

GOVERNMENT OF MANIPUR
DIRECTORATE OF HEALTH SERVICES

Comprehensive Guidelines for Management of Post-COVID Sequelae for Doctors

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Background

As we enter the second year of pandemic, patients with ongoing symptoms after recovery from COVID-19 are increasingly recognized as a growing population in need of attention. It has been found that many patients have been experiencing short to long-term sequelae of the disease. Some patients have residual sequelae/symptoms which may or may not be causally linked to COVID-19. In the absence of universally accepted definition, Post-COVID Syndrome by consensus is defined as signs and symptoms that develop during or after an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by alternative diagnosis. Recent literature also divides post-COVID patients into subacute or ongoing symptomatic COVID (4-12 weeks beyond acute COVID-19) and chronic COVID or Post-COVID syndrome (symptoms persisting beyond 12 weeks of onset of acute COVID-19). Another terminology which is in vogue is the 'Long COVID' that is defined by National Institute for Health and Care Excellence as symptoms that continue or develop after acute COVID-19. The timeline of COVID-19 phases and their definitions are shown in figure 1.

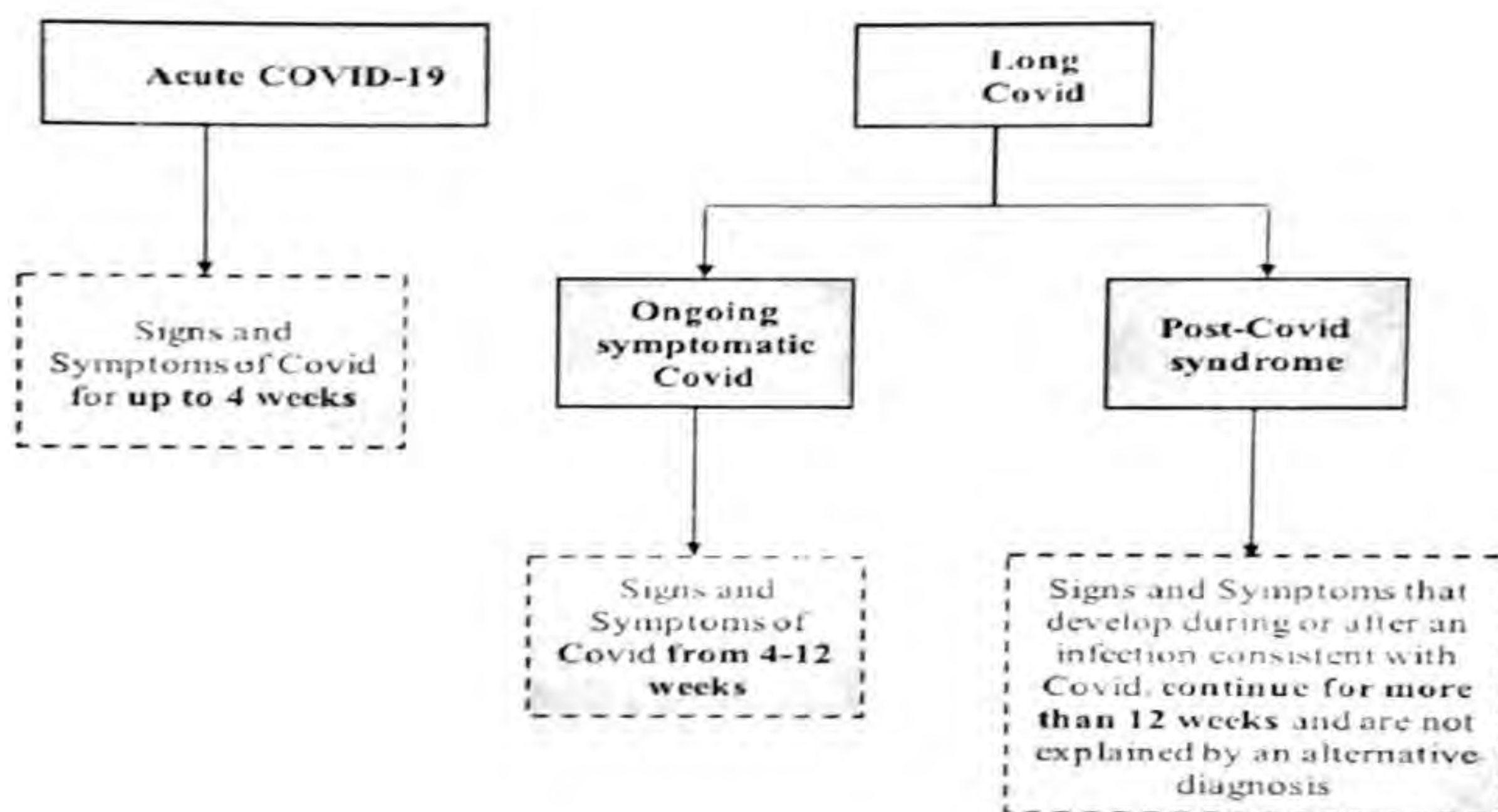


Figure 1: Terminology and Definition of Long Covid

Scope of the document

The purpose of this document is to guide doctors on managing post-COVID complications affecting cardiovascular, gastrointestinal, nephrological, neurological and respiratory systems.

Contents

Background.....	1
A. Guidelines on Post-COVID Cardiovascular Sequel.....	3
Cardiovascular sequelae Post-COVID.....	3
Clinical features: Signs and symptoms	3
Investigations	4
Management.....	4
Conclusion.....	6
B. Guidelines on Post-COVID Gastrointestinal Sequelae	7
Background	7
Risk factors for developing Post COVID GI and Liver manifestations	7
Classification of GI symptoms	7
Management of Post-COVID gastrointestinal manifestations	9
Gastrointestinal checklist for long COVID syndrome.....	10
Symptoms.....	10
Investigations.....	10
C. Guidelines for Screening and Management of Post-COVID-19 Nephrological sequelae	12
Background: Common kidney diseases can be grouped into following major groups.....	12
Common Post-COVID Nephrology related conditions.....	12
What are the symptoms and signs to suspect Post-COVID nephrological related complications? When do we suspect Post- COVID nephrological complications/ sequelae.....	13
What are the minimum facilities required for treating these conditions.....	15
D. Guidelines for Management of Post-COVID Neurological Sequelae	16
Background	16
Common Post-acute COVID-19 Neurological Symptoms:.....	16
Diagnosis and management of Post-COVID sequelae	20
Investigations for Post-COVID patients with neurological sequelae	20
Care and follow – up of Post-COVID patients:.....	21
Annexure 1	23
Annexure 2: IV Antiepileptics for management of SE	24
E. Guidelines for the Management of Long-Term Respiratory Effects of COVID-19	25
When do we suspect that the patient is having long term respiratory effects of COVID-19.....	25
What should be the initial evaluation of a patient with suspected long-term respiratory effects of COVID-19.....	26
Initial treatment offered to patients with Post-COVID respiratory sequelae?	28
Management of specific Post-Covid pulmonary conditions.....	29



A. Guidelines on Post-COVID Cardiovascular Sequel

Cardiovascular sequelae Post-COVID

Cardiovascular sequelae not only occur in symptomatic COVID-19 patients but have also been reported in asymptomatic patients. Up to 20%–30% of patients hospitalized with severe COVID-19 have evidence of myocardial involvement manifested by elevated troponin levels, venous thrombo-embolism, heart failure and arrhythmias. Elevated troponins in acute symptomatic patients have been associated with poor outcomes and higher in-hospital mortality rates. There are multiple mechanisms proposed to explain cardiovascular complications of COVID-19. Direct cardiomyocyte damage or damage secondary to hypoxia, microvascular dysfunction, thrombosis, and cytokine storm have been implicated. Given the high prevalence of cardiac injury, it is reasonable to expect a spectrum of heart disease with some residual post-myocarditis abnormalities in severe cases. Myocardial involvement is presumed to be the initiator of inflammatory process and subsequent fibrosis (detectable on cardiac magnetic resonance imaging) and long-term sequelae too. The long-term sequelae include increased cardio-metabolic demands, myocardial fibrosis or myocardial scar, persistent left ventricular dysfunction, heart failure, arrhythmias, inappropriate sinus tachycardia and autonomic dysfunctions.

Many of the lingering signs and symptoms in patients after recovery from COVID-19 especially fatigue, dyspnea and chest pain — are non-specific. This may occur *de novo* in an asymptomatic COVID-19 patients or in symptomatic COVID-19 patients with no clinically apparent cardiac involvement during the acute phase. Patients who develop viral myocarditis, myocardial infarction, pulmonary embolism, stress-induced myocardial injury and arrhythmias during the acute phase are at higher risk of developing long-term cardiovascular complications and poor outcomes. These subsets of patients typically have comorbidities such as diabetes, hypertension, obesity, dyslipidemia and chronic kidney disease which would complicate their recovery after the acute phase.

Chest pain has been reported in ~20% of COVID-19 survivors at sixty-day follow-up. Palpitations have been reported in ~10% of COVID-19 survivors at sixty-day follow-up. Ongoing chest pain and palpitations have been reported in 5% and 9% respectively at six-month follow-up post-acute COVID-19. Stress cardiomyopathy is 4-5 times more common during the COVID-19 pandemic when compared to pre-pandemic periods (7.8% versus 1.5-1.8%). Myocardial inflammation detected on cardiac MRI was found in as many as 60% of affected people more than 2 months after a diagnosis in one study. However, such high prevalence of myocardial involvement has not been replicated in other studies and the clinical implications, if any, of these findings is not known. Retrospective studies have found the rate of venous thromboembolism in the post-acute COVID-19 setting to be <5%. However, the vast majority of patients who have asymptomatic/mild.

COVID-19 do not have any serious sequelae. Case control studies have shown no excess cardiac involvement in survivors of COVID-19 infection as compared to controls.

