immunocompromised individuals [20].
Safety: No adverse events were reported in the study.		

PICO question 6: In patients with long COVID, should immunomodulators be used *versus* no immunomodulators?

Evidence summary

A summary of evidence on immunomodulators for the treatment of extrapulmonary long COVID can be found in table 9.

Explanation

Immunomodulators are agents that modulate the immune system by either enhancing or suppressing immune responses. Currently, clinical guidelines do not provide established recommendations for the use

TABLE 7 Summary of evidence on extrapulmonary long COVID for PICO question 4: In patients with long COVID, should probiotics be used *versus* no probiotics?

Studies included	Study participants	Summary
Three RCTs (two published in peer-reviewed journals and one available as a preprint) [21, 59, 80]		
Musculoskeletal system		
One RCT	463 adults with long COVID (291 had muscle pain, 262 had joint pain and 189 had inability to exercise)	Compared with placebo, probiotics (SIM01, an oral synbiotic containing three bacterial strains) alleviated: - joint pain (OR 2.10, 95% CI 1.27–3.47) - inability to exercise (OR 2.32, 95% CI 1.23–4.38) - muscle pain (OR 1.71, 95% CI 1.07–2.72) [21].
Neuropsychological system		
One RCT	463 adult patients with long COVID (323 had difficulty in concentration, 305 had insomnia, 369 had memory loss)	Compared with placebo, probiotics (SIM01, an oral synbiotic containing three bacterial strains) alleviated: - difficulty in concentration (OR 2.64, 95% CI 1.69–4.14) - memory loss (OR 1.97, 95% CI 1.27–3.04) - insomnia (OR 1.76, 95% CI 1.12–2.77) [21].
Gastrointestinal system		
One RCT	463 adults with long COVID (374 had gastrointestinal upset)	Compared with placebo, probiotics (SIM01, an oral synbiotic containing three bacterial strains) alleviated: gastrointestinal upset (OR 1.99, 95% CI 1.30–3.05) [21].
Systemic symptoms		
Three RCTs	463 adults with long COVID (298 had general unwellness, 398 had fatigue)	Compared with placebo, probiotics (SIM01, an oral synbiotic containing three bacterial strains) alleviated: - fatigue (OR 2.27, 95% CI 1.52–3.40) - general unwellness (OR 2.36, 95% CI 1.43–3.90) [21].
	38 patients with long COVID	This RCT [59] assessed VSL#3 (consisting of Lactobacilli, Bifidobacteria and <i>Streptococcus thermophilus</i>), and reported a greater reduction in long COVID-related fatigue at 4 weeks compared with placebo, measured by Chalder Fatigue Scale Likert score.
	26 patients with long COVID	This RCT [80] evaluated a synbiotic mixture (including <i>L. rhamnosus</i> DSM 32550, Humiome <i>L. plantarum</i> DSM 34532, <i>B. lactis</i> DSM 32269 and DSM 32946). After 3 months of intake, participants showed significant reductions in post-exercise malaise compared with placebo (% change in VAS score from baseline: 37.5% <i>versus</i> 68.0%).
Safety: No significant adverse events were reported in any of the included RCTs, despite the use of different probiotics.		
CI: confidence interval; OR: odds ratio; RCT: randomised controlled trial; VAS: visual analogue scale.		

TABLE 8 Summary of evidence on extrapulmonary long COVID for PICO question 5: In patients with long COVID, should glucocorticoids be used *versus* no glucocorticoids?

Studies included	Study participants	Summary
Four studies (three RCTs and one before-and-after study); updated meta-analysis conducted for olfactory disorders		
Gustatory system		
Three RCTs and one before-and-after study	215 adults with long COVID with olfactory dysfunction	Olfactory disorders: • Meta-analysis from three RCTs [83–85] showed modest improvement in olfactory scores (mean difference 1.66, 95% CI 1.10–2.23), but no effect on self-reported recovery (appendix 2). • One study [86] combining glucocorticoids with other therapies suggested some benefit, especially when treatment started early, but results were not robust.
Safety:		
• No serious adverse events were reported across studies. • Local injections occasionally caused mild bleeding and pain. • Long-term safety (e.g. risk of infections, osteoporosis, gastrointestinal bleeding) was not adequately studied.		
CI: confidence interval; RCT: randomised controlled trial.		

of immunomodulators in long COVID management. This guideline identified six studies suggesting potential benefits of immunomodulators in adult patients with long COVID, but the overall evidence remains limited and restricted to combination with glucocorticoid steroids. Given the heterogeneity of available studies, small sample sizes and a lack of consensus regarding key aspects such as dosing regimens, duration, combination therapy and safety precautions, no recommendation can be made for or against immunomodulators in long COVID. Clinical trial registries indicate that multiple studies are underway investigating immunomodulators such as anakinra, intravenous immunoglobulin and baricitinib for adult patients with long COVID [92–97].

