

The Chronic Effects of COVID-19 or “Long COVID”

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Abstract

The term “long COVID” is used to refer to patients who have persisting symptoms for 4 weeks or more after onset of COVID-19. The prevalence of these symptoms is reported to range from 10-80%. The commonest symptoms include fatigue, dyspnoea, chest pain, hair loss, loss of sense of taste and smell, cognitive difficulties, anxiety and depression. Serious complications in this period include thrombo embolic events (stroke, myocardial infarction, limb ischemia and venous thromboembolism), infections, pulmonary fibrosis and multi system inflammatory syndrome. Patients with post COVID-19 symptoms should be first evaluated in primary care and those with serious issues referred to appropriate specialties. The others should be provided with supportive and symptomatic care including respiratory care, nutrition, immunization, mental health support, management of comorbidities and if indicated anticoagulation and treatment of infections. The routine use of steroids, antifibrotics, anticoagulants, anti depressants and antibiotics in these patients should be avoided.

Keywords: long COVID, post acute COVID-19, chronic COVID-19, fatigue, thromboembolism, dyspnoea, pulmonary fibrosis

Introduction

It is now being increasingly recognized that many people infected with COVID-19 continue to experience disabling symptoms weeks to months after recovery from the acute illness and are unable to return to their normal life.^[1] These post COVID-19 symptoms also termed as “long COVID” or “long haulers” cause considerable morbidity in the affected population.^[2] While it is reasonable to expect persistent symptoms in patients with severe COVID-19, this syndrome also afflicts patients with mild symptoms and those treated on an outpatient basis.^[3] The purpose of this article is to explore this syndrome in a frequently asked question (FAQ) fashion and guide practising physicians in the management of this phenomenon.

How do we define “long COVID”?

While several definitions have been proposed the most widely accepted is classification of this syndrome

into “ongoing symptomatic COVID” as symptoms experienced between 4 weeks up to 12 weeks from the onset of first symptom of COVID-19 and “Post COVID syndrome” as symptoms experienced for more than 12 weeks after onset of the first symptom of COVID-19.^[4] Absence of an alternative diagnosis is an important inclusion criteria. A prior positive RT PCR/ antigen test is not essential for the diagnosis as many people may not have been tested or could have tested negative.

How prevalent is problem of post-acute COVID-19/ long COVID?^[4,5]

There have been many studies from different countries that have described these symptoms and their prevalence (Table 1). Unfortunately we do not have studies from India yet. These studies report very high prevalence of post-acute symptoms in COVID pa-

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tients ranging from 30-80%. The UK COVID-19 symptom study in which COVID patients were asked to report the symptoms on a mobile application reports the prevalence of post COVID-19 symptoms in 10% of the patients ⁽⁶⁾. The most prevalent symptoms of long COVID are fatigue, dyspnoea, chest pain, joint pain, palpitations, anosmia and dysgeusia, hair loss, cognitive symptoms (memory and attention deficits) and psychosocial distress (loneliness, anxiety, depression and sleep disorders). It was also observed that symptoms were relapsing and remitting with bad days and good days.

Even if we assume that less than 10% of patients with COVID-19 have long COVID, assuming a total worldwide burden of 130 million infections till date, the numbers of patients suffering from these symptoms will be staggering.^[7]

Serious post COVID-19 effects include persisting hypoxemia, infections, thromboembolic episodes and cardiac dysfunction. In the study from 38 Michigan hospitals, USA, 6.7% patients had died by day 60 of discharge and 15% had needed readmission.^[8]

Who are the people who are likely to get long COVID?