Clinical features: Signs and symptoms

Profound fatigue is the most common symptom in most people with Long COVID. Other symptoms such as chest pain, dyspnea and palpitations are well described symptoms in patients with cardiac sequelae. Chest pain consistent with typical angina should be differentiated from atypical or non-anginal chest pain on the basis of location, aggravating and relieving factors. Likewise, respiratory causes of dyspnea need to be differentiated from cardiac causes. Heightened suspicion of dyspnea of cardiac origin especially in the setting of acute coronary syndrome, pulmonary embolism, myocarditis and tachyarrhythmias is the key for early diagnosis of worsening cardiac status and initiating appropriate treatment. Palpitations in Post-COVID syndrome could be due to inappropriate sinus tachycardia, postural orthostatic tachycardia syndrome consequent to hyperadrenergic state or premature ventricular contractions or ventricular arrhythmias consequent to myocardial fibrosis and scarring. Syncope of neurological origin has to be differentiated from that of cardiogenic causes by detailed history, meticulous examination and pertinent investigations like ECG and Holter examination. Heart



failure should be suspected in patients with heart disease (Pre-COVID or during acute infection) having tachycardia, neck vein distention, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, pedal edema, hepatomegaly, a left ventricular third heart sound.

Investigations

Patients with cardiovascular complications during acute infection or those experiencing persistent cardiac symptoms may be monitored with serial clinical, electrocardiogram and echocardiogram evaluations during follow-up. An algorithm to identify patients with cardiac injury during acute and convalescent phase is shown in figure 2. Patients evaluated at Post-COVID clinics with persistent cardiac symptoms described above should undergo chest radiograph, ECG and cardiac biomarkers (Troponins/NT-pro-BNP) to assess cardiovascular involvement.

Additional diagnostic tests such as echocardiography, cardiac MRI, cardio-pulmonary exercise testing, rhythm monitoring by Holter, chest CT and lower extremity Doppler testing maybe indicated based on symptoms and screening investigations.

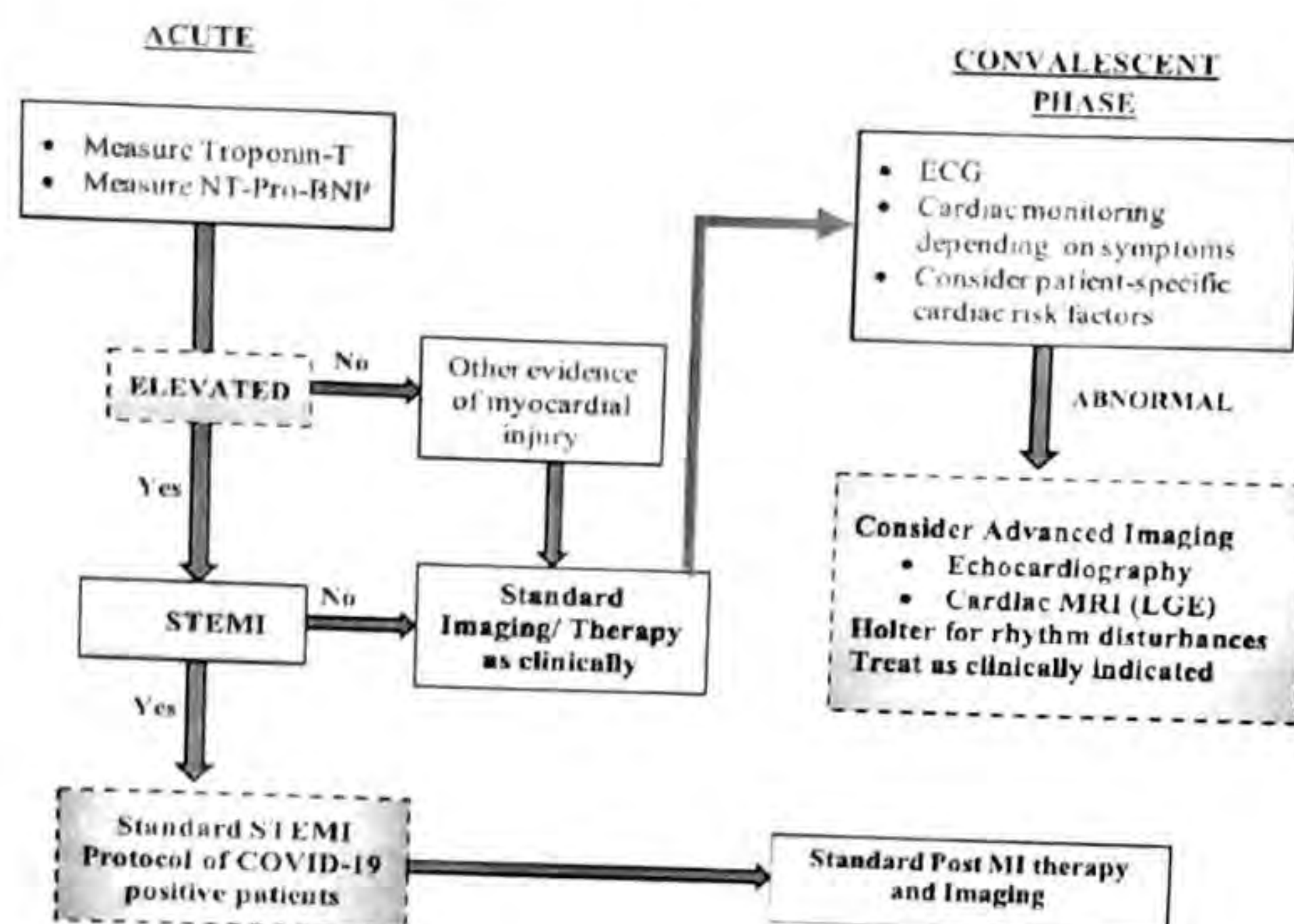


Figure 2: Recommendations to identify patients with cardiac injury during acute and convalescent phase.

Abbreviations: COVID-19: Coronavirus disease 2019; ICM: Ischemic cardiomyopathy;

LGE-MRI: Late Gadolinium Enhancement- Magnetic Resonance Imaging; STEMI: ST-segment Elevation Myocardial Ischemia

Management

The management of patients with Post-COVID cardiovascular complications depends on the status of pre-existing cardiac comorbidities and the cardiac condition developed during the acute phase (myocardial infarction, pulmonary embolism, tachyarrhythmias etc) or during recovery. Common do's and don'ts during Post COVID period have been summarized in table 1.

Table 1: Common do's and don'ts during Post-COVID period

Do's during Post COVID period	Don'ts during Post COVID period
<ul style="list-style-type: none"> • Frequent hand washing and social distancing • Restructure routines at home • Greater emphasis on healthy weight • Healthy eating habits • Moderate intensity exercise (30 minutes per day- 5 times a week) • Avoid alcohol • No smoking or tobacco products • Avoid self-medication • Arrange for telemedicine contacts for follow up with physician/cardiologist • Vaccination after 3 months post recovery if not vaccinated prior • Important to control HT, DM and dyslipidemia. Follow guideline directed medical therapy for cardiovascular risk factors like HT, DM, dyslipidemia and cardiac conditions as prescribed by physician/ cardiologist <p>Practice meditation, Yoga within your tolerance limits</p>	<ul style="list-style-type: none"> • Persistent symptoms (such as fatigue, cough, breathlessness, fever): limit activity to 60% of maximum heart rate (220- age in years) until 2-3 weeks after symptoms resolve • Intense cardiovascular exercise in known cardiac patients and all cardiovascular training in case of athletes to be avoided for 3 months. • Do not stop medications or take over the counter medications without consulting your cardiologist <p>Do not ignore warning signs such as high grade fever, oxygen saturation < 93%, chest pain, dizziness, syncope or palpitations.</p>

Impact of cardiopulmonary exercise in Post-COVID patients is not clearly known yet. However, general rules that are applicable to this subset of patients include one week of low level stretching and strengthening before exercise in patients with mild COVID-19 post recovery. In presence of mild Post-COVID symptoms, limiting exercise to slow walking and increasing rest period if symptoms worsen would be recommended. In patients with persistent symptoms (such as fatigue, cough, breathlessness, fever), limiting activity to 60% maximum heart rate (220-age in years) until 2-3 weeks after symptoms resolve. Intense cardiovascular exercise is to be avoided in all patients for 3 months. Athletes are advised to take three months of complete rest from cardiovascular training followed by specialist follow-up, with return to sport guided by functional status, biomarkers, absence of dysrhythmias, and evidence of normal left ventricular systolic function.

Patients with cardiac comorbidities/conditions such as diabetes mellitus, hypertension, obesity, atrial fibrillation and prior myocardial infarction and heart failure should be managed meticulously as per guideline directed medical therapy. Patients with cardiovascular diseases should be on statins, antiplatelet drugs in addition to the drugs for management of their risk factors including hypertension and diabetes. Adequate treatment of cardiac risk factors such as diabetes, hypertension, obesity and dyslipidemia in addition to the lifestyle modifications described above is the need of the hour in this ongoing pandemic to not only avoid development of new cardiac complications, but also preventing



decompensation in those with pre-existing heart disease. Serial follow up of these patients biannually or annually is the key to ensure drug compliance and avoid further major adverse cardiac event.

Focusing on patients with heart failure with reduced ejection fraction, the nonpharmacological treatment in people with congestive heart failure include educating people about self-management, limiting dietary sodium to < 2g/day and fluid intake to < 2 L/day (1.5 L for severe CHF), explaining the symptoms of dyspnea, edema and bloating and smoking cessation. They are advised to report or reach through telemedicine to their cardiologist for worsening symptoms and for regular follow-up. Prior experience suggests higher risk of cardiovascular events after severe viral infections in patients with cardiovascular disease. Data from the ongoing pandemic is scarce as of now and it is encouraged to get vaccinated for COVID-19 and pneumococcal disease. Guideline directed medical therapy for heart failure includes beta blockers, Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)/Angiotensin Receptor-Neprilysin Inhibitor (ARNi)/ Angiotensin Receptor Blockers (ARB), mineralocorticoid receptor blockers and diuretics. Patients with atrial fibrillation will require anticoagulation for stroke prevention as dictated by CHA2DS2Vasc score. Patients with confirmed DVT/pulmonary embolism require anticoagulation prophylaxis preferable with novel oral anticoagulants or warfarin to maintain the INR (International normalized ratio) in the range of 2-3.