PICO question 7: In patients with long COVID, should cognitive behavioural therapy be used versus no cognitive behavioural therapy?

Evidence summary

A summary of evidence on CBT for the treatment of extrapulmonary long COVID can be found in table 10.

Explanation

CBT, a therapeutic approach centred on modifying cognitive patterns and behaviours, has shown potential in alleviating certain symptoms associated with long COVID by reshaping cognitive frameworks, improving emotional regulation and promoting behavioural activation [52]. However, current evidence is limited, with studies featuring small sample sizes and inconsistent outcome measures, and a lack of large-scale RCTs. Our meta-analysis showed high heterogeneity across studies, with most outcomes showing nonsignificant improvements supported by low-certainty evidence. Fatigue was the only symptom

TABLE 9 Summary of evidence on extrapulmonary long COVID for PICO question 6: In patients with long COVID, should immunomodulators be used *versus* no immunomodulators?

Studies included	Study participants	Summary
One case series and one case report [90, 91]		
Musculoskeletal system		
One case series	3 adults with long COVID	Methotrexate and leflunomide were tried in three patients with joint pain [91], but two discontinued due to adverse events.
Systemic symptoms		
One case report	1 adult with long COVID	Anakinra was reported effective and well tolerated in a case of steroid-dependent multisystem inflammatory syndrome [90].
Safety: No serious adverse events were reported for MMF, JAK inhibitors or tacrolimus in the available studies.		
JAK: Janus kinase; MMF: mycophenolate mofetil.		

TABLE 10 Summary of evidence on extrapulmonary long COVID for PICO question 7: In patients with long COVID, should cognitive behavioural therapy be used *versus* no cognitive behavioural therapy?

Studies included	Study participants	Summary
Four studies (one RCT and three before-after studies); updated meta-analyses conducted for anxiety, depression, social functioning and fatigue)		
Mental health		
Updated meta-analysis including two before-and-after studies	93 adults with long COVID	Compared with baseline (pre–post comparison), CBT had no significant improvement in: - anxiety (SMD 0.32, 95% CI –0.19 to 0.83) - depression (SMD 0.25, 95% CI –0.10 to 0.60) [52, 53].
One quasi-experimental study	40 adults with long COVID	Compared with usual care, CBT significantly reduced stress [54]. However, owing to the limited number of studies for each outcome, meta-analysis was not feasible.
Systemic symptoms		
Updated meta-analysis including one RCT and one before-and-after study	144 adults with long COVID	Compared with no CBT or baseline (pre–post comparison), CBT had no significant improvement in: social functioning (SMD 5.63, 95% CI –3.91 to 15.17) [53, 98].
Updated meta-analysis including one RCT and one before-and-after study	177 adults with long COVID	Compared with no CBT or baseline (pre–post comparison), CBT significantly alleviated: fatigue (SMD 4.01, 95% CI 1.17–6.85) [52, 98].
One before-and-after study	63 adults with long COVID	Compared with baseline (pre–post comparison), CBT significantly increased self-efficacy [52]. However, owing to the limited number of studies for each outcome, meta-analysis was not feasible.
Safety: No serious adverse events have been reported for CBT in the available studies.		
CI: confidence interval; CBT: cognitive behavioural therapy; RCT: randomised controlled trial; SMD: standardised mean difference.		

for which CBT demonstrated statistically significant benefits. Notably, current assessment tools largely focus on somatic symptoms and functional limitations, potentially neglecting cognitive and social dimensions of mental fatigue. These tools are subject to bias and often fail to clearly distinguish between physical and mental fatigue. In addition, while CBT shows potential for anxiety, depression and social functioning in patients with long COVID, its overall effectiveness remains inconclusive and requires further validation through robust clinical trials [52–54].

Given the frequent co-occurrence of psychological symptoms with persistent physical discomfort, reduced quality of life and other complex presentations in long COVID, pharmacological interventions may offer faster and more effective relief during acute or severe episodes. As such, this guideline suggests CBT as an adjunctive therapy, particularly for patients who do not respond adequately to pharmacological treatments. From a safety perspective, CBT is a non-pharmacological intervention with a favourable risk profile. No serious adverse events have been reported. However, the implementation of CBT requires trained psychotherapists, and the availability of such resources may be limited in certain regions, potentially restricting its practical application. To date, existing guidelines have not provided clear recommendations regarding the use of CBT in long COVID management. Although a 2023 expert consensus endorsed CBT as first-line treatment for insomnia in patients with long COVID [99], owing to lack of evidence, this guideline does not offer a recommendation regarding the use of CBT in the context of insomnia.

Despite these limitations, CBT remains a promising therapeutic option for patients with long COVID, particularly those experiencing prominent fatigue and psychological symptoms, owing to its potential benefits and low risk of harm.

PICO question 8: In patients with long COVID, should rehabilitation exercise be used versus no rehabilitation exercise?

Evidence summary

A summary of evidence on rehabilitation exercise for the treatment of extrapulmonary long COVID can be found in table 11.