It is obvious that people who have been sicker, hospitalized and required critical care have more chronic symptoms than patients with milder disease. A study by Halpen et al reported that patients with higher body mass index, pre-existing respiratory disease are likely to have more post discharge symptoms.^[9] In a Chinese study the prevalence of symptoms at 6 months follow up was more in women than in men and more in older than younger people.^[10]

In another study from the UK, persistent cough, hoarse voice, headache, diarrhoea, skipping meals, and shortness of breath in the first week were predictive of a two to three times greater risk for longer term symptoms.^[11]

Table 1: Studies reporting on post-acute COVID-19 symptomatology ^[4,5]

| Country | Population and methods | Findings |
|-------------------|--|---|
| China | 1733 hospitalized patients (75% needed oxygen and 4% ICU care) with in person evaluation at 6 months with investigations | 76% had at least 1 symptom Fatigue 63%, sleep difficulties 26%, anxiety/ depression 23%, loss of sense of smell/ taste 7/11%, hair loss 22% |
| USA | 1250 hospitalized patients with telephone survey at 60 days | 7% had died, 15% required readmission 488 completed survey; 32% had symptoms, 18% worsening symptoms, dyspnoea 23%, cough, 15% and loss of taste/ smell 13% |
| Italy | 143 hospitalized patients FU at 60 days | 87% had persistent symptoms, 55% had 3 or more symptoms. Fatigue 53%, dyspnoea 43%, joint pains 27%, chest pain 21% and decline in quality of life by 44% |
| France | 150 patients with non-critical illness | 2/3 had persistent symptoms 1/3 had symptoms that were worse than the acute illness |
| UK | 110 hospitalized patients (75% required oxygen and 16% ICU) at 3 months | Any symptom 74%, fatigue 39%, joint pain 4.5%, dyspnoea 24%, cough 12%, chest pain 12%, loss of taste and smell 12%, |
| Spain | 277 hospitalized patients 8% required ICU care at 3 and 4 months FU | At 3 months: 3 or more symptoms 50%, fatigue 35%, joint pain/ muscular pain 20%, dyspnea 34%, cough 21%, loss of taste/ smell 21%, headache 18% In the same study the symptoms had significantly declined at 4 months |
| France | 120 hospitalized (20% needed ICU care) at 3-4 months | Fatigue 55%, dyspnoea 41%, cough 16%, chest pain 11%, sleep disturbances 30%, loss of taste and smell 10/13%, hair loss 20% |
| Systematic review | 15 studies, 47,910 patients 14-110 days of follow up | Any symptom 80%, fatigue 58%, headache 44%, attention disorder 27%, hair loss 25%, dyspnoea 24% |

What is the pathophysiologic mechanism for chronic symptoms of COVID-19?^[4]

Similar syndromes were also reported in patients recovering from SARS and MERS infections, though in MERS this was seen only in those who had severe disease.

The exact cause for long COVID-19 are not known. It is believed that these symptoms may be due to persistent viremia due to weak or absent antibody response, inflammatory and other immune reactions, procoagulant state, deconditioning, mental factors and stress all contribute. It is also believed that following a state of widespread immune activation there is a phase of immune paresis that leads to increased susceptibility to infections.

In fact many of the manifestations of long COVID overlap with those of chronic fatigue syndrome/ myalgic encephalomyelitis (CFS/ME) the pathogenesis of

which is also believed to be a viral infection triggering an aberrant immune response.^[12]

What are the manifestations of long COVID?

Fever

Prolonged and persistent fever is sometimes seen in patients recovering from COVID-19. These patients complain of fever ranging from 99-100°F daily with exhaustion and fatigue (personal experience). Often this fever is dismissed as a consequence of aggressive temperature monitoring, but the truth is that many patients feel unwell. This fever may or may not be associated with raised inflammatory markers and may or may not respond to paracetamol and NSAIDs.

Hematologic^[4]

