



Long COVID: Diagnosis and Treatment of Respiratory Syndrome in Post COVID-19 Conditions

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Abstract

The ongoing COVID-19 pandemic has given rise to another medical burden that came from the symptoms experienced by patients after acute infection with SARS-CoV-2, a condition often called as Long COVID. As the number of COVID-19 cases remain rising, various studies and scientific researches are being conducted to understand more about Long COVID, and findings have consistently shown increased burden due to Long COVID that needs more attention from the clinical world. This article review collects various sources regarding the diagnosis and management of respiratory syndrome in post-COVID-19 conditions. Long COVID, currently referred to as a post-COVID-19 condition, consists of symptom(s) that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, with symptoms lasting at least two months and cannot be explained by any alternative diagnosis. Symptoms that occur are very diverse from various organ systems, including the respiratory system. Knowledge regarding the possible symptoms as well as a thorough evaluation is needed to identify and diagnose post-COVID-19 conditions, and multidisciplinary management through a tiered system may help reach more cases of post-COVID-19 conditions. The treatment for post-COVID-19 conditions needs to be adjusted to the patient's condition, and the administration of pharmacological therapy such as steroids, bronchodilators, and mucolytics/antioxidants has to be based on clinical symptoms and radiological abnormalities.

Keywords: Long COVID, post-COVID-19 conditions

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Submitted: February 24th, 2022

Accepted: April 26th, 2022

Published: July 30th, 2022

J Respirol Indones. 2022

Vol. 42 No. 3: 250–6

<https://doi.org/10.36497/jri.v40i3.279>

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INTRODUCTION

The term Long COVID first appeared and was highlighted on social media in May 2020 by Perego to refer to the condition of persistent symptoms after acute SARS-CoV-2 infection. The symptoms experienced can be the same as the acute condition of COVID-19 and new symptoms. The spectrum of symptoms experienced is also very wide, ranging from cardiorespiratory, digestive, neuromusculoskeletal to psychiatric symptoms.^{1–4}

There is no agreement on the definition and terminology for this condition, with several other names such as long haulers, post-COVID syndrome, post-acute COVID-19, sequelae post-acute COVID-19, and chronic COVID syndrome referring to the same condition.⁵

In October 2021, World Health Organization (WHO) released special case definitions for post-COVID-19 conditions from studies using the Delphi

consensus method. This consensus involved clinicians and expert researchers, and patients with post-COVID-19 conditions.⁵

This study defines post-COVID-19 conditions as:

1. Conditions in individuals with a history of confirmed or probable COVID-19 infection usually occur within three months after COVID-19, and symptoms persist for at least two months. Another diagnosis cannot explain them.
2. Common symptoms include fatigue, shortness of breath, cognitive dysfunction, and other symptoms that generally affect daily living functioning.
3. No minimum of symptoms required for diagnosis.
4. Symptoms can be new-onset after recovering from acute COVID-19 infection, or symptoms persist since acute COVID-19 and may fluctuate or relapse over time.

5. Different definitions can be found in children.

The Indonesian Society of Respiriology or Persatuan Dokter Paru Indonesia (PDPI) Clinical Practice Guideline on COVID-19 also adopted the definition from the study and defined Long COVID as: A post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19, with symptoms lasting at least two months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, and cognitive dysfunction that impact daily functioning. Symptoms may develop after recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms can also fluctuate or recur from time to time.⁶

The increase in COVID-19 cases due to Omicron variants currently raises a new question: Can infection with Omicron variants also cause post-COVID-19 conditions? Scientists' opinions are currently divided, and further studies are needed regarding the incidence of post-COVID-19 conditions in cases of Omicron infection, considering that this variant was newly discovered in November 2021, so there are no studies that can show its effect on the incidence of post-Covid-19 conditions. Dr. Anthony Fauci believes that post-COVID-19 conditions can occur due to any infection variant, with a history of mild or severe symptoms. Meanwhile, other scientists predict that Omicron will not increase the incidence of post-COVID-19 conditions because its infection does not cause a persistent increase in inflammatory markers in the body.⁷