Conclusion

COVID-19 impacts cardiovascular system in the recovery phase and is part of the overall Post- COVID syndrome. Physicians managing Post-COVID clinics should be aware of these symptoms and cardiovascular implications of COVID-19 sequelae. Discrete screening, appropriate investigations and evidence-based treatment of cardiovascular Long COVID is mandated to reduce long term impact of COVID-19.



B. Guidelines on Post-COVID Gastrointestinal Sequelae

Background

Coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2). The virus has air borne transmission, but SARS-CoV-2 could also be isolated from the stool samples of COVID-19 patients indicating the possibility of faeco-oral transmission. Beside the common respiratory symptoms, some COVID-19 patients experience gastrointestinal symptoms such as ageusia, lack of appetite, nausea, vomiting, dyspepsia, diarrhea, abdominal pain and hepatitis. Most symptoms pertaining to GI tract are mild and self-limiting. Presence of angiotensin converting enzyme 2 (ACE 2) receptors in the epithelium of gastrointestinal (GI) tract facilitates the entry and replication of the virus in the GI system resulting in GI manifestations. In some patients GI symptoms may appear before the onset of fever and respiratory symptoms. Numerous studies have been published on the prevalence of GI and liver manifestations during active COVID-19, the prevalence of Post COVID GI and liver manifestations is not known.

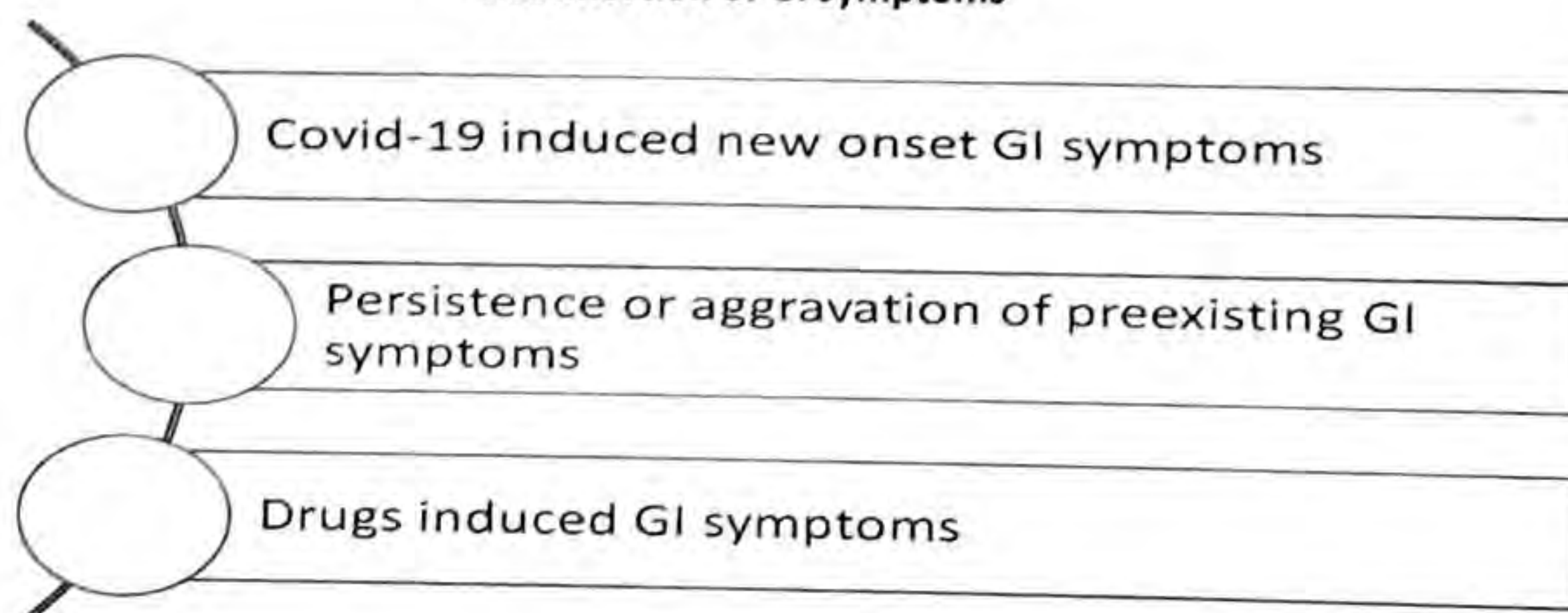
Risk factors for developing Post COVID GI and Liver manifestations

- Severe disease
- Older age
- Admission to intensive care
- Respiratory tract infection
- Gut dysbiosis due to antivirals and antibiotic use during hospitalization
- Liver injury due to COVID-19, drugs or alternative medication intake
- Polypharmacy

Prevalence of GI and liver manifestations during COVID-19

Symptom	Prevalence	Remarks
Diarrhea	8%	<ul style="list-style-type: none">• May be presenting symptom• More common in hospitalized patients• Rule out drugs or infectious cause of diarrhea
Nausea/Vomiting	8%	<ul style="list-style-type: none">• Avoid Polypharmacy
Abdominal pain	4%	<ul style="list-style-type: none">• May be the presenting symptom• rule out other causes
Elevated OT/PT	15%	<ul style="list-style-type: none">• Seen in patients with severe disease,• Exclude drug induced liver injury• Compare with the baseline values if available

Classification of GI symptoms

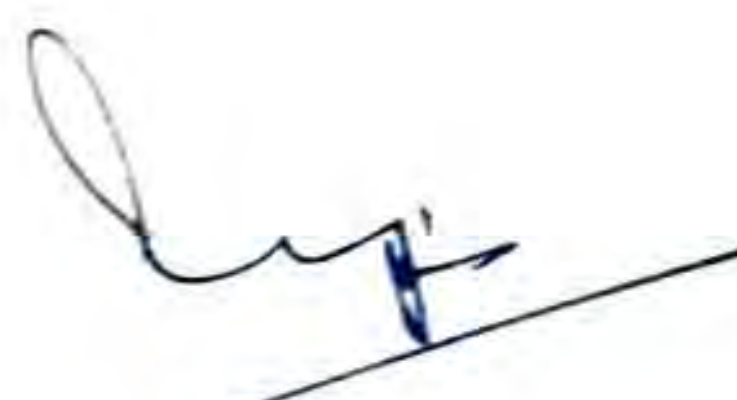


Differences between COVID-19 induced and drug induced liver injury

Parameters	COVID-19 induced	Drug induced
AST, ALT	AST>ALT	ALT>AST
ALP	Normal / ↑	↑ / Normal
Serum bilirubin	Normal / ↑	↑ / Normal
Degree of enzyme elevation	< 5 times ULN	> 5 times ULN
Temporal association with drug	No	Yes
Abnormal LFT at presentation	Yes	No

Drugs used in COVID-19 management and GI side effects

Drug	Class	GI side effects
Azithromycin	Antibiotic	Diarrhea, Cholestatic hepatitis, nausea, Pain abdomen
Hydroxychloroquine	Antimalarial	Abdominal pain, anorexia, diarrhoea, nausea, vomiting
Lopinavir	Antiviral	Dysgeusia, nausea, vomiting, pain abdomen, diarrhea, elevated amylase and lipase
Remdesivir	Antiviral	Nausea, transaminitis
Favipiravir	Antiviral	Nausea, vomiting, diarrhea, transaminitis
Tocilizumab	IL6 inhibitor	Transaminitis



Management of Post-COVID gastrointestinal manifestations

Dyspepsia

Assess: Severity, relationship to COVID-19 illness, drug intake and alarm features

Alarm features +ve UGIE	H pylori stool antigen/ Breath test +ve Anti-H pylori Rx	COVID-19 related Reassurance Antacids and PPI	Drug related Stop Drug Antacids and PPI
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Diarrhea

Assess: Severity, hydration, hemodynamic status, relationship to COVID-19 illness, drug intake and for pre-existing diarrhea

Drug induced Stop agent ORS	COVID-19 related Reassurance Diet modification	Pre-existing IBD/ IBS/ Cellac/ Lactose Intolerance Rx: as per guidelines	Antibiotic induced R/o C difficile Infection Rx: Probiotics
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Abdominal pain

Assess: Severity, hemodynamic status, relationship to COVID-19 illness, drug intake and for pre-existing pain

Drug induced Stop agent Antacids	? Covid related pancreatitis/ gastritis/ cholecystitis US/ CECT/ S.Amylase/S.Lipase/ LFT/ HbMG Rx as per standard guidelines	? Pre-existing illness exacerbation Rx: as per guidelines	? Ischemia AXR. Erect and supine, CECT
Drug induced Stop agent Antacids	? Covid related pancreatitis/ gastritis/ cholecystitis US/ CECT/ S.Amylase/S.Lipase/ LFT/ HbMG Rx as per standard guidelines	? Pre-existing illness exacerbation Rx: as per guidelines	? Ischemia AXR. Erect and supine, CECT

Gastrointestinal checklist for long COVID syndrome

Symptoms

Sl No	Symptoms	During COVID-19 disease		Post-COVID disease recovery	
		Yes / No	Severity (0-10)	Yes/ No	Severity (0-10)
1.	Nausea				
2.	Vomiting				
3.	Dysguesia				
4.	Loss of appetite				
5.	Abdominal pain				
6.	Hematemesis /melena				
7.	Dysphagia				
8.	GERD				
9.	Constipation				
10.	Fatigue				