The most striking hematologic manifestation is the procoagulant state induced by COVID-19. While the risk is greatest in hospitalized patients with severe disease, thromboembolic episodes are known to occur after discharge and even in those patients with mild disease. In some patients occurrence of a thrombotic event draws attention to the previous COVID infection which was often mild and undocumented. This procoagulant state manifests as stroke, myocardial infarction, limb ischemia/gangrene, deep vein thrombosis with pulmonary embolism. The overall prevalence of these complications is believed to be < 5% of all patients. A study of 163 patients from the United States where no post discharge thrombo prophylaxis was given reported a 2.5% cumulative incidence of thrombosis at 30 days following discharge at a median duration of 23 days post-discharge. In this same study, there was a 3.7% cumulative incidence of bleeding at 30 days post-discharge, mostly related to mechanical falls. A prospective study from Belgium at 6 weeks post-discharge follow-up assessed d-dimer levels and venous ultrasound in 102 patients; 8% received post-discharge thrombo prophylaxis. Only one asymptomatic venous thromboembolism (VTE) event was reported. Similarly, no deep venous thrombosis (DVT) was seen in 390 participants who had ultrasonography of lower extremities in the post-acute COVID-19 Chinese study. Larger ongoing studies, such as CORONA-VTE, CISCO-19 and CORE-19, will help to establish more definitive rates of such complications.

Pulmonary^[4]

Many patients with severe COVID-19 disease have residual pulmonary dysfunction at discharge with concern about development of fibrosis in the long term. Some patients are discharged on home oxygen therapy (6% in the USA post COVID study) and some with

tracheostomies. Fifty percent of patients in a national cohort study from Spain who had undergone tracheostomies for COVID-19 could not be decannulated before discharge.

Dyspnoea is a common complaint in these patients as well as even in those who did not have significant pulmonary involvement. Apart from pulmonary parenchymal involvement, dyspnoea is also due to deconditioning, neuromuscular weakness and psychologic causes. Cough is another frequent complaint that often interferes with sleep.

Studies in patients with severe COVID-19 at 3-6 months follow up show reduced diffusion capacity, restriction of lung function and abnormal CT findings.^[4] In the first of its kind of study in India, 42 discharged patients with COVID pneumonia were evaluated with lung function tests at 6-8 weeks and 12-16 weeks post discharge and CT scan at 3 months post discharge.^[13] At the first follow up, 80% demonstrated abnormal diffusion capacity and 48% had restrictive lung defect (FVC < 80% of normal). However at the 2nd follow up at 12-16 weeks there was significant improvement with 30% having normal DLCO and 80% having normal FVC. The baseline CT scan was abnormal in all with mean lung involvement of 50% and 50% had features of organizing pneumonia. By 3 months 25% had normal CT scan and others had residual abnormalities though improved as compared to before. It is notable that none of the study patients at our hospital had received antifibrotics or prolonged steroids. Hence this recovery can be attributed to natural course of the disease. Studies from other centres have also reported good recovery in lung function and CT abnormalities in COVID-19 patients over 1 year suggesting that long term prognosis of lung abnormalities appears good and similar to that seen with influenza and other viral ARDS.

Cardiac^[4]

Cardiac involvement in acute COVID-19 can manifest as myocarditis, myocardial infarction and arrhythmias. Interestingly follow up cardiac MRI studies even in asymptomatic athletes have shown evidence of myocardial inflammation in 15% and previous myocardial injury in 30% of the patients. Chest pain and palpitations are common symptoms reported in follow up studies. Other complications include inappropriate sinus tachycardia and postural orthostatic tachycardia syndrome. Myocardial infarction (MI) due to the procoagulant state during the follow up period is also reported. It is difficult to establish causality with COVID-19 in patients with MI who already have atherosclerotic coronary artery disease. However occur-

rence of MI in young patients with no antecedent risk factors for CAD does implicate COVID-19 in causation in these patients.

Neuropsychiatric^[4]

A post viral syndrome consisting of malaise, fatigue, myalgia, depressive symptoms and non-restorative sleep is commonly seen even in those with non-severe disease. Migraine like headaches are also common. Around 10-15% complain of absence of sense of smell and taste at 3-4 months which also contributes to anorexia and depression. Anxiety about when these sensations will return is commonly observed (personal observation). Parosmia (altered smell) may also be seen which is even more distressing. Cognitive impairment also called "brain fog" which manifests as defects in concentration, memory, language and executive functions is disabling. Additionally, patients discharged from critical care units have other sequelae such as critical illness neuromyopathy and hypoxic anoxic damage.