OVERVIEW

A. Diagnostic Approach

History and Physical Examination

At the first visit of a patient suspected of having a post-Covid-19 conditions, a complete history and physical examination is required to obtain all the symptoms and complaints of a post-COVID-19 conditions covering various systems. Although clinical manifestations can be categorized based on the system with predominant complaints, it does not

mean that complaints in other systems can be immediately ruled out.^{8,9} Some important points in the history of post-COVID-19 conditions that need to be considered are:

1. History of acute COVID-19 infection, both confirmed and suspect.
2. Complaints during acute infections and current complaints.
3. Onset and duration of complaints after COVID-19 infection compared to the beginning of acute infection.
4. Comorbid history and other diseases.^{1,8}

Guideline or *Panduan Praktik Klinik* (PPK) PDPI said the history that can be explored in suspicion of post-COVID-19 conditions is as following:¹⁰

1. Patient history of possible or confirmed COVID-19.
2. There are symptoms/lung and breathing disorders that are permanent > 4 weeks of the onset of COVID-19 symptoms.
3. There are one or more of the following symptoms and signs:
 - a) Non-productive or productive cough
 - b) Shortness of breath/heavy breathing/breathing panting/easily tired
 - c) Limited activity
 - d) Chest pain
 - e) Throat pain or itchy throat.

Possible other etiologies besides post-COVID-19 conditions in each complaint need to be studied thoroughly in patients to eliminate the differential diagnosis. On a general examination, it is also necessary to give attention to danger signs such as hypoxemia or desaturation, cardiac chest pain, and Multisystem Inflammatory Syndrome in Children (MIS-C) that need immediate treatment. The physical examination can shows normal findings or abnormalities, thus the findings of routine physical examination do not rule out the possibility of diagnosis.^{6,9}

Supporting Examination

The minimum essential supporting examination that can be done on examination of post-

COVID-19 conditions is a complete blood test, kidney function, liver function, electrolytes, inflammatory markers, ECG, and plain chest x-ray.² PDPI demonstrates complete supporting examinations for diagnosis and management of respiratory syndrome on post-Covid-19 conditions, including:

1. Laboratory tests in the form of complete blood tests, CRP, ferritin, SGOT, SGPT, ureum, creatinine, blood sugar, HbA1c, blood gas analysis, electrolyte, D-dimer, PT, APTT, Fibrinogen, IgM and IgG antibodies of SARS-CoV-2, and PCR SARS-CoV-2 (according to indications).
2. Measurement of peripheral oxygen saturation (SpO₂).
3. Radiological examination in the form of AP/PA chest x-ray, thoracic ultrasound, chest CT scan, and lung perfusion scan (according to indications).
4. Lung function examination in the form of a 6-minute walking test, diffusion capacity, and cardiopulmonary exercise test.
5. ECG examination.
6. Bronchial provocation test (according to indications).
7. Assessment of quality of life through questionnaires, such as the World Health

Organisation Quality of Life assessment (WHOQOL) questionnaire instrument.⁶

In addition, the supporting examination needed to rule out the differential diagnosis also needs to be done according to patient complaints, as listed in Table 1.^{2,8}

In addition to laboratory supporting examinations, the use of tools for diagnosis and scoring can help assess patient complaints and see the effects of post-COVID-19 conditions on daily life. Table 2 shows the types of examination tools used in the post-COVID-19 diagnosis approach.⁸ Some diagnosis of differential respiratory complaints in post-COVID-19 conditions are as follows:⁶

1. Nasopharyngitis or pharyngitis
2. Acute bronchitis
3. Bacterial pneumonia
4. Pulmonary tuberculosis
5. Interstitial pulmonary disease
6. Lung embolism
7. Heart failure
8. Kidney failure
9. Chronic obstructive pulmonary disease (COPD)
10. Asthma
11. Bronchiectasis
12. Obstructive Sleep Apnea Syndrome (OSAS)
13. Mycosis

Table 1. Additional supporting examination according to complaints for differential diagnosis^{2,8}

Category	Laboratory Test
Rheumatologic condition	Antibody antinuclear, rheumatoid factor, anti-cyclic citrullinated peptide, anti-cardiolipin, and creatine phosphokinase
Coagulase disturbance	D-dimer, fibrinogen
Myocardial injury	Troponin
Distinguishes pulmonary cardiac symptoms	<i>B-type natriuretic peptide</i>