Explanation

Rehabilitation exercise is a key component of long COVID management for patients without PEM. SRs included in this guideline indicate that rehabilitation interventions may improve physical capacity and quality of life in patients with long COVID [32, 33, 51]. However, the magnitude of benefit is generally

TABLE 11 Summary of evidence on extrapulmonary long COVID for PICO question 8: In patients with long COVID, should rehabilitation exercise be used *versus* no rehabilitation exercise?

Studies included	Study participants	Summary
Three SRs (one SR, one living SR, one network meta-analysis) [32, 33, 51]		
Musculoskeletal system		
One SR	14 RCTs, 1244 adults with long COVID	Compared with usual care, rehabilitation interventions (breathing exercises and breathing exercises in combination with resistance and/or aerobic training) showed no significant differences in: lower limb muscle strength and endurance (SMD -0.77, 95% CI -1.94 to 0.44) (four RCTs, 371 adults with long COVID) [32].
Neuropsychological system		
One SR	Eight RCTs, 985 adults with long COVID	Compared with standard physiotherapy, multicomponent exercise of progressively increasing intensity had no significant effect on: - mental health (MD 2.06, 95% CI -3.52 to 7.64) (one RCT, 60 adults with long COVID) [33]. Compared with standard physiotherapy, the active breathing techniques had no significant effect on: - mental health (MD 0, 95% CI -3.69 to 3.69) (one RCT, 110 adults with long COVID) [33].
Systemic symptoms		
Three SRs	14 RCTs, 1244 adults with long COVID	Compared with usual care, rehabilitation interventions (breathing exercises, breathing exercises in combination with resistance and/or aerobic training, and strengthening and aerobic exercises) may improve: - exercise capacity (SMD -0.56, 95% CI -0.87 to -0.22) (seven RCTs, 389 adults with long COVID) - quality of life (SMD -0.41, 95% CI -0.73 to -0.06) (five RCTs, 366 adults with long COVID) [32].
	Eight RCTs, 985 adults with long COVID	Compared with usual care, inspiratory muscle training showed no significant effect on: - quality of life (MD -1.30, 95% CI -5.90 to 3.30) (one RCT, 158 adults with long COVID) [33]. Compared with standard physiotherapy, multicomponent exercise of progressively increasing intensity may improve: - physical function (MD 6.96, 95% CI 2.7 to 11.22) (one RCT, 60 adults with long COVID) [33]. Compared with standard physiotherapy, active breathing techniques may improve: - fatigue (MD -9.97, 95% CI -11.17 to -8.77) (one RCT, 60 adults with long COVID) [33]. Compared with continuous aerobic exercise, intermittent aerobic exercise probably improves: - physical function (MD 3.80, 95% CI 1.12 to 6.48) (one RCT, 110 adults with long COVID) [33]. Compared with high-intensity aerobic strength training, low-intensity aerobic strength training may improve: - quality of life (8 weeks: MD 8.50, 95% CI 8.08 to 8.92; 24 weeks: MD 10.40, 95% CI 9.97 to 10.83) (one RCT, 73 adults with long COVID) [33].
	10 RCTs, 765 adults with long COVID [#]	Compared with usual care, face-to-face rehabilitation may improve physical function (MD 29.06 , 95% CI 2.76 to 55.37), but showed no significant effect on quality of life (physical domain: MD 6.58 , 95% CI -0.14 to 13.30 ; mental domain: MD 2.14 , 95% CI -4.36 to 8.64) [51]. Compared with usual care, telerehabilitation showed no significant effect on physical function (MD 3.13 , 95% CI -26.57 to 32.82), and may improve quality of life (physical domain: MD 5.17 , 95% CI -1.52 to 11.86 ; mental domain: MD 7.12 , 95% CI 0.61 to 13.64) [51]. Indirect comparison results showed that no significant difference was observed between face-to-face rehabilitation and telerehabilitation in their effect on: - physical function evaluated by 6MWD or 30 s sit-to-stand test (MD -25.94, 95% CI -65.61 to 13.73) - the physical domain of quality of life (MD 1.41, 95% CI -8.07 to 10.90) [51] - the mental domain of quality of life (MD -4.98, 95% CI -14.19 to 4.22) [51].
Safety: No significant adverse events were reported in any of the included SRs.		
6MWD: 6-min walking distance; CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; SMD: standardised mean difference; SR: systematic review. [#] : the numbers of participants for the specific outcome were not adequately reported in the included studies; therefore, the data presented here reflected the total number of participants included in each study.		

modest, and the certainty of most evidence is low to very low [32, 33]. Patients can receive these interventions from healthcare providers online or face-to-face, with telerehabilitation and in-person rehabilitation demonstrating differential effects across specific outcomes [51].