Examination

Sl no	Examination Findings	During COVID-19 disease	Post-COVID disease recovery
1.	Pallor		
2.	Icterus		
3.	Pedal edema		
4.	Hepatomegaly		
5.	Splenomegaly		
6.	Signs of vitamin deficiency		

Investigations

Sl no	Investigations	During COVID-19 disease	Post-COVID disease recovery
1.	AST		
2.	ALT		
3.	ALP		
4.	Deranged PT/aPTT		
5.	aPTT		
6.	Amylase		
7.	Lipase		



Do's and Don'ts in COVID-19

Do's	Don'ts
<ul style="list-style-type: none">• Get COVID-19 vaccine• Sanitize hands frequently• Follow social distancing norms• Wear mask properly• Use bleach agent (Sodium hypochlorite 0.5%) to disinfect toilets• Adequate intake of water• Take healthy diet rich in fruits• Seek health professional through telemedicine facility for advice• Ensure adequate physical activity and exercise at home	<ul style="list-style-type: none">• Don't eat junk food• Avoid use of non-prescription drugs• Avoid self-medication• Consult the nearest COVID-19 facility• Avoid overcrowding• Don't panic if you get infected• Avoid unnecessary Google search• Avoid unnecessary visits to the hospitals and clinics for minor illnesses

C. Guidelines for Screening and Management of Post-COVID-19 Nephrological sequelae

Background: Common kidney diseases can be grouped into following major groups

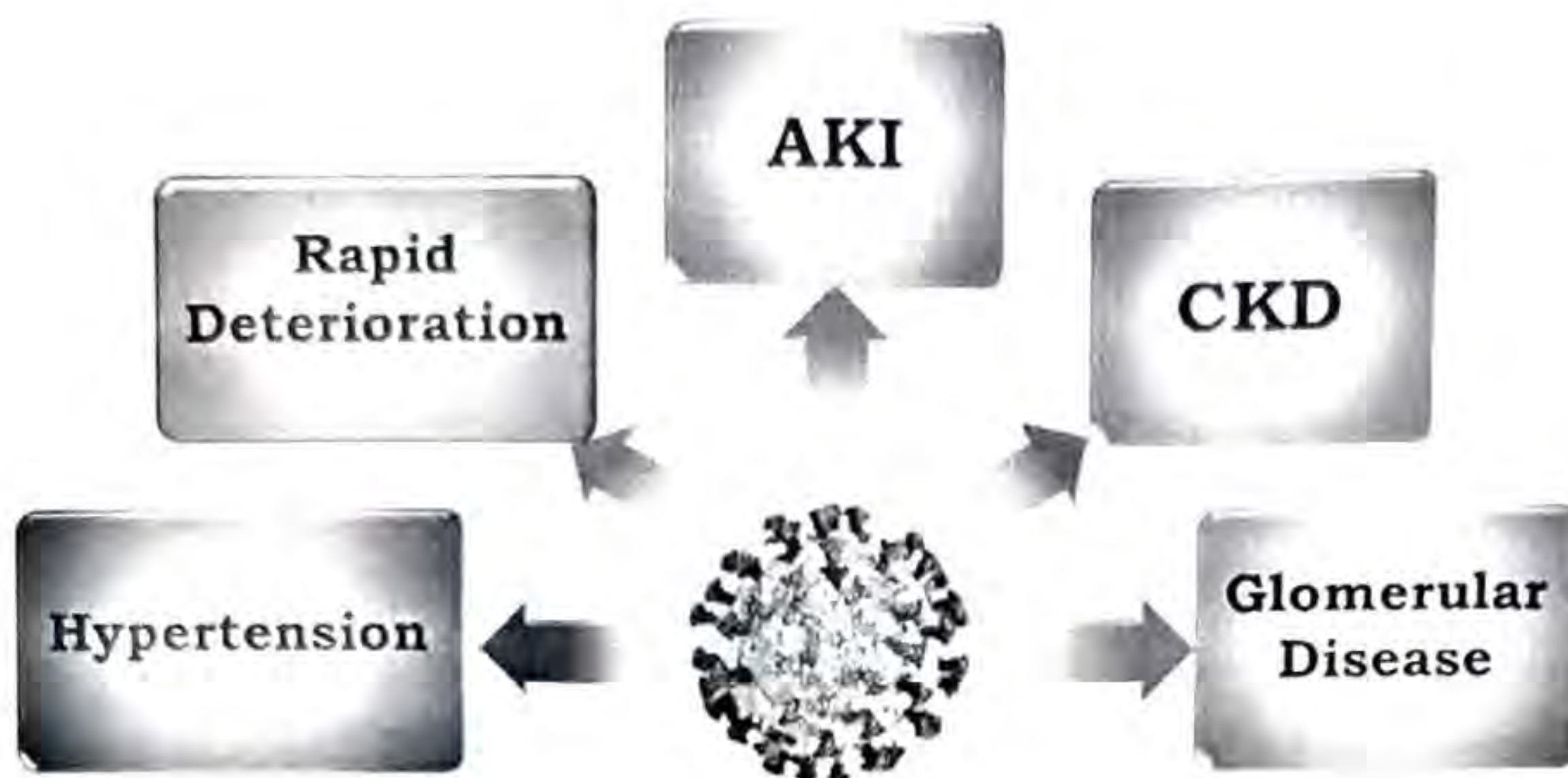
- A. **Acute Kidney Injury:** acute kidney injury (AKI) is recent onset (In days to few weeks) of kidney dysfunction characterized by an increase in creatinine, therefore reduction in estimated glomerular filtration rate (eGFR) with or without oliguria and has potential of complete recovery in more than 80-90% cases. 10-20% cases of severe AKI are at risk of developing chronic kidney disease (CKD).
- B. **Chronic Kidney disease:** Chronic kidney disease (CKD) is defined as evidence of kidney disease with or without $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$. Evidence of kidney disease can be in the form of abnormal urinary albumin excretion $> 30 \text{ mg/day}$, urinary sediment abnormality and/or abnormal radiological kidney abnormality. Once CKD is correctly diagnosed, it does not recover and has tendency of progression to advanced kidney damage, called end stage kidney disease (ESKD), when patient needs renal replacement therapy (RRT); that is dialysis and/or kidney transplant.
- C. **Glomerular diseases:** Many kidney diseases involve glomerulus and can be grouped under glomerular diseases. Considering degree of proteinuria, kidney dysfunction and rapidity of onset of disease, the glomerular diseases can be further classified into clinical syndromes like; acute glomerulonephritis (GN), nephrotic syndrome, acute nephritic syndrome, rapidly progressive GN and asymptomatic urinary abnormalities.
- D. **Hypertension:** More than 90% cases of hypertension are primary hypertension but out of 10% cases of secondary hypertension, kidney is commonest cause resulting in secondary hypertension.

1. Common Post-COVID Nephrology related conditions

1.1 What are the usual Post-COVID related nephrological complications/sequelae?

"Sequelae" is a pathological condition resulting from a prior disease, therapy or other trauma. A typical sequela is a chronic complication of an acute condition: long term effect of a temporary disease or injury. The common kidney related complications following- COVID are as follows

- New onset Acute Kidney Injury (AKI) in native kidney or transplant kidney
- Rapid progression of pre-existing CKD in native kidney or transplant kidney
- Progression of CKD to End Stage kidney Disease (ESKD) in native kidney or transplant kidney
- New onset glomerular disease – proteinuria, hematuria and renal dysfunction
- New onset hypertension or worsening of hypertension



1.2 How common are these conditions? What is the epidemiological burden in terms of prevalence etc.

AKI is an independent predictor of mortality and poor outcomes in COVID-19 patients. COVID-19 is known to cause AKI in about 46% of severe COVID-19 requiring ICU admissions. Around 20- 30% ICU patients with AKI will need renal replacement therapy. Approximately 1/3 of the COVID-19 patients with AKI, who survived will not recover kidney function to baseline values within 3 weeks after discharge from hospital. COVID-19 linked AKI also leads to faster decline in pre-existing kidney dysfunction.

The prevalence of CKD among patients with recovered COVID-19 varies from 5% to 20%. Hematuria and proteinuria are found in 15% to 25% of COVID-19 patients. Few cases of COVID-19 associated collapsing glomerulopathy has been reported in African patients. More information and data are needed on long – term renal outcomes of COVID-19 patients.

1.3 Post-COVID AKI sequelae:

Patients with incomplete recovery of AKI at discharge needs to be followed: regularly (every monthly) for a minimum period of 3 months to document late AKI recovery or diagnosing patients going to CKD. Patients with recovered AKI at discharge also needs to be followed up as up to 14% have been shown to develop kidney dysfunction.

2. What are the symptoms and signs to suspect Post-COVID nephrological related complications? When do we suspect Post-COVID nephrological complications/ sequelae.

Symptoms to suspect Post-COVID nephrological complication:

- Fatigue and unexplained weakness
- Nocturia (frequent urination during night which disturbs sleep)
- Increased froth in urine
- Anorexia (loss of appetite)
- Headache
- Swelling on leg
- Increase requirement of anti-hypertensives
- Breathing difficulty
- Orthopnea (Breathing difficulty during lying down)

It is important to note that often there are no symptoms of Post-COVID-19 related nephrological problems and patients are asymptomatic.