Table 2. Inspection tools according to complaints for post-COVID-19 conditions⁸

Category	Inspection Tools
Functional/quality of life status	Patient-Reported Outcomes Measurement Information System (PROMIS) (e.g., Cognitive Function 4a); Post-COVID-19 Functional Status Scale (PCFS); EuroQol-5D (EQ-5D)
Respiratory Conditions	Modified Medical Research Council Dyspnea Scale (mMRC)
Neurology Conditions	Montreal Cognitive Assessment (MoCA); Mini Mental Status Examination (MMSE); Compass 31 (for dysautonomia); Neurobehavioral Symptom Inventory
Psychiatrist condition	General Anxiety Disorder-7 (GAD-7); Patient Health Questionnaire-9 (PHQ-9); PTSD Symptom Scale (PSS); Screen for Posttraumatic Stress Symptoms (SPTSS); PTSD Checklist for DSM-5 (PCL-5); Impact of Event Scale-Revised (IESR); Hospital Anxiety and Depression Scale (HADS)
Physical activity capacity	1-minute sit-to-stand test; 2-minute step test; 10 meter walk test (10MWT); 6-minute walk test
Balance and risk of falling	BERG Balance Scale; Tinetti Gait and Balance Assessment Tool
Other	Wood Mental Fatigue Inventory (WMFI); Fatigue Severity Scale; Insomnia Severity Index (ISI); Connective Tissue Disease Screening Questionnaire; Tilt-table testing (e.g., for POTS); Orthostatic HR assessment

B. Management

Management of post-COVID-19 conditions need to be done in a planned program because it requires a multidisciplinary evaluation and periodic evaluation approach. Patient visits to management of post-COVID-19 conditions are recommended to be done at least three times, including:

1. The first visit as an initial assessment, to plan further examination and management by working diagnosis. This examination can be carried out in the 4th week after the COVID-19 infection, with the condition of the PCR swab of the patient has been negative.
2. The second visit to evaluate the findings of the first examination and adjust the diagnosis and management with the results of new examinations. This examination is carried out in weeks 8-10 after the COVID-19 infection.
3. The third visit was conducted for the evaluation of complaints and evaluation of the long-term complaints experienced by patients.^{2,8}

Multidisciplinary Management

In post-COVID-19 conditions management, especially in cases that experience multiorgan symptoms, a multidisciplinary approach and referral to related specialists are needed, especially for further complaints of pulmonology, cardiology, and psychiatry.^{2,8,9}

For this reason, NHS suggested that there are three levels of team handling teams after Covid-19, namely:¹⁰

1. Level 1, Covid Multidisciplinary Team (MDT), which handles post-COVID-19 patients with prolonged symptoms (>3 months) or multidisciplinary cases, with complaints that interfere with the independence of patients in daily activities and require input from ≥ 2 professionals. This team can include pulmonologist, cardiologist, medical rehabilitation, nurses, physiotherapists, occupational therapists, dietitians, coordinators, researchers, team managers, and administrative support officers.

2. Level 2, the Community Therapy Team, which handles post COVID-19 patients with mild/medium complexity, requires input from 1 professional discipline.
3. Level 3, primary service, which handles post COVID-19 patients with mild symptoms that last for 1–2 months, can recover with independent management.

Noteworthy for multidisciplinary management is the need for a system of recognition of cases of post-COVID-19 conditions, a multidisciplinary team that is pursued, and a referral system between service levels.

Some management that can be given to patients in primary services are:^{2,9,11}

1. Medical management such as antibiotics if secondary infections are found and symptomatic such as paracetamol and NSAIDs.
2. Self Management Guidance Complaints, including determining realistic targets for the development of complaints, connecting with support groups, and contacting for further consultation.
3. Optimal management for accompanying diseases.
4. Rehabilitation guidance and planning for complaints

Post-COVID-19 Respiratory Syndrome Management

In general, patients with the post-COVID-19 respiratory syndrome can be given non-pharmacological therapy in the form of:⁶

1. Maintain a healthy lifestyle
2. Eat balanced nutrition
3. Get enough rest and meditation
4. Do the exercise gradually if it can be done
5. Breathing exercises for patients with shortness of breath
6. Olfactory exercises for patients with complaints of anosmia
7. Quit smoking
8. Keep applying the health protocols (wearing masks, washing hands, maintaining distance, avoiding crowds, limiting mobility)

9. SARS-COV-2 vaccination one month after recovery in patients with mild-moderate symptoms and three months later in patients with severe-critical symptoms.