A study demonstrated the cost-effectiveness of rehabilitation programmes for patients with long COVID who had previously been hospitalised for COVID-19, while data on non-hospitalised patients remaining limited [100]. Based on current evidence, we suggest that patients with long COVID should receive personalised rehabilitation training under the guidance and supervision of healthcare professionals, particularly patients with a history of hospitalisation for COVID-19 or symptoms that significantly affect activities of daily living and functional status. These recommendations are consistent with existing long

COVID guidelines [10–12, 101]. Patients with PEM or post-exertional symptom exacerbation often demonstrate limited tolerance to rehabilitation training. In such cases, the main focus should be on activity management (rest/pacing) rather than physical exertion [102]. Further research on this topic is needed.

Suggestions for future research

To advance the understanding and management of long COVID, a coordinated research agenda is urgently needed. Uptake of a standardised long COVID definition and core outcome is crucial to ensure comparability across studies and strengthen the evidence base. Despite increasing attention, data remain sparse, particularly among children and vulnerable populations, hindering the development of inclusive and equitable clinical guidance. High-priority research areas include elucidating disease burden and subtypes, identifying risk factors and preventive strategies, improving diagnostic and evaluation tools, and generating robust evidence on treatment effectiveness through well-designed clinical trials (appendix 1: table S2).

Limitations

This guideline has several limitations. First, among the 26 steering and consensus group members, nine (35%) are affiliated with institutions in Europe or North America. Patient involvement was limited to three representatives, potentially missing perspectives from low- and middle-income countries. While the majority of panel members were based in Asia, we do not believe this compromises the methodological rigour of the guideline development process. Second, existing SRs and one monoclonal antibody study using non-WHO definitions of long COVID were included, broadening the evidence base but adding heterogeneity. Third, most evidence came from observational studies of variable quality, leading to low to very low certainty of evidence for many recommendations due to bias, inconsistency (e.g. high I^2 values in meta-analyses) and imprecision. Fourth, language restrictions were not imposed during the evidence search. However, inclusion criteria were limited to English publications, which may introduce language bias. Finally, the guideline mainly addresses adults, and does not cover emerging variants or outcomes beyond the search cutoff.

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References

- 1 World Health Organization. WHO Coronavirus Disease (COVID-19) dashboard. <https://covid19.who.int/table> Date last accessed: 12 February 2026.
- 2 Davis HE, McCorkell L, Vogel JM, et al. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023; 21: 133–146.
- 3 Vivaldi G, Pfeffer PE, Talaie M, et al. Long-term symptom profiles after COVID-19 vs other acute respiratory infections: an analysis of data from the COVIDENCE UK study. *EClinicalMedicine* 2023; 65: 102251.
- 4 Al-Aly Z, Davis H, McCorkell L, et al. Long COVID science, research and policy. *Nat Med* 2024; 30: 2148–2164.
- 5 Bowe B, Xie Y, Xu E, et al. Kidney outcomes in long COVID. *J Am Soc Nephrol* 2021; 32: 2851–2862.
- 6 Xie Y, Xu E, Bowe B, et al. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022; 28: 583–590.
- 7 Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol* 2022; 10: 311–321.
- 8 Xie Y, Xu E, Al-Aly Z. Risks of mental health outcomes in people with COVID-19: cohort study. *BMJ* 2022; 376: e068993.