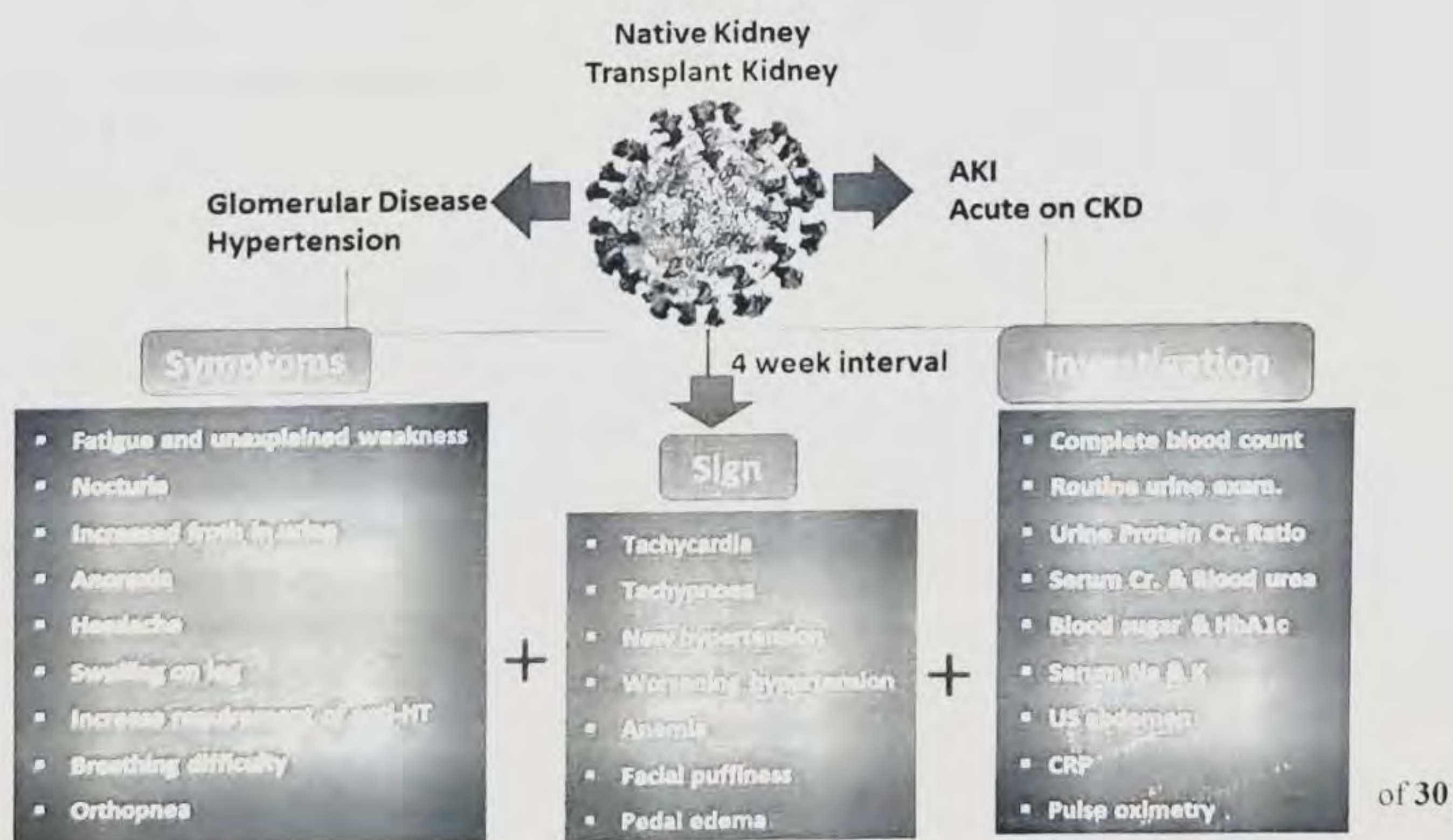
Signs of Post-COVID related nephrological complications:

- Tachycardia
- Tachypnoea
- New onset hypertension or worsening hypertension
- Anemia, new onset or worsening from before
- Facial puffiness
- Pedal edema

It is important to note that often there are no signs of Post-COVID related nephrological problems and patients may be asymptomatic.

3. What are the common investigations to be conducted to confirm the diagnosis?

- Complete Blood Count
- Routine complete urine examination
- Spot urine protein/creatinine ratio
- Serum creatinine and blood urea
- Blood sugar and HbA1c
- Serum Na and K
- 24-hour urine protein
- Ultrasound of Kidneys
- C-reactive protein
- Pulse oximetry



4. What are the minimum facilities required for treating these conditions?

If a Post-COVID patient is diagnosed with nephrological sequelae, he should be managed at a health care facility having support of Nephrologist and there should be access for dialysis services.

5. What are common do's and don'ts? How can we prevent the nephrological complications? What are the important messages for the public?

Care and follow-up of Post-COVID patients for potential nephrological complications:

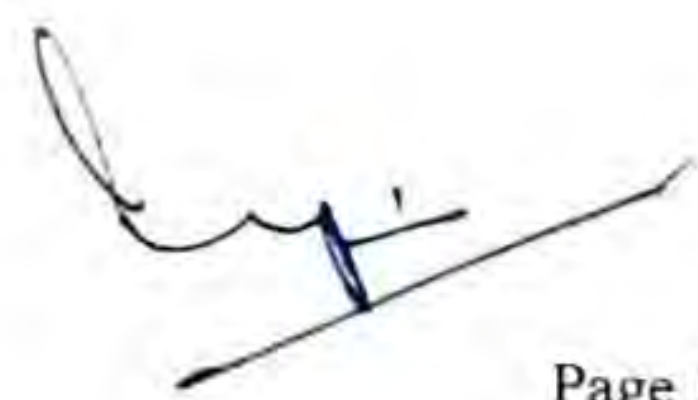
The Post-COVID 19 patients should regularly follow up with a primary care physician under supervision of nephrologist:

Do's:

- Maintain a healthy lifestyle and healthy weight; avoid weightgain.
- Drink adequate water
- Restrict salt and fat in diet
- Follow advice of doctor in relation to intake of amount and type of protein
- Start with home cooked simple food, eat small meals with intervals.
- Reduce stress: get good sleep, stay connected with friends and family members.
- Proper control of any underlying co-morbidities like Diabetes, hypertension.
- Moderate exercise, yoga and meditation at least 45 minutes/day and 5 days/week.
- Get your kidney function tests done, as advised by doctor.
- Have a positive attitude.

Don'ts:

- Take citrous fruits and leafy vegetable if asked to avoid.
- Self-medicate
- Avoid ayurvedic medicines unless advised by a competent doctor.
- Take nicotine and alcohol products.



D. Guidelines for Management of Post-COVID Neurological Sequelae

Background:

As literature regarding the manifestations of COVID-19 has increased, there has been growing recognition of the long-term sequelae due to this disease. These long-term sequelae have been denoted by the terms such as "chronic" COVID-19, long haulers, "long" COVID-19, Post-covid conditions etc. However, there is no universally acceptable definition of "chronic" COVID-19. These symptoms occur after resolution of the acute infectious phase of the illness. As per current literature, the terms post-acute COVID-19 and "chronic" COVID-19 have been defined as symptoms or disease sequelae persisting 3 weeks and 3 months after the onset of first COVID-19 symptoms respectively. These sequelae can involve multiple systems and can lead to a myriad of neurological symptoms. Post-COVID Syndrome can include symptoms related to Residual inflammation, Organ damage, Impact on pre-existing health conditions or Non-specific effects due to hospitalization or prolonged ventilation (post-intensive care syndrome).

The COVID-19 infectious agent, SARS-CoV-2, has a high affinity for human angiotensin- converting enzyme 2 (ACE2) receptor. This receptor is also expressed in neurons and glial cells, which could explain the reported neurological manifestations such as Olfactory neuropathy (anosmia), Peripheral neuropathy and Brain disorders.

In post-mortem studies, viral particles have been found in the cerebrospinal fluid and cytoplasm of neocortex and hypothalamus neurons, as well as neuronal degeneration and necrosis, edema, glial cell hyperplasia, and cellular infiltrates. It has been suggested that in cured patients, SARSCoV-2 remains latent in the central nervous system for a long time, being able to reactivate and trigger neurological complications.

Prevalence of Post-COVID symptoms:

Multiple studies have provided variable estimates regarding post-acute COVID-19 symptoms. The prevalence of these symptoms ranges from 10% to 87.4% across various studies. A recent report from the CDC suggested that 35% individuals suffering from COVID-19 did not fully recover and had some lingering symptoms. Variability in the numbers reported in literature may be due to the small sample size of the studies, recall as well as selection bias among participants in the study, difference in time period for defining Post-COVID sequelae/symptoms across studies.

Common Post-acute COVID-19 Neurological Symptoms:

- Fatigue (most common sequelae)
- Changes in concentration
- Impaired memory
- Persistent muscle weakness and myalgias
- Headaches
- Sleep disorders
- Dizziness
- Impairment in smell (Anosmia) and taste (ageusia)
- Rarely new onset status epilepticus, stroke, acute inflammatory demyelinating polyneuritis (AIDP), autonomic dysfunction such as orthostaticsymptoms.
- Non-specific sensory complaints such as paresthesias, numbness, tingling in limbs



Pathophysiology

1. Weak immunologic response and incomplete virus eradication resulting in ongoing inflammation
2. Genetic predisposition
3. Direct invasion of CNS by virus and neurodegeneration
4. Dysregulated immune reaction

Risk factors

Probable factors which would predict long term symptoms include

1. Severe COVID-19 requiring hospital admission
2. Older age
3. Obesity
4. More than 5 symptoms in the first week of acute COVID-19

Fatigue

Most commonly reported symptom. The reported frequency is in the range of 16% to 55%. It may be assessed using Chalder fatigue scale. It is a 11-point questionnaire with a Minimum -0, maximum-11 scores and a cut off score ≥ 4

If the symptoms are persisting for more than 6 months check whether the condition fits in chronic fatigue syndrome. (the three cardinal symptoms (fatigue, aggravation of symptoms with exercise, and unrefreshing sleep) be present for more than six months and be moderate or severe in severity for at least 50% of the time.)

Chronic fatigue syndrome/ myalgic encephalitis. Diagnostic criteria.