COVID-19 patients on follow up manifest a range of psychiatric problems including post traumatic stress disorder (PTSD), anxiety, insomnia, depression and obsessive compulsive symptomatology with prevalence ranging from 20-50%. In a large study of 62,000 COVID-19 survivors in the USA, Psychiatric manifestations including depression, anxiety, insomnia, posttraumatic stress disorder were reported in 18%. Besides in a subset of 44,000 patients with no history of psychiatric disorders a new psychiatric illness was reported in 5.8% (anxiety disorder 4.7%; mood disorder 2%; insomnia 1.9%; dementia (among those ≥ 65 years old) 1.6%). The prevalence of psychiatric side effects could be lower in India due to better social/family support in the Indian setting, but data is lacking.

Serious neurologic manifestations include stroke (ischemic/ hemorrhagic) and posterior reversible encephalopathy syndrome. Post COVID-19 strokes have been seen in young patients with no other risk factors for cerebrovascular disease suggesting causal association with antecedent COVID-19. Sometimes it is the stroke that draws attention to the previous mild/ non-documented COVID-19 illness. Post COVID encephalomyelitis (probably immune mediated) have also been described with good response to steroids.^[14]

Endocrine^[4]

New onset diabetes mellitus and diabetic ketoacidosis in patients without previous risk factors for diabetes have been noted in post COVID-19 state. This is believed to be due to viral/ immune damage of the insulin secreting cells of islets of Langerhans. The long term outcomes of this new onset diabetes is unknown. Similarly thyrotoxicosis due to sub-acute thyroiditis and immune mediated Hashimoto's or Grave's disease have also been reported on follow up.

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Renal^[4]

Acute kidney injury and renal dysfunction even requiring dialysis is noted in many patients with COVID-19 in the acute stage. However almost 80% recover normal renal function over follow up but close monitoring and avoidance of nephrotoxic drugs is recommended.

Gastrointestinal and Hepatic^[4]

While gastrointestinal symptoms are common in the acute phase and prolonged fecal excretion of the virus is noted, prolonged GI symptoms are uncommon. Chronic effects include diarrhoea, irritable bowel syndrome, dyspepsia and alteration of the gut microbiome. Similarly while liver enzyme derangements are common in acute phase, liver function usually improves on follow up.

Dermatologic^[4]

Skin rashes especially pityriasis versicolor, reactivation of herpes zoster, chill blains and urticarial vasculitis are seen during follow up. Hair loss is seen in up to 20% of patients in some studies and is due to telogen effluvium.

Infections

While not alluded to in international studies, infections have emerged as an important post COVID-19 phenomena in Indian patients. Infections can be attributed to coexisting comorbidities including diabetes, use of drugs including steroids and tocilizumab during the acute phase, organ damage due to COVID-19, the immune perturbations of COVID-19 and finally as a consequence to intensive care interventions. It is quite common in India for steroids to be given in large doses for a long time (personal experience) which significantly increases the risk of infections. These infections can be bacterial or fungal. Secondary pneumonia is the commonest infection and can be due to wide variety of bacteria, aspergillus and mucorales. Urinary tract infections are also common. Mucormycosis has emerged as a serious infection in Indian patients following COVID-19 with many cases being reported.^[15] Rhino orbital cerebral mucormycosis followed by pulmonary mucormycosis are the common sites and usually occur at a median period of 2 weeks following COVID-19 diagnosis.^[16] The outcomes have been poor with around 80% mortality.

Multisystem Inflammatory Syndrome (MIS)^[17]