- 9 Perlis RH, Lunz Trujillo K, Safarpour A, et al. Association of post-COVID-19 condition symptoms and employment status. *JAMA Netw Open* 2023; 6: e2256152.
- 10 Yelin D, Moschopoulos CD, Margalit I, et al. ESCMID rapid guidelines for assessment and management of long COVID. *Clin Microbiol Infect* 2022; 28: 955–972.
- 11 National Institute for Health and Care Excellence. COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19 (NG188). London, National Institute for Health and Care Excellence (NICE), 2020.
- 12 Kim Y, Kim SE, Kim T, et al. Preliminary guidelines for the clinical evaluation and management of long COVID. *Infect Chemother* 2022; 54: 566–597.
- 13 Spanish Society of General and Family Physicians. Guía Clínica para la Atención al Paciente LONG COVID/COVID Persistente [Clinical Guide for the Care of Long COVID/Persistent COVID Patients]. www.semg.es/index.php/consensos-guias-y-protocolos/363-guia-clinica-para-la-atencion-al-paciente-long-covid-covid-persistente Date last accessed: 12 February 2026.
- 14 Giuliano M, Tiple D, Agostoni P, et al. Italian good practice recommendations on management of persons with Long-COVID. *Front Public Health* 2023; 11: 1122141.
- 15 Antoniou KM, Vasarmidi E, Russell AM, et al. European Respiratory Society statement on long COVID follow-up. *Eur Respir J* 2022; 60: 2102174.
- 16 Brouwers MC, Kerkvliet K, Spithoff K. The AGREE reporting checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016; 352: i1152.
- 17 Chen Y, Yang K, Marusic A, et al. A reporting tool for practice guidelines in health care: the RIGHT statement. *Ann Intern Med* 2017; 166: 128–132.
- 18 Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation’s direction and strength. *J Clin Epidemiol* 2013; 66: 726–735.
- 19 Geng LN, Bonilla H, Hedlin H. Nirmatrelvir-ritonavir and symptoms in adults with postacute sequelae of SARS-CoV-2 infection: the STOP-PASC randomized clinical trial. *JAMA Intern Med* 2024; 184: 1024–1034.
- 20 Rabascall CX, Lou BX, Navetta-Modrov B, et al. Effective use of monoclonal antibodies for treatment of persistent COVID-19 infection in a patient on rituximab. *BMJ Case Rep* 2021; 14: e243469.
- 21 Lau RI, Su Q, Lau ISF, et al. A synbiotic preparation (SIM01) for post-acute COVID-19 syndrome in Hong Kong (RECOVERY): a randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis* 2024; 24: 256–265.
- 22 Myall KJ, Mukherjee B, Castanheira AM, et al. Persistent post-COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. *Ann Am Thorac Soc* 2021; 18: 799–806.
- 23 Torres F, Shedd C, Kaza V, et al. Outpatient management of post-COVID syndrome – single center experience. *Heart Lung* 2024; 67: 137–143.
- 24 Ntiamoah P, Biehl M, Ruesch V, et al. Corticosteroid treatment for persistent pulmonary infiltrates following COVID-19 infection: clearing the fog? *Ann Thorac Med* 2024; 19: 74–80.
- 25 Mizera J, Genzor S, Sova M, et al. The effectiveness of glucocorticoid treatment in post-COVID-19 pulmonary involvement. *Pneumonia (Nathan)* 2024; 16: 2.
- 26 Goel N, Goyal N, Nagaraja R, et al. Systemic corticosteroids for management of ‘long-COVID’: an evaluation after 3 months of treatment. *Monaldi Arch Chest Dis* 2021; 92: 10.4081/monaldi.2021.1981.
- 27 Dhooria S, Chaudhary S, Sehgal IS, et al. High-dose versus low-dose prednisolone in symptomatic patients with post-COVID-19 diffuse parenchymal lung abnormalities: an open-label, randomised trial (the COLDSTER trial). *Eur Respir J* 2022; 59: 2102930.
- 28 Gul S, Demirkol B, Eren R, et al. The clinical, functional, and radiological effect of long-term used immunosuppressive therapy for post-COVID-19 interstitial lung disease. *Sarcoidosis Vasc Diffuse Lung Dis* 2023; 40: e2023049.
- 29 Singh PK, Sharma VK, Lalwani LK, et al. Role of Janus kinase inhibitors in the management of pulmonary involvement due to long COVID-19 disease: a case control study. *Turk J Emerg Med* 2023; 23: 149–155.