For pharmacological therapy, management of the syndrome is adjusted to the patient's condition, including: (a) clinical symptoms are absent, radiological abnormalities are present; (b) clinical symptoms are present, radiological abnormalities are not present; and (c) clinical symptoms are present, radiological abnormalities are present. The treatments given are pharmacological therapy, pulmonary rehabilitation, oxygen therapy, nutritional therapy, and psychotherapy.⁶ The management

algorithm for each patient condition recommended by PDPI can be seen in Figure 1.

Supportive examinations for evaluation that can be carried out are laboratory, radiology, and lung function tests, and the need for additional examinations based on complaints and the results of these supporting examinations. This is necessary to monitor the repair of lung parenchymal damage due to SARS-CoV-2 infection. In patients with post-COVID inflammatory lung disease, corticosteroids can be given, while other treatments such as preventing pulmonary fibrosis after acute infection using antifibrotic therapy are still in the research stage.¹

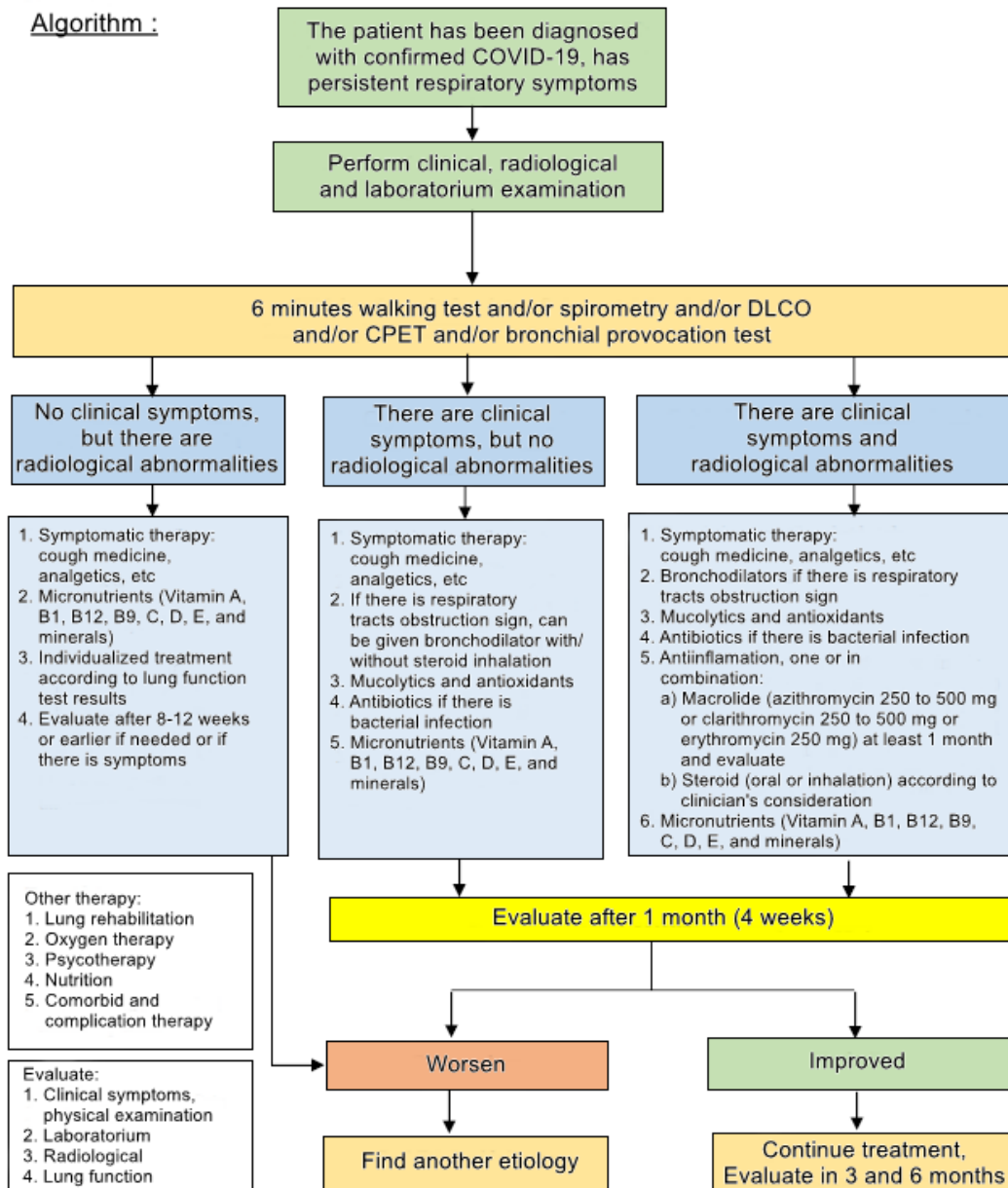


Figure 1. Post-COVID-19 respiratory syndrome management algorithm from PDPI¹²

Steroid Use

A cohort study conducted by Myall KJ et al.¹² in post-COVID-19 patients with evidence of interstitial lung disease (ILD) at 4 weeks post-discharge from treatment for acute infections demonstrated a benefit of steroid use on ILD improvement in patients assessed based on patient complaints, lung function (FEV₁ and FVC), and chest CT scan imaging. In this study, patients were given a maximum initial dose of 0.5 mg/kg prednisolone and then tapered off for up to 3 weeks.

The key to giving steroids to improve ILD in post-COVID-19 patients is the early recognition of ILD cases by a multidisciplinary team so that patients can be given immediate intervention.¹²

Use of Bronchodilators

A study by Maniscalco M et al.¹³ evaluated the effect of administering a bronchodilator of 400 g salbutamol to post-COVID-19 patients with a maximum time of 2 months from the onset of acute infection. This study shows an increase in FEV₁ and FVC in post-COVID-19 patients, both those with COPD and concomitant asthma, so bronchodilators should be considered for patients with obstructive symptoms.