MIS is the most dramatic manifestation of COVID-19 in children (MIS-C) (or Pediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2, PIMS-TS as termed in the UK). It occurs 2-6 weeks after the acute illness which is often mild/ goes unnoticed. MIS is believed to be due to an aberrant immune response and mimics Kawasaki disease (a medium vessel vasculitis). Presenting features include fever (always present) with GI manifestations (abdominal pain, diarrhoea, vomiting often mimicking appendicitis), mucocutaneous manifestations (rash, conjunctival congestion, strawberry tongue), neurologic features (seizures, encephalopathy) and cardiac dysfunction (coronary artery aneurysms, low ejection fraction and shock). Respiratory involvement is uncommon unlike the acute COVID-19 state. The severity spectrum varies from mild disease (presenting only as fever) to fulminant (toxic shock). Laboratory abnormalities include neutrophilia, thrombocytopenia/ thrombocytosis, elevated inflammatory markers including CRP, IL-6, procalcitonin, ferritin, hyponatremia/ hypoalbuminemia, elevated troponin and brain natriuretic peptide. Close differentials are tropical infections like dengue, malaria, rickettsial infections, bacterial sepsis and streptococcal/ staphylococcal toxic shock syndrome. Standard definitions for diagnosis of MIS-C have been proposed by WHO/ US CDC and Royal College, UK. The criteria apart from clinical/laboratory features include exclusion of all other infectious causes and positive RT PCR/ COVID- antibodies or history of contact with COVID-19 or previous COVID-19 illness.

MIS has been now described in adults and should be suspected in adults presenting with significant fever with associated organ dysfunction and high inflammatory markers with no other infectious causes and positive COVID-19 PCR or serology.^[18]

Recently MIS in newborns born to mothers who have had COVID-19 in pregnancy has also been reported.^[19]

How should patients with long COVID-19 be evaluated in primary care?^[20]

The main objective of primary care evaluation is to identify patients with serious medical issues and refer them to the appropriate specialty and provide supportive/ symptomatic management to others with less serious symptoms.

The initial evaluation should include a complete history from the date of the first symptom and under-

standing the nature and severity of current symptoms. A detailed examination should be carried out including temperature, heart rate, blood pressure, respiratory rate, pulse oximetry, and systemic examination.

Investigations may not be necessary in all. Where indicated they may include a complete blood count, C reactive protein, Liver and renal function tests, ferritin, D-dimer, troponin I, brain natriuretic peptides, ECG, CXR and 2D ECHO, creatine kinase. Other investigations include CXR, spirometry, diffusion capacity of the lung for carbon monoxide (DLCO) and plain CT scan of chest is recommended in patients with significant respiratory involvement. Routine testing for COVID-19 antibodies to document protection against future reinfection is often requested by patients is not recommended.

Red flag signs include worsening breathlessness, persistent high fever, saturation < 96%, unexplained chest pain, new confusion, focal weakness or limb discoloration. Such patients should be referred immediately to the appropriate specialists/ emergency care.

How should patients with long COVID be managed?^[4, 20, 21]

The primary approach should be counselling and allaying the anxiety of patients and informing them of red flag signs and when to seek emergency care. The previous prescription should be reviewed and unnecessary/ unindicated drugs tapered or stopped (eg steroids, thrombo prophylaxis). Patients should be urged to quit smoking and alcohol, limit caffeine and increase physical activity in a graded manner. There is a recent systematic review that suggests some benefit with use of Vitamin C in managing fatigue due to long COVID.^[22] Fever should be managed symptomatically with paracetamol and NSAIDS. The routine use of steroids to control fever should be avoided. Return to full activity in competitive sport athletes who had cardiac involvement in the acute stage is only recommended after complete symptomatic improvement, return of cardiac markers to normal and resolution of cardiac MRI findings.^[23]

Respiratory Care

Home pulse oximetry monitoring is recommended in patients who had significant respiratory involvement during the acute phase and those with dyspnoea. The patient should be asked to record saturation using a clean finger without nail polish after rest for 20 minutes. The highest reading should be recorded once the trace has stabilized. Saturation should also be recorded after walking for 6 minutes where a fall of more than

3% is considered significant. Acceptable saturations are between 94-98%. Saturation below 92% is an indication for oxygen therapy. In those with lung disease and hypoxia the acceptable range is 88-92%. If there is a disconnect between the pulse oximeter recordings and clinical condition, then the pulse oximeter should be checked.