- 30 Yomota M, Tanaka M, Kobayashi T, *et al.* Interstitial lung changes and persistent COVID-19 in a patient with follicular lymphoma: a case report. *Respirol Case Rep* 2024; 12: e01298.
- 31 Ohgushi M, Ogo N, Yanagihara T, *et al.* Tacrolimus treatment for post-COVID-19 interstitial lung disease. *Intern Med* 2022; 61: 585–589.
- 32 Pouliopoulou DV, Macdermid JC, Saunders E, *et al.* Rehabilitation interventions for physical capacity and quality of life in adults with post-COVID-19 condition: a systematic review and meta-analysis. *JAMA Netw Open* 2023; 6: e2333838.
- 33 Zeraatkar D, Ling M, Kirsh S, *et al.* Interventions for the management of long COVID (post-COVID condition): living systematic review. *BMJ* 2024; 387: e081318.
- 34 Huang L, Li X, Gu X, *et al.* Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med* 2022; 10: 863–876.
- 35 Ribeiro Carvalho CR, Lamas CA, Visani de Luna LA, *et al.* Post-COVID-19 respiratory sequelae two years after hospitalization: an ambidirectional study. *Lancet Reg Health Am* 2024; 33: 100733.
- 36 Han X, Chen L, Guo L, *et al.* Long-term radiological and pulmonary function abnormalities at 3 years after COVID-19 hospitalisation: a longitudinal cohort study. *Eur Respir J* 2024; 64: 2301612.
- 37 Man MA, Rosca D, Bratosin F, *et al.* Impact of pre-infection COVID-19 vaccination on the incidence and severity of post-COVID syndrome: a systematic review and meta-analysis. *Vaccines (Basel)* 2024; 12: 189.
- 38 Byambasuren O, Stehlik P, Clark J, *et al.* Effect of COVID-19 vaccination on long COVID: systematic review. *BMJ Med* 2023; 2: e000385.
- 39 Chow NKN, Tsang CYW, Chan YH, *et al.* The effect of pre-COVID and post-COVID vaccination on long COVID: a systematic review and meta-analysis. *J Infect* 2024; 89: 106358.
- 40 Watanabe A, Iwagami M, Yasuhara J, *et al.* Protective effect of COVID-19 vaccination against long COVID syndrome: a systematic review and meta-analysis. *Vaccine* 2023; 41: 1783–1790.
- 41 Thompson MG, Stenehjem E, Grannis S, *et al.* Effectiveness of COVID-19 vaccines in ambulatory and inpatient care settings. *N Engl J Med* 2021; 385: 1355–1371.
- 42 Amantadine Therapy for Cognitive Impairment in Long COVID. <https://clinicaltrials.gov/ct2/show/NCT06055244> Date last accessed: 12 February 2026.
- 43 RECOVER-VITAL: Platform Protocol, Appendix to Measure the Effects of Paxlovid on Long COVID Symptoms. <https://clinicaltrials.gov/study/NCT05965726> Date last accessed: 12 February 2026.
- 44 RECOVER-VITAL: Platform Protocol to Measure the Effects of Antiviral Therapies on Long COVID Symptoms. <https://clinicaltrials.gov/ct2/show/NCT05595369>. Date last accessed: 12 February 2026.
- 45 imPROVing Quality of LiFe In the Long COVID Patient (PROLIFIC). <https://clinicaltrials.gov/study/NCT05823896> Date last accessed: 12 February 2026.
- 46 A Decentralized, Randomized Phase 2 Efficacy and Safety Study of Nirmatrelvir/Ritonavir in Adults With Long COVID. <https://clinicaltrials.gov/study/NCT05668091> Date last accessed: 12 February 2026.
- 47 An Open-label, Clinical Feasibility Study of the Efficacy of Remdesivir for Long-COVID (ERASE-LC). <https://clinicaltrials.gov/study/NCT05911906> Date last accessed: 12 February 2026.
- 48 Ensitrelvir for Viral Persistence and Inflammation in People Experiencing Long COVID (PREVAIL-LC). <https://classic.clinicaltrials.gov/ct2/show/NCT06161688> Date last accessed: 12 February 2026.
- 49 Al-Aly Z. SARS-CoV-2 antivirals and post-COVID-19 condition. *Lancet Infect Dis* 2025; 25: 6–8.
- 50 Gerayeli FV, Park HY, Milne S, *et al.* Single cell sequencing reveals cellular landscape alterations in the airway mucosa of patients with pulmonary long COVID. *Eur Respir J* 2024; 64: 2301947.
- 51 Martínez-Pozas O, Corbellini C, Cuenca-Zaldívar JN, *et al.* Effectiveness of telerehabilitation versus face-to-face pulmonary rehabilitation on physical function and quality of life in people with post COVID-19 condition: a systematic review and network meta-analysis. *Eur J Phys Rehabil Med* 2024; 60: 868–877.
- 52 Huth D, Bräscher AK, Tholl S, *et al.* Cognitive-behavioral therapy for patients with post-COVID-19 condition (CBT-PCC): a feasibility trial. *Psychol Med* 2024; 54: 1122–1132.
- 53 Compagno S, Palermi S, Pescatore V, *et al.* Physical and psychological reconditioning in long COVID syndrome: results of an out-of-hospital exercise and psychological-based rehabilitation program. *Int J Cardiol Heart Vasc* 2022; 41: 101080.
- 54 Younesi Bahar S, Matinnia N, Yazdi-Ravandi S. Effect of cognitive therapy based on positive thinking on depression, stress, and anxiety of mothers after recovering from COVID-19. *Advances in Cognitive Sciences* 2023; 25: 95–107.
- 55 Anwar F, Altayb HN, Al-Abbasi FA, *et al.* Antiviral effects of probiotic metabolites on COVID-19. *J Biomol Struct Dyn* 2021; 39: 4175–4184.
- 56 Khani S, Hosseini HM, Taheri M, *et al.* Probiotics as an alternative strategy for prevention and treatment of human diseases: a review. *Inflamm Allergy Drug Targets* 2012; 11: 79–89.
- 57 Jensen S, Thomsen AR. Sensing of RNA viruses: a review of innate immune receptors involved in recognizing RNA virus invasion. *J Virol* 2012; 86: 2900–2910.
- 58 Mendes de Almeida V, Engel DF, Ricci MF, *et al.* Gut microbiota from patients with COVID-19 cause alterations in mice that resemble post-COVID symptoms. *Gut Microbes* 2023; 15: 2249146.