It should be noted that this improvement in lung function, when compared with similar studies before the pandemic, showed a lower increase in FEV₁ and FVC, i.e., a 41.8 mL increase in FEV₁ in the post-COVID-19 study compared to 77.2 mL in the pre-pandemic healthy study population. This is suspected as a result of persistent lung damage in post-COVID-19 patients.

Mucolytic/Antioxidant Use

The use of mucolytics/antioxidants is recommended in patients with obstructive disorders such as COPD, and in post-COVID-19 patients with multiple obstructive disorders, these drugs may be considered. The comparative analysis study of Rogliani P et al.¹⁴ showed that erdosteine, carboxysteine, and N-acetylcysteine significantly reduced the risk of acute exacerbations of COPD. Among the three types of mucolytics/antioxidants,

erdosteine showed the highest efficacy and the most minor side effects.

Evaluation of Post-COVID-19 Condition Management

The evaluation was carried out at 1 month, 3 months, and 6 months post-therapy by monitoring:

1. Clinical symptoms
 - a) Cough (evaluate changes in cough symptoms)
 - b) Shortness of breath (evaluate changes in breathlessness)
 - c) Chest pain (evaluate changes in chest pain)
2. Recovery from illness (COVID-19)
3. Physical examination of the lungs, including assessment of oxygen saturation (SpO₂)
4. Laboratory examination (as needed)
5. Radiological (evaluate residual lung lesions radiologically)
6. Examination of lung function (evaluation of improvement in lung function)

CONCLUSION

Post-COVID-19 conditions occur in individuals with a history of possible or confirmed SARS-CoV-2 infection with symptoms that last at least two months and cannot be explained by an alternative diagnosis. Symptoms are very diverse from various organ systems, including the respiratory system. Knowledge of the complaints that can be experienced, as well as a thorough evaluation to identify and diagnose post-COVID-19 conditions, and multidisciplinary management through a tiered system can help reach cases of post-COVID-19 conditions. The treatment given needs to be adjusted to the patient's condition, and the administration of pharmacological therapy such as steroids, bronchodilators, and mucolytics/antioxidants needs to be based on clinical symptoms and radiological abnormalities.

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