1. Chronic fatigue syndrome (essential criteria)
 - Substantial impairment in the ability to perform activities carried out prior to the disease for more than six months
 - Profound fatigue not relieved by rest
 - Discomfort or aggravation after physical exertion
 - Unrefreshing sleep
2. Chronic fatigue syndrome (at least one of the two additional criteria must be present)
 - Cognitive impairment (impairment of executive functions or thinking that worsens with exertion, stress or pressure)
 - Orthostatic intolerance (symptoms worsen when standing and improve when lying down or raising the lower limbs)
 - Patients who meet criteria for myalgic encephalitis must also have cognitive impairment.



Smell and taste disturbances

Infection with SARS-CoV-2 can lead to chemosensory disorders, with hyposmia/anosmia and ageusia/dysgeusia. These symptoms usually occurs during the acute phase and persist. There are no reports of new onset anosmia or ageusia during the Post-COVID period. The studies show median adjusted frequency of 23.6% (IQR, 12.4%-40.7%) for anosmia and 15.6% (IQR,10.1%- 23.9%) for ageusia or dysgeusia during the Post-COVID period. Patients may be asked to the deficit in a Likert scale of 0-10 and the effect on quality of life may be assessed using Questionnaire of Olfactory Disorders (QOD) questionnaire. Studies have shown that smell and taste dysfunction recover at a median duration of 31 days. However, some amount of dysfunction may persist in around 1/3rd of people.

Dysautonomia

Dysautonomia can cause dizziness, palpitation, exercise intolerance, chest tightness, presyncope and syncope particularly when changing posture from lying to standing. Once the cardiac and respiratory causes are ruled out autonomic dysfunction should be ruled out. One report showed abnormal autonomic function tests in 12% patients recovering from COVID-19.

If symptoms are lasting more than 3 months look for the possibility of Postural orthostatic tachycardia syndrome (POTS)

1. Increase in HR >30 BPM in adults and 40 in children within 10 minutes of adopting upright posture
2. Absence of postural hypotension
3. Symptoms of orthostatic intolerance
4. >3 months

Headache

Studies have described varying frequency of headache during Post-COVID period ranging from 2-60%. A recent meta-analysis showed that the frequency of headache comes down from 47% at the time of admission to 8% at 6 months. Majority of the patients have tension type like headache and migraine type headache is less common. However, patients with preexisting migraine can have an increase in the frequency. Some patients can have features fulfilling daily persistent headache ache.

Cognitive impairment

Reported in around 12-50% patients. May persist beyond 1 year. Most frequent deficits are im-paired attention, concentration, executive function and memory. Brain fog is another common manifestation of Long-COVID, an umbrella term used to describe the constellation of cognitive function impairment such as confusion, short-term memory loss, dizziness, and inability to concentrate. ICU admission and mechanical ventilation during the acute illness may contribute to the long-term cognitive impairment.

Sleep disorders

Sleep dysfunction and insomnia can occur in around 18-30%% and it may persist beyond one year in majority. The sleep quality may be assessed with Insomnia severity index or Pittsburgh sleep quality index (Appendix)

Neuromuscular diseases

Myalgia, fatigue and hyper-CK-emia are the most common triad forms (40–70%) of skeletal muscle affection in COVID-19 cohorts. Quadriceps and biceps weakness may be found in >75% survivors of COVID-19 illness and it may persist it beyond 1 year even up to 70% people. – A COVID-19 disease requiring intensive care with invasive ventilation can lead to ICUAW ("ICU- acquired weakness" [ICU: intensive care unit]), a clinical picture in which CIP ("critical illness polyneuropathy") and CIM ("critical illness myopathy") intertwine. There seems to be no massively increased risk for neuromuscular patients suffering from SARS- CoV-2 infection.

Guillain-Barré syndrome (acute inflammatory demyelinating polyneuritis - AIDP)

The neurological symptoms usually appear within 5–10 days after a COVID-19 diagnosis, although GBS may develop even weeks after infection. Due to the risk of cardiovascular complications, in particular respiratory insufficiency and cardiac arrhythmias, a rapid diagnosis and immediate therapy including critical care admission is recommended. Clinically, mild courses up to severe tetraparesis. Cranial nerve involvement with bilateral Facial nerve palsy, ocular muscle palsy or Miller Fisher syndrome are also reported. Often the rapidly progressive course leads to respiratory insufficiency and need of ventilation.

Stroke

Ischemic strokes and, more rarely, intracerebral hemorrhage (ICH) occur in patients with COVID- 19 disease and are associated with a more severe course of the disease. However, strokes have also been reported as Post-COVID sequelae. A confirmed or presumed infection with SARSCoV-2 in patients with acute stroke should not lead to different treatment than for other stroke patients. They should receive the same acute diagnostics and acute treatment as all stroke patients, Patho-mechanism

- Activation of the coagulation system
- Disseminated intravascular coagulation
- Vascular complications as an expression of severe organdamage

Epilepsy

The patients with chronic epilepsy have reduced access to doctors and drugs and can therefore suffer drug withdrawal attacks. For this reason, it is important to ensure that patients with pre-existing epilepsy always have access to outpatient neurological care and that sufficient and timely antiepileptic drugs are prescribed to prevent supply shortages. As part of Post-COVID syndrome status epilepticus have been reported



Diagnosis and management of Post-COVID sequelae:

History

Take a precise history of the onset of the first COVID-19 symptoms. Enquire regarding persistent fatigue, decreased ability to exercise, decreased ability to carry out routine daily activities, slowness in thinking, attention, concentration, confusion (Post-COVID fog), dizziness, persistent headaches and sleep issues (increased sleep latency and/or maintenance)

Examination:

1. Vitals (Blood pressure, pulse rate and rhythm, Respiratory rate, Pulse Oximetry and saturation among all COVID-19 survivors).
2. Cognitive assessment: Mini-mental status examination / Montreal Cognitive Assessment Test / 6-IT test as a screening tool among those having cognitive complaints. Detailed lobar function testing in those having an abnormal MMSE.
3. Detailed neurological examination (including power testing) in those complaining of muscle aches, myalgias, persistent weakness in limbs.
4. Sensory examination to rule out objective sensory loss among those presenting with sensory symptoms of paresthesias, pin-pricking, tingling and numbness.

Investigations for Post-COVID patients with neurological sequelae:

Extent of investigations required depends on the symptoms or symptom complex, rapidity with which the symptoms progress, severity of these symptoms and the effect of these on the person's day to day functioning and sense of wellbeing.

- a. Hemogram with ESR
- b. Liver function tests
- c. Kidney function tests
- d. Fasting blood sugar

Specific investigation among COVID-19 patients with neurological sequelae/symptoms:

- a. CPK (those with muscle aches, myalgias and persistent weakness)
- b. Nerve conduction studies for Patients having sensory motor complaints with suspected neuropathy including Guillain Barre syndrome after thorough neurological examination
- c. CSF analysis: only to be considered for select patients with severe cognitive, persistent neuropsychiatric or behavioural issues (to rule out other causes, active meningoencephalitis or Post-COVID autoimmune mediated encephalitis) or suspected immune mediated neuropathy is suspected.
- d. Patients with brain fog or cognitive neurological dysfunction should be administered higher cognitive function assessment.
- e. Brain MRI may be required in selected patients with worsening and significant cognitive neuropsychiatric manifestations.

- f. Patients suspected to have autoimmune involvement of nervous system should undergo detailed assessment for autoimmune antibodies.
- g. Autonomic function studies: Start with measuring blood pressure and heart rate after 5 minutes lying supine, and then 3 minutes after standing. Orthostatic hypotension may be diagnosed if there is a fall of >20 mmHg systolic and >10 mmHg diastolic after standing for 3 minutes. For detailed evaluation in indicate cases, tertiary care referral may be required.
- h. EEG – for patients with status epilepticus if a non-convulsive status is suspected.
- i. Polysomnogram- In patients with significant sleep dysfunction for which tertiary care referral may be done.
- j. Patients with mild innocuous symptoms may be thoroughly examined and followed up at appropriate intervals. The patients may present with multisystem symptoms.

Care and follow – up of Post-COVID patients:

Depending on the presentation of an individual the patients appropriate generally accepted guidelines for management and care of patients should be followed. There is no evidence based specific care guidelines of patients with Post-COVID symptoms. The duration of some of the symptoms or sequelae of some of the Post-COVID illnesses is not as yet clearly defined. Usually, symptoms are self-limiting and will resolve on their own. It is important to avoid prescribing indiscriminate medication to patients. Formal consultations are sparingly used only for selected patients with severe persistent symptoms.

Management fatigue

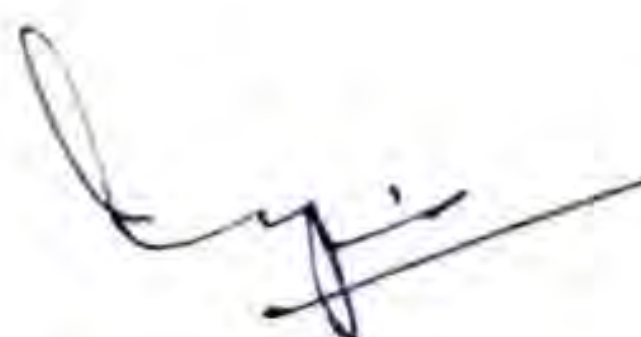
Self-management and support. No COVID specific guidelines. Look for the other system involvement such as cardiorespiratory and autonomic and refer accordingly. Take adequate rest, sleep and maintain hydration. Avoid unnecessarily using over the counter analgesics. Management protocol for chronic fatigue syndrome such as graded exercise therapy (GET) may be adopted for selective patients, self-management strategy such as “pacing” where the patients adjusts the activities to avoid exertion may be advised. There are some reports of utility of Vit-C supplementation. Aerobic exercises, balance training, breathing training, and resistance strength training (start with low intensity and gradually raise the duration and intensity) may also be beneficial

Management dysautonomia

- Patient education
- Structured aerobic and resistance training and non-orthostatic exercises such as cycling on a recumbent bike / swimming etc.
- Fluid (2-3 L/day) and salt (1-2 tablespoon) supplementation
- Avoid precipitating factors: coffee, alcohol, prolonged standing, hot humid condition and dehydration, drugs such as duloxetine, nortryptiline
- Compression garments
- Pharmacological agents: fludrocortisone, midodrine

Management headache

- As in other situations
- Look for the red flags
- Treatment according to the type and frequency of headache



Management cognitive dysfunction

There is no COVID specific protocol. As in routine clinical practice assess the patient using validated tools and try to rule out treatable causes of cognitive impairment. Requires a holistic approach. Patients should be assured that most of them will recover. Measures such as repeated cognitive exercises, alleviating stress, coping strategies and utilizing the help of speech, language and occupational therapists if available may be useful. Engaging in cross word puzzles, simple number games (like sudoku), reading newspapers, books could help in improving cognitive abilities.