- 59 Marinoni B, Rimondi A, Bottaro F, *et al.* The role of VSL#3 in the treatment of fatigue and other symptoms in long COVID-19 syndrome: a randomized, double-blind, placebo-controlled pilot study (DELong#3). *medRxiv* 2023; preprint [https://doi.org/10.1101/2023.06.28.23291986].
- 60 Eddy RL, Mummy D, Zhang S, *et al.* Cluster analysis to identify long COVID phenotypes using ¹²⁹Xe magnetic resonance imaging: a multicentre evaluation. *Eur Respir J* 2024; 63: 2302301.
- 61 Bramante CT, Buse JB, Liebovitz DM, *et al.* Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. *Lancet Infect Dis* 2023; 23: 1119–1129.
- 62 Olawore O, Turner LE, Evans MD, *et al.* Risk of post-acute sequelae of SARS-CoV-2 infection (PASC) among patients with type 2 diabetes mellitus on anti-hyperglycemic medications. *Clin Epidemiol* 2024; 16: 379–393.
- 63 Johnson SG, Abedian S, Sturmer T, *et al.* Prevalent metformin use in adults with diabetes and the incidence of long COVID: an EHR-based cohort study from the RECOVER program. *Diabetes Care* 2024; 47: 1930–1940.
- 64 Adegunsoye A, Baccile R, Best TJ, *et al.* Pharmacotherapy and pulmonary fibrosis risk after SARS-CoV-2 infection: a prospective nationwide cohort study in the United States. *Lancet Reg Health Am* 2023; 25: 100566.
- 65 Grana C, Ghosn L, Evrenoglou T, *et al.* Efficacy and safety of COVID-19 vaccines. *Cochrane Database Syst Rev* 2022; 12: CD015477.
- 66 Fernandez-de-Las-Penas C, Torres-Macho J, Catahay JA, *et al.* Is antiviral treatment at the acute phase of COVID-19 effective for decreasing the risk of long-COVID? A systematic review. *Infection* 2024; 52: 43–58.
- 67 Jiang J, Li Y, Jiang Q, *et al.* Early use of oral antiviral drugs and the risk of post COVID-19 syndrome: a systematic review and network meta-analysis. *J Infect* 2024; 89: 106190.
- 68 Use and Effectiveness of COVID-19 Vaccines Using State Vaccine Registries and Insurance Claims Data. 2023. https://clinicaltrials.gov/study/NCT05876377 Date last accessed: 12 February 2026.
- 69 PAXlovid loNg cOvid-19 pRevention triAl With recruitMent In the Community in Norway (PanoramicNOR). 2023. https://clinicaltrials.gov/study/NCT05852873 Date last accessed: 12 February 2026.
- 70 COVID-19 Vaccination Status and The Clinical Outcomes of Long COVID-19 Patients (SURVIVOR). https://clinicaltrials.gov/study/NCT05587868 Date last accessed: 12 February 2026.
- 71 Hammond J, Leister-Tebbe H, Gardner A. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. *N Engl J Med* 2022; 386: 1397–1408.
- 72 Beatty RM. Long COVID-19 symptoms remedied by anti-viral treatment in neurosurgical patients. *Am J Infect Dis* 2023; 19: 39–44.
- 73 Stewart DD. Can nitazoxanide and/or other anti-viral medications be a solution to long COVID? Case report with a brief literature review. *Clin Case Rep* 2023; 11: e8162.
- 74 Cohen AK, Jaudon TW, Schurman EM, *et al.* Impact of extended-course oral nirmatrelvir/ritonavir in established long COVID: a case series. *Commun Med* 2025; 4: 261.
- 75 Visvabharathy L, Orban ZS, Koralnik IJ. Case report: treatment of long COVID with a SARS-CoV-2 antiviral and IL-6 blockade in a patient with rheumatoid arthritis and SARS-CoV-2 antigen persistence. *Front Med (Lausanne)* 2022; 9: 1003103.
- 76 Anti-SARS-CoV-2 Monoclonal Antibodies for Long COVID (COVID-19). www.clinicaltrials.gov/expert-search?term=NCT05877508 Date last accessed: 12 February 2026.
- 77 Long-term Follow-up of a Randomized Multicenter Trial on Impact of Imatinib and Infliximab on Long-COVID in Hospitalized COVID-19 Patients. www.clinicaltrials.gov/expert-search?term=NCT05220280 Date last accessed: 12 February 2026.
- 78 To Evaluate the Safety and Efficacy of Meplazumab in Treatment of Post-COVID-19. www.clinicaltrials.gov/expert-search?term=NCT05813587 Date last accessed: 12 February 2026.
- 79 Impact of Monoclonal Antibody Treatment on Post-Acute COVID-19 Syndrome (MABPACs). www.clinicaltrials.gov/expert-search?term=NCT05013723 Date last accessed: 12 February 2026.
- 80 Ranisavljev M, Stajer V, Todorovic N, *et al.* The effects of 3-month supplementation with synbiotic on patient-reported outcomes, exercise tolerance, and brain and muscle metabolism in adult patients with post-COVID-19 chronic fatigue syndrome (STOP-FATIGUE): a randomized placebo-controlled clinical trial. *Eur J Nutr* 2024; 64: 28.
- 81 Maftai NM, Raileanu CR, Balta AA, *et al.* The potential impact of probiotics on human health: an update on their health-promoting properties. *Microorganisms* 2024; 12: 234.
- 82 Gerayeli FV, Eddy RL, Sin DD. A proposed approach to pulmonary long COVID: a viewpoint. *Eur Respir J* 2024; 64: 2302302.
- 83 Lasheen H, Abou-Zeid MA. Olfactory mucosa steroid injection in treatment of post-COVID-19 olfactory dysfunction: a randomized control trial. *The Egyptian Journal of Otolaryngology* 2023; 39: 118.
- 84 Hosseinpour M, Kabiri M, Rajati Haghi M, *et al.* Intranasal corticosteroid treatment on recovery of long-term olfactory dysfunction due to COVID-19. *Laryngoscope* 2022; 132: 2209–2216.
- 85 Vaira LA, Hopkins C, Petrocelli M, *et al.* Efficacy of corticosteroid therapy in the treatment of long-lasting olfactory disorders in COVID-19 patients. *Rhinology* 2021; 59: 21–25.