Cough and dyspnea are common complaints. Once serious causes are ruled out, cough should be managed with symptomatic medications (dextromethorphan, anti-reflux remedies) and dyspnoea with breathing exercises. About 80% of the work of breathing is done by the diaphragm. After illness or general deconditioning, the breathing pattern is altered with reduced diaphragmatic movement and greater use of neck and shoulder accessory muscles. This results in shallow breathing, increasing fatigue and breathlessness, and higher energy expenditure. The "breathing control" technique is aimed at normalising breathing patterns and increasing the efficiency of the respiratory muscles (including the diaphragm) resulting in less energy expenditure, less airway irritation, reduced fatigue, and improvement in breathlessness. The patient should sit in a supported position and breathe in and out slowly, preferably in through the nose and out through the mouth, while relaxing the chest and shoulders and allowing the tummy to rise. They should aim for an inspiration to expiration ratio of 1:2. This technique can be used frequently throughout the day, in 5-10 minute bursts (or longer if helpful). Other breathing techniques—such as diaphragmatic breathing, slow deep breathing, pursed lip breathing, yoga techniques, "pranayama" are also helpful strategies.

Worsening dyspnoea, cough and oxygenation in post COVID-19 state can be due to atelectasis, progressive fibrosis, inter current infection and pulmonary thromboembolism and needs urgent evaluation and referral.

As discussed earlier the long term outcomes of COVID-19 associated respiratory dysfunction is good. Hence the need of anti fibrotics such as perfenidone and nintedanib in preventing/ halting post COVID-19 fibrosis is uncertain and clinical trials are underway. Besides cost and side effects are also issues. Hence routine use of these drugs is not recommended at present. In a study from China prolonged use of corticosteroids was associated with better lung function outcomes in some patients at 6 months follow up and hence slow taper of steroids in patients with significant respiratory dysfunction and persistent hypoxemia may be considered. All patients with significant respiratory involve-

ment need periodic DLCO, lung function and imaging.

Nutrition

Nutritional counselling plays an important role since many of these patients especially those with critical disease. Protein, vitamins especially vitamin D, minerals should be supplemented. In India there are several myths regarding food and illness and the same should be clarified.

Anticoagulation

While, all guidelines recommend anticoagulation in hospitalized patients with COVID-19, post discharge anticoagulation at present is recommended only for those with documented thrombotic episodes or those who have other risk factors for thromboembolism.[24] Anticoagulation outside these indications is not currently recommended due to risk of bleeding. Randomized trials to evaluate the role of post discharge anticoagulation in all patients and anticoagulation in non-hospitalized patients are underway. These include COVID-PREVENT, ACTIV4 and PREVENT-HD trials and are assessing the role of novel oral anticoagulants (NOACS) and aspirin in thrombo prophylaxis. The decision to give post discharge thrombo prophylaxis should be individualized. Many of the patients recovering from COVID are already on dual antiplatelet agents and then adding another anticoagulant may further increase the risk of bleeding. Besides many patients with severe COVID-19 have been discharged after a long hospital stay (sometimes 3-4 weeks) during which they received standard VTE prophylaxis. The risk of VTE is less in these patients as the duration since onset of illness is long and usually the inflammation has settled. This is in contrast to patients who despite severe disease have been discharged home early due to bed unavailability where extension of VTE prophylaxis may be considered. Physical activity and ambulation should be promoted.

Management of Infections

This requires rational investigative and therapeutic aggressive approach. The prior use of immunomodulatory drugs can blunt the fever and patients can deteriorate rapidly. The clinical setting, radiologic findings should be taken into account before starting empiric therapy. Appropriate microbiologic investigations including blood and urine cultures, sputum cultures, fungal biomarkers including galactomanan and beta D glucan should be sent and ID consult sought. Empiric therapy should also take into account the fact that many of these patients have been in the intensive care unit and exposed to high level antibiotics, received immunomodulatory therapy and are like-

ly infected with drug resistant organisms and possibly fungi. Treatment should be suitably optimized after receiving microbiology reports. Infections such as mucormycosis need multidisciplinary approach.