Management of sleep dysfunction

Good sleep hygiene is advised for those having sleep difficulties. Avoid caffeine and alcohol use before bedtime, avoid excessive use of phones/computers at bedtime, soothing or calming sleep music in a quiet dimly lit room may help in improving sleep latency. Avoid self-medicating with benzodiazepines. It is better to consult a doctor than to self-medicate.

Management GBS

NCS -a demyelinating pattern of damage usually dominates, although axonal processes are also reported.

CSF diagnosis is necessary to exclude an infectious etiology. In most cases a cytoalbuminous-dissociation appears

The therapy does not differ from the usual treatment for GBS.

Intravenous immunoglobulins (2 g/kg bw) is preferred/ plasma exchange also may be considered.

Corticosteroids should be avoided.

Management stroke

It is important to recognize stroke symptoms and initiate a Protocol Based Stroke Management Some of the warning signs are sudden onset

- Difficulty in speaking or understanding words
- Loss of feeling or strange feeling on one side of the body
- Weakness of the face, arm or leg on one side of the body
- Unexplained dizziness or loss of balance
- Decreased or blurred vision
- Severe unexplained headache

Since the window for thrombolysis is 4.5 hours a quick assessment should be made FAST

Ask the patient to smile

Ask the patient to raise arms Ask

the patient to say a phrase

And ask about the time of onset of symptoms

Refer the patient to a centre with stroke management facility



Management of Status Epilepticus: Management plan does not differ in Post-COVID conditions compared to routine management. When the etiology is unclear and CSF does not suggest infection a more detailed investigation may be useful, including Anti-N-methyl-D- aspartate (NMDA) antibody and Anti-voltage gated potassium channel antibody. Investigations such as CSF, brain imaging, EEG and drug monitoring etc. to be used judiciously

First Line agents

Lorazepam/Diazepam/Midazolam

Second line agents

Phenytoin/phosphenytoin/sodium valproate/ Lacosamide/Levetiracetam/Phenobarbitone

Refractory SE

Irrespective of the timeframe, SE that persists despite adequate administration of benzodiazepines and at least one antiepileptic drug is labelled refractory SE (RSE). More aggressive measures should be taken, with intubation and mechanical ventilation of the patient and frequently hemodynamic support with pressors or inotropes. Drugs such as propofol, Thiopentone, ketamine and midazolam may have to be used Patients may be referred to higher centers in case of unresponsiveness.

Therapeutic options under trial

Nicotinamide riboside, a dietary supplement, for cognitive symptoms and fatigue.

Use of monoclonal antibodies such as Leronlimab and tocilizumab for the management of Post-COVID syndrome

When to return to work

There is a consensus expert recommendation that besides 2 weeks of convalescence, one should have a normal electrocardiogram and transthoracic echocardiography prior to returning to competitive sports and this may be followed for those indulged in extreme physical activities. The first 2 weeks of exercise should be minimal exertion, with gradual progression with self- monitoring of symptoms.

Annexure 1

	less than usual (0)	No more than usual (0)	More than usual (1)	Much more than usual (1)
1. do you have problems with tiredness?				
2. do you need to rest more?				
3. do you feel sleepy or drowsy?				
4. do you have problems starting things?				
5. do you lack energy?				



6. do you have less strength in your muscles?				
7. do you feel weak?				
8. do you have difficulties concentrating?				
9. do you make slips of the tongue when speaking?				
10. do you find it more difficult to find the right word?				
	Better than usual	no worse than usual	worse than usual	Much worse than usual
11. how is your memory?				

Annexure 2: IV Antiepileptics for management of SE

Drug	Loading Dose	Maintenance Dose	Main Side Effects / Remarks
Phenytoin	18-20 mg/kg IV, up to 50 mg/min (25 mg/min in older patients or patients with Cardiovascular instability)	5-7 mg/kg/day orally / IV, divided every 8 hrs.	Hypotension, sedation, ataxia, cardiorespiratory depression, arrhythmia, infusion site injury * Alkaline pH PURPLE GLOVE SYN-DROME Enzyme inducer.
Fosphenytoin (water soluble pro-drug of phenytoin)	18-20 phenytoin equivalents/kg IV, up to 150 mg/min	5-7 phenytoin equivalents/kg/day/ IV, divided every 8 hrs.	Hypotension, arrhythmia, non-allergic pruritis. * Lesser risk from extravasation.
Valproate	20-40 mg/kg IV, up to 3 mg/kg/min (probably safe up to 6 mg/kg/min)	30-60 mg/kg/day, divided every 6 hrs.	Vomiting, thrombocytopenia, hepatic toxicity, pancreatitis hyperammonemia, tremors.
Levetiracetam	2500-4000 mg IV, up to 500 mg/min	2-12 g/day orally/IV, divided every 6 hrs.	Mild sedation, psychosis, behavioral and mood changes * No cardiovascular re-actions.
Lacosamide	400 mg IV over 5 min	400-600 mg/day IV, divided every 12 hrs.	Mild sedation, may prolong PR interval
Phenobarbital	20 mg/kg IV, up to 60 mg/min	1-4 mg/kg/day orally/ IV, divided every 6-8 hrs.	Hypotension, respiratory depression, skin rash, sedation * Enzyme inducer.



E. Guidelines for the Management of Long-Term Respiratory Effects of COVID-19

The respiratory system bears the maximum brunt of the direct viral damage that may persist for several weeks following initial infection. There is a considerable variation in the terminology used to denote these long-term effects of COVID-19. The National Institute of Health and Care Excellence (United Kingdom) has coined the term "Post-COVID syndrome" for persistent symptoms and signs beyond 12 weeks of illness onset which could not be explained by an alternative etiology. Additionally, the terms "Long COVID" and "Post-COVID conditions" have been used to denote the new, persistent or returning health problems beyond 4 weeks of onset of acute COVID-19. Other terms which have been used include chronic COVID-19, post-acute sequelae of COVID-19 and long-haul COVID-19.

These long-term effects of COVID-19 can be due to the damage inflicted by the virus itself, by widespread damage due to cytokine storm, by the immune response of the body, due to underlying co-morbidities, as a consequence of the therapy used to treat the disease, or a combination of all of them. The pulmonary abnormalities encountered after recovery from the acute COVID-19 illness include diffuse lung disease (inflammatory and/or fibrotic), respiratory muscle weakness (mostly in patients who have received mechanical ventilation), sequelae of pulmonary thromboembolism, and pulmonary infections (including mycosis).

Amongst hospitalized patients with COVID-19, up to 80% may continue to experience breathlessness at 3 months after discharge, but the prevalence of significant breathlessness (modified Medical Research Council grade 2 or more) is generally less than 10%. The computed tomography (CT) of the chest may show abnormalities in up to 90% of these patients at three months. However, physiologically, a lesser proportion (50-60%) of hospitalized patients would have pulmonary function test abnormalities at three months after discharge.

When do we suspect that the patient is having long term respiratory effects of COVID-19? The persistence of respiratory symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms should raise the suspicion for sequelae. If no alternate reason is found for these respiratory symptoms, the condition is termed as Long COVID. The cardinal symptoms of post-acute COVID-19 respiratory sequelae include the following

- Shortness of breath
- Dry cough
- Chest pain



There are certain warning signs that may be suggestive of serious abnormalities (Box 1).

Box 1. Dangerous symptoms and signs

(Suggestive of serious cardiorespiratory illness among patients with Post-acute COVID-19 syndrome)

Symptoms

- Acute or severe chest pain
- Acute or severe dyspnea/respiratory distress
- Hypotension
- Hemoptysis
- High grade fever

Signs

- Spo2 <90%
- Increased respiratory rate or heart rate
- Cyanosis of tongue or finger tips (cyanosis)
- Increased use of accessory muscles

Who are the persons at a higher risk for the development of Post-COVID pulmonary sequelae?