- 86 Vento MG, Marinelli C, Ferrari L, et al. Recovery of smell and taste in patients with persistent COVID-19-related hyposmia and dysgeusia by targeting inflammation and endothelial dysfunction. *Cureus* 2024; 16: e54925.
- 87 Kim S, D'Anniballe VM, Finlay JB, et al. Analysis of mucosal immune dysregulation and safety and tolerability of endoscopic topical steroid therapy for long-COVID hyposmia: randomized, double-blinded pilot study. *Commun Med (Lond)* 2025; 6: 60.
- 88 Asvapoositkul V, Samuthpongton J, Aeumjaturapat S, et al. Therapeutic options of post-COVID-19 related olfactory dysfunction: a systematic review and meta-analysis. *Rhinology* 2023; 61: 2–11.
- 89 Wu TJ, Yu AC, Lee JT. Management of post-COVID-19 olfactory dysfunction. *Curr Treat Options Allergy* 2022; 9: 1–18.
- 90 Rinaldi E, Tomelleri A, Campochiaro C, et al. Efficacy of interleukin-1 blockade with anakinra in the management of post-COVID-19 steroid-dependent multisystem inflammatory syndrome: a case report. *Scand J Rheumatol* 2023; 52: 230–232.
- 91 Yadav S, Bonnes SL, Gilman EA, et al. Inflammatory arthritis after COVID-19: a case series. *Am J Case Rep* 2023; 24: e939870.
- 92 Immunotherapy for Neurological Post-Acute Sequelae of SARS-CoV-2 (IN-PASC). 2022. <https://clinicaltrials.gov/study/NCT05350774> Date last accessed: 12 February 2026.
- 93 REVERSE-Long COVID: A Multicenter Randomized, Placebo-Controlled Clinical Trial of Immunomodulation (With Baricitinib) for Long COVID Related Cognitive Impairment and ADRD (Alzheimer's Disease and Related Dementias). 2023. <https://clinicaltrials.gov/study/NCT05858515> Date last accessed: 12 February 2026.
- 94 Intravenous Immunoglobulin Replacement Therapy for Persistent COVID-19 in Patients With B-cell Impairment: a Multicenter Randomized Controlled Trial. 2023. <https://clinicaltrials.gov/study/NCT06159283> Date last accessed: 12 February 2026.
- 95 Safety and Efficacy of Anakinra Treatment for Patients With Post Acute Covid Syndrome (PRECISION). 2023. <https://clinicaltrials.gov/ct2/show/NCT05926505>. Date last accessed: 12 February 2026.
- 96 Randomized Double-Blind Placebo-Controlled Trial Evaluating Baricitinib on PERSistent NEurologic and Cardiopulmonary Symptoms of Long COVID (REVERSE-LC). 2024. <https://clinicaltrials.gov/study/NCT06631287>. Date last accessed: 12 February 2026.
- 97 RECOVER-AUTONOMIC: A Platform Protocol for Evaluation of Interventions for Autonomic Dysfunction in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC). 2024. <https://clinicaltrials.gov/study/NCT06305780>. Date last accessed: 12 February 2026.
- 98 Kuut TA, Müller F, Csorba I, et al. Efficacy of cognitive-behavioral therapy targeting severe fatigue following coronavirus disease 2019: results of a randomized controlled trial. *Clin Infect Dis* 2023; 77: 687–695.
- 99 Melamed E, Rydberg L, Ambrose AF, et al. Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of neurologic sequelae in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). *PM R* 2023; 15: 640–662.
- 100 Nwankwo H, Mason J, Underwood M, et al. Cost-effectiveness of an online supervised group physical and mental health rehabilitation programme for adults with post-COVID-19 condition after hospitalisation for COVID-19: the REGAIN RCT. *BMC Health Serv Res* 2024; 24: 1326.
- 101 World Health Organization. Clinical Management of COVID-19: Living Guideline. Geneva, World Health Organization (WHO), 2022.
- 102 Canadian Guidelines for Post COVID-19 Condition (CAN-PCC). Recommendations. <https://can-pcc.reccmap.org/recommendations> Date last accessed: 12 February 2026.