Management of MIS^[25]

The management strategy depends on severity of disease and whether cardiac involvement is present or not. Patients should be admitted and cardiac involvement determined by biomarkers, ECG and ECHO. Patients with only fever and raised inflammatory markers can be managed symptomatically or with steroids at 1-2 mg/kg/ day for 2 weeks; aspirin at 5 mg/kg/day (max 80 mg should be given for 6 weeks. Sick patients need admission to critical care unit with good supportive care, intravenous immunoglobulins, steroids, low dose aspirin and anticoagulation. In refractory cases tocilizumab, infliximab and anakinra may have to be used. The key in MIS is to rule out infectious causes. With the progression of the epidemic COVID-19 antibodies can be present in many patients without a causal relationship to the new onset fever.

Management of Comorbidities

The follow up should be taken as an opportunity to optimize management of the various comorbidities such as diabetes and hypertension seen in these patients. Overweight and obese patients should be offered appropriate counselling for weight loss.

Mental Health Support

As discussed earlier mental health and cognitive issues are common. Counselling, selective use of medication, social support are strongly recommended. Patients may need financial support owing to illness related expenses, work absenteeism and loss of job and the same should be mobilized through support groups.

Immunization

Immunization against influenza and pneumococcal disease is recommended for all patients with comorbidities, those above the age of 65 years and those with significant residual respiratory dysfunction. Vaccination should be done at recovery with the most recent killed quadrivalent influenza vaccine and conjugated pneumococcal vaccine followed 2 months later by the polysaccharide pneumococcal vaccine.

Patients who have recovered from COVID-19 should be offered the COVID-19 vaccines at least 1 month and preferably 3 months after recovery as studies show that vaccination can boost pre-existing antibody levels.

Can anything be done to prevent post COVID-19 symptoms?

Appropriate management of the acute COVID-19 illness can reduce long term respiratory morbidity. Similarly, rational use of steroids and other immunomodulatory drugs can reduce the frequency of post COVID-19 infections.

Conclusions

While it is important to focus attention on managing acute COVID-19, the problem of post COVID health issues also needs to be addressed adequately. Table 2 summarizes "long COVID" in a nutshell. Establishing multi-disciplinary clinics especially for these patients will streamline diagnosis and management. Indian guidelines on this important aspect of COVID-19 are awaited.

Table 2: "Long COVID" in a nutshell

| | |
|-----------------------|---|
| Definition | Symptoms that persist beyond 4 weeks of onset of the first COVID-19 symptom |
| Prevalence | Varies with severity of initial illness and duration of follow up but can range from 10-80% |
| Common manifestations | Fatigue, Dyspnoea, Chest pain, cough, loss of sense of smell and taste, brain fog, hair loss, sleep disturbances, anxiety, depression, post-traumatic stress disorder |
| Serious complications | Thromboembolic episodes including stroke, MI, VTE, limb gangrene, infections (mucormycosis), respiratory fibrosis, MIS |
| Evaluation | Clinical (history and examination) to detect red flag signs and appropriate referral. Investigations if indicated |
| Management | Symptomatic and supportive care. Home pulse oximetry, breathing exercises, anticoagulation in select situations, nutrition management, mental health support, management of comorbidities, immunization |

References:

1. Oronsky B, Larson C, Hammond TC, Oronsky A, Kesari S, Lybeck M et al. A Review of Persistent Post-COVID Syndrome (PPCS). Clin Rev Allergy Immunol. 2021 Feb 20:1-9.
2. The Lancet. Facing up to long COVID. Lancet. 2020; 396(10266):1861.
3. Jacobson KB, Rao M, Bonilla H, Subramanian A, Hack I, Madrigal M et al. Patients with uncomplicated COVID-19 have long-term persistent symptoms and functional impairment similar to patients with severe COVID-19: a cau-