There are certain groups of patients who may be at a higher risk for pulmonary sequelae (Box2)

Box 2. High risk group patients of Post-COVID pulmonary sequelae

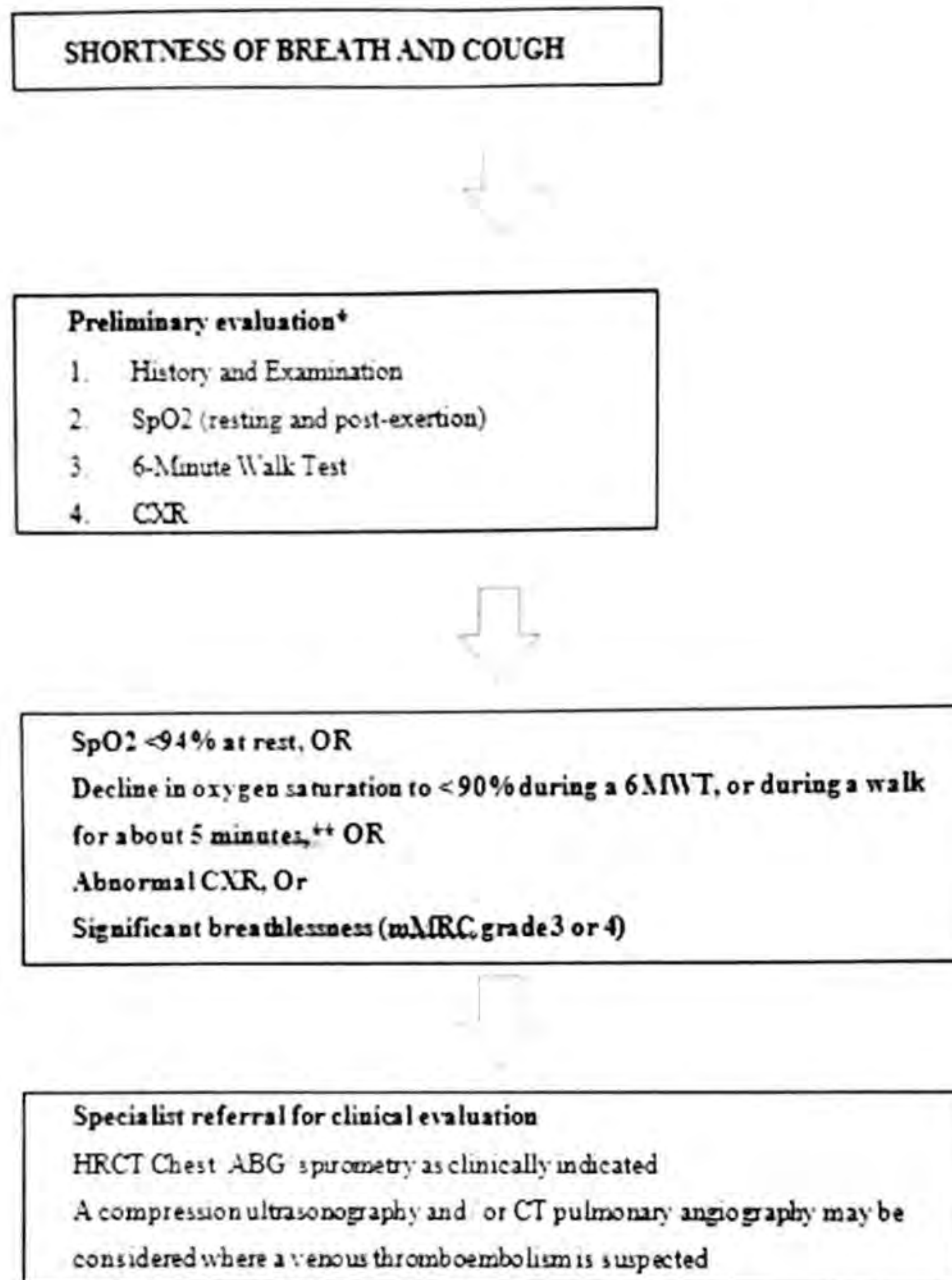
- Age > 60 years
- Smoker
- Comorbidities- DM/HTN/CAD
- Pre-existing respiratory disease (eg: asthma, COPD, ILD)
- Requiring Oxygen therapy at home
- Patient who required MV/ NIV during the acute COVID-19 illness

What should be the initial evaluation of a patient with suspected long-term respiratory effects of COVID-19?

The proposed algorithm for the evaluation of patients with symptoms suggestive of Post- COVID respiratory sequelae is depicted in Figure 1.



Figure 1. Proposed algorithm for the evaluation of patients with symptoms suggestive of Post-COVID respiratory sequelae



6-MWT- six-minute walk test, ABG-arterial blood gases, CXR- chest radiograph, DLCO- diffusion capacity for carbon monoxide, HRCT- high resolution computed tomography, mMRC- modified Medical Research Council, SpO2-oxygen saturation

*An ECG and/or echocardiography may be considered in case of acute onset chest pain

**Beyond the first three months, a decline in oxygen saturation below 94% would be considered abnormal

The following clinical features might suggest specific illnesses in the Post-acute COVID phase (Table 1)

Table 1. Differential diagnoses for common clinical symptoms and signs related to the cardiorespiratory system in the Post-acute COVID phase

Clinical symptom/sign/feature	Suspect the following*
Acute breathlessness/hypoxemia/respiratory distress	Myocardial infarction Pulmonary thromboembolism Pneumothorax
Acute chest pain	Myocardial infarction Pulmonary thromboembolism Pneumothorax
Ongoing dry cough	Postnasal drip Gastroesophageal reflux Bronchitis/bronchial asthma Post COVID diffuse lung disease (inflammatory/fibrotic)
Ongoing breathlessness	Post COVID diffuse lung disease (inflammatory/fibrotic) Chronic pulmonary thromboembolism
Fever	Systemic infection (look for symptoms and signs of other system involvement) Pneumonia (bacterial/fungal) Pulmonary Tuberculosis
Palpitations	Anxiety Hyperthyroidism Arrhythmias Pulmonary thromboembolism
Significant sputum production	Pneumonia Tracheobronchitis Other respiratory infections
Hemoptysis	Pulmonary thromboembolism Pulmonary mycosis Exacerbation of pre-existing chronic bronchitis Pulmonary tuberculosis
Hypotension	Myocardial infarction Pulmonary thromboembolism Pneumothorax Pneumonia with sepsis Sepsis (due to any other system infection)

*This list is not exhaustive, but only suggests the more common disorders encountered in the Post-acute COVID phase

Initial treatment offered to patients with Post-COVID respiratory sequelae?

The treatment of Post-COVID respiratory sequelae involves treatment of specific pathologic conditions such as Post-COVID diffuse lung disease (PC-DLD), pulmonary embolism, pulmonary infections, or others. It also involves the management of respiratory symptoms.

 Page 28 of 30

Management of specific Post-Covid pulmonary conditions

The treatment of specific pathologic conditions should be offered by physicians experienced in the management of these disorders. A guidance is provided below.

a) Post-COVID Diffuse Lung Disease

The lung parenchymal abnormalities that persist after the recovery from the acute COVID-19 illness may represent either a persistent inflammatory pathology or pulmonary fibrosis. An HRCT chest is helpful in characterizing the extent and type of such abnormalities. Currently, there is no conclusive scientific evidence available to guide the treatment of these abnormalities. Observational studies show that these radiological abnormalities resolve in most patients without any specific treatment. The management of suspected lung fibrosis should be handled by experts with previous experience of managing fibrotic interstitial lung disease.

b) Pulmonary embolism

Therapeutic anticoagulation should be administered to patients with pulmonary embolism. The minimum duration of such treatment should be 3 months. Prolongation beyond this period would depend on the assessment of the risk of relapse and must be done by a specialist. Prophylactic anticoagulation is generally stopped at the time of discharge from hospital; however, it may be continued as per clinical requirement under careful supervision.

c) Pulmonary infections

Secondary bacterial pneumonia should be managed with oral/intravenous antibiotics according to standard guidelines. Physicians should be aware that most such patients would have had contact with a healthcare facility during the acute COVID-19 illness, therefore, they are at a higher risk of having resistant microbes. As there has been a rise of cases of pulmonary fungal infection, especially mucormycosis, careful attention should be paid to exclude these infections in patients with fever, sputum, and/or hemoptysis. The treatment of such infections should be offered at experienced centers with the help of antifungal agents and/or surgical interventions, as indicated.

d) Management of symptoms and general ill health

Certain general measures should be followed by all patients having Post-COVID symptoms. These include a nutritious diet, a regular schedule of exercise appropriate for the age and physical status, a regular monitoring of important parameters (such as oxygen saturation at rest and on exercise, especially for patients with respiratory sequelae). Domiciliary oxygen and pulmonary rehabilitation may be indicated in certain individuals. Patients with breathlessness, and or cough may benefit from breathing exercises. Certain pharmacological measures may be required to manage cough and breathlessness. The comorbid illnesses should be managed appropriately.

e) Management of Cough

1. Cough should be treated according to the underlying cause.
2. Appropriate evaluation for infections should be performed for productive cough.
3. Dry cough due to lung disease can be managed with simple antitussive agents such as dextromethorphan.
4. If cough is associated with wheeze, inhaled bronchodilators (with or without inhaled corticosteroids) may be administered.
5. Cough arising from gastroesophageal reflux and post-nasal drip can be treated using ant reflux medications (H2-receptor blockers, proton pump inhibitors, etc.) and antihistaminic agents (with or without antitussives), respectively. Warm saline gargles or lozenges may help soothe the throat in case of upper airway -related cough.

f) Management of breathlessness

1. Management can be treated according to the underlying cause.
2. In hypoxemic patients, domiciliary oxygen therapy, as detailed above helps in reducing breathlessness. A structured pulmonary rehabilitation program helps in reducing breath- lessness.
3. Patients who cannot be enrolled in a structured pulmonary rehabilitation program should be advised to maintain a good walking schedule in accordance with their age and physical status. Care should be taken to avoid overexertion and exercising to the extent of inducing hypoxemia.
4. Certain breathing exercises may help reduce breathlessness.

Patients should be advised to stop exercising, if they develop any of the following:

- 1) Nausea or vomiting
- 2) Breathlessness
- 3) Dizziness
- 4) Significant sweating
- 5) Chest tightness
- 6) Increased pain

g) Domiciliary oxygen therapy:

Domiciliary oxygen therapy is generally required for patients with resting or exertional oxygen saturation below 90%. It may be delivered from an oxygen concentrator or oxygen cylinder, via nasal prongs.

h) Pulmonary rehabilitation:

A structured pulmonary rehabilitation is advisable for patients with moderate / severe COVID-19, especially those who remain symptomatic after the acute episode. This should include exercise training as well as inspiratory muscle exercises, preferably under supervision. Optimum sessions are of 30-45 minutes duration for at least 2-3 times per week and for at-least 8-12 weeks. If done at home, the use of videoconferencing may be useful for monitoring the sessions.