- tionary tale during a global pandemic. *Clin Infect Dis*. 2021 Feb 7:ciab103.
4. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021 Mar 22.
 5. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo P, Cuapio A et al. More Than 50 Long-Term Effects of COVID-19: A Systematic Review and Meta-Analysis. *Res Sq [Preprint]*. 2021 Mar 1:rs.3.rs-266574. doi: 10.21203/rs.3.rs-266574/v1
 6. Office for National Statistics [Internet]. 2020. Prevalence of long COVID symptoms and COVID-19 complications. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/datasets/prevalenceoflongcovidsymptomsandcovid19complications>.
 7. WHO COVID-19 dashboard [Internet]. [Cited 2021 April 4]. Available at <https://covid19.who.int/>.
 8. Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *Ann Intern Med*. 2020 Nov 11:M20-5661.
 9. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, Walshaw C, Kemp S, Corrado J, Singh R, Collins T, O'Connor RJ, Sivan M. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol*. 2021 Feb;93(2):1013-1022.
 10. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021 Jan 16; 397(10270):220-232.
 11. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC et al. Attributes and predictors of long COVID. *Nat Med*. 2021 Mar 10.
 12. White P. Long COVID: don't consign ME/CFS to history. *Nature*. 2020; 587(7833):197.
 13. Singhania SV, Simon C, Raut A, Parvatkar N. Pulmonary sequelae of moderate to severe COVID pneumonia, a 3-month follow-up study. *Lung India* 2021.
 14. Soman R, Rote S, Singh J, Jadhav K, Eashwarnath R, Chavan D. COVID-19 and Meningoencephalitis with Cerebellitis. In: *Case Book of COVID-19*. Eds Rajeev Soman and Tanu Singhal. Kothari Publishers, 2021. Mumbai; 226-231.
 15. Agrawal R. Alarming Life-threatening MUCORMYCOSIS rises in this Covid-19 Pandemic in India. 2020 Dec 26. [Cited 2021 April 4]. Available from: <https://www.pediatricconcall.com/pediatric-news/alarmed-life-threatening-mucormycosis-rises-in-this-covid-19-pandemic-in-india/37>
 16. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A et al. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. *Mycopathologia*. 2021 Feb 5:1-10.
 17. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P et al. PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA*. 2020 Jul 21; 324(3):259-269.
 18. Varyani U, Singhal T, Sheth S, Shetty K, Harshe P, Shah S. An unusual cause of fever and jaundice. *Indian J Med Microbiol*. 2021 Feb 20:S0255-0857(21)00016-5.
 19. Khaund Borkotoky R, Banerjee Barua P, Paul SP, Heaton PA. COVID-19-Related Potential Multisystem Inflammatory Syndrome in Childhood in a Neonate Presenting as Persistent Pulmonary Hypertension of the Newborn. *Pediatr Infect Dis J*. 2021 Apr 1; 40(4):e162-e164.
 20. Venkatesan P. NICE guideline on long COVID. *Lancet Respir Med*. 2021; 9(2):129.
 21. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ*. 2020 Aug 11; 370:m3026.
 22. Vollbracht C, Kraft K. Feasibility of Vitamin C in the Treatment of Post Viral Fatigue with Focus on Long COVID, Based on a Systematic Review of IV Vitamin C on Fatigue. *Nutrients*. 2021; 13(4):1154.
 23. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, Ellis H, Goodall D, Gough M, Lewis S, Norman J, Papadopoulou T, Roscoe D, Sherwood D, Turner P, Walker T, Mistlin A, Phillip R, Nicol AM, Bennett AN, Bahadur S. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. *Br J Sports Med*. 2020 Aug;54(16):949-959.
 24. National Institute of Health [Internet]. Antithrombotic Therapy in Patients with COVID-19. [Cited 2021 April 4]. Available from: [https://www.covid19treatmentguidelines.nih.gov/antithrombotic-therapy/#:~:text=For%20nonhospitalized%20patients%20with%20COVID,a%20clinical%20trial%20\(AIII\)](https://www.covid19treatmentguidelines.nih.gov/antithrombotic-therapy/#:~:text=For%20nonhospitalized%20patients%20with%20COVID,a%20clinical%20trial%20(AIII)).
 25. Kabeerdoss J, Pilania RK, Karkhele R, Kumar TS, Danda D, Singh S. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. *Rheumatol Int*. 2021;41(1):19-32.

