

# Clinical Guidelines: Long COVID-19

Clinical consensus guidelines for patients with chronic COVID-19 symptoms, also known as “long-haulers.”

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## Contents

- Introduction ..... 2
- Epidemiology ..... 2
- Symptom Complexes..... 2
- Treatment ..... 2
  - Neurological Symptoms ..... 3
  - Cardiovascular Symptoms..... 5
  - Pulmonary Symptoms ..... 7
  - Neuropsychiatric Symptoms..... 8
  - Sleep Disorders..... 10
  - Gastrointestinal Symptoms ..... 11
  - Considerations for Older Adults..... 13
  - Phases of Rehabilitation..... 13
- References: ..... 15

## Introduction

By December 2020, 14 million individuals in the United States had been infected with COVID-19 (WHO). Illness from SARS-CoV2, or COVID-19, has immediate and long-term consequences, which can be conceptualized in three phases (Datta et al., 2020). Phase one acute illness lasts days to weeks and is caused by viral replication and initial immune response. A less common phase two post-acute hyperinflammatory illness (multisystem inflammatory syndrome in children, MIS-C and multisystem inflammatory syndrome in adults, MIS-A) occurs two to five weeks after onset of infection and is caused by dysregulated immune response. Those with this syndrome may suffer from cardiovascular, gastrointestinal, dermatologic and mucocutaneous manifestations similar to Kawasaki disease. In phase three, late inflammatory and virological sequelae may persist for months, and their etiology is unclear. This is known as chronic COVID-19, or Long COVID-19. For our purposes, Long COVID-19 is defined by the persistence of COVID-19 symptoms 28 days after initial onset of symptoms (Del Rio et al., 2020). Notably, severity of acute illness may not correlate with the likelihood of late sequelae of COVID-19. Many patients are young and previously healthy. Most children who are diagnosed with COVID-19 experience mild (if any) symptoms. Throughout the pandemic, however, we have noted that some children may develop symptoms also seen in adults with Long COVID-19, including prolonged fatigue, brain fog and school problems, dizziness and palpitations, among others. Specific diagnostic and treatment modalities for children may be needed.

## Epidemiology

After recovery from acute illness, many patients struggle with prolonged symptoms and disability. At 14-21 days post-infection, 34% of respondents previously diagnosed with symptomatic COVID-19 had not yet returned to their usual state of health (Tenforde et al., 2020). Another study of patients who had mild to moderate symptoms of COVID-19 during that initial illness found that 69% of patients at Day 30 had at least one chronic symptom, and at Day 60, 66% still had at least one persistent symptom (Carvalho-Schneider et al., 2020). Older patients and those with more chronic medical conditions tended to have a higher risk of persistent symptoms, while obesity and previous psychiatric conditions were independent risk factors (Tenforde et al., 2020).

## Symptom Complexes

While the lung is the organ most affected by SARS-CoV-2, COVID-19 infection has multisystem effects, including systemic inflammation, immune dysregulation, hypothalamic-pituitary-adrenocortical axis activation leading to immunosuppression and lymphopenia, a hypercoagulable state, encephalopathy and encephalitis, and systemic organ failure (Iadecola et al. 2020). Therefore, the symptoms of COVID-19 are broad and variable. No individual symptom or clusters of symptoms has proven specific for the diagnosis of COVID-19. Presentation varies from mild symptoms, such as fever, headache, cough, dyspnea, myalgia, and anosmia to acute respiratory distress syndrome (ARDS), which can cause death (Nath, 2020). Beyond acute phase, patients can continue to experience symptoms, with fatigue, headache, and dyspnea being common (Sudre et al. 2020). At OHSU, we offer subspecialty consultation based on the predominant symptom complexes. These symptom complexes are not meant to be restrictive; there is a high degree of variation in symptoms among patients.

## Treatment

Clinical trials involving treatment of this entity are lacking. Therefore, evidence-based guidelines lag behind the needs of patients. In this guideline, we draw upon the experience and expertise of a multidisciplinary

team at OHSU, including physician-patients with Long COVID-19 as well as an environmental survey of national centers to develop management recommendations that are based on the best available science and expert opinion. Those centers include University of California-San Francisco, University of Iowa, Mount Sinai Hospital, University of Pennsylvania, Albert Einstein College of Medicine, and Northwestern University.

There are no specific treatments available for Long COVID-19 at this time. After ruling out serious ongoing complications, care is focused on pragmatic and symptomatic management with an emphasis on holistic support, while avoiding unnecessary testing (Greenhalgh et al., 2020). Patient counseling should include education about the persistent and the relapsing/remitting nature of symptoms. Patients should be encouraged to mobilize their support networks early. Self-care should be encouraged in the form of sleep hygiene, eating a healthy diet, and maintaining mild physical activity. Patience and pacing are virtues for our patients with Long COVID-19. Rehabilitation programs under the guidance of a physical therapist may be beneficial and occur in a graded fashion.

## Neurological Symptoms

Acute neurological manifestation of COVID-19 is present in about a third of patients in acute settings (Mao et al., 2020). Symptoms can be divided into central nervous system manifestation (headache, dizziness, ataxia, acute cerebrovascular disease) and peripheral nervous system manifestation (nerve pain, smell and taste impairment) (Mao et al., 2020). Acute neurological symptoms arise from the combination of these mechanisms: cerebrovascular changes, peripheral organ dysfunction, systemic inflammation, and direct viral neuroinvasion (Heneka et al., 2020).

Chronic neurological symptoms include brain fog, headache, vertigo, and smell and taste dysfunction. These symptoms are thought to arise from disruption of brain homeostasis, activation of nociceptive receptors, and damage to vascular and neuronal tissues (Zubair et al., 2020).

### Evaluation

Table 1 includes suggested tests and studies to consider in an initial evaluation of neurological symptoms. Table 2 lists tests suggested for evaluation of headaches presenting with the corollary “red flag” symptoms, which include headaches that are associated with double vision, peripheral vision loss, weakness/numbness, ataxia or altered mental status or exacerbated with postural changes, coughing, sneezing, or Valsalva maneuver.

*Table 1: Suggested tests and studies for initial evaluation of neurological symptoms*

Symptoms	Testing
Persistent dizziness/vertigo	Autonomic reflex testing
Seizure, seizure-like activity	Ambulatory EEG
Cognitive decline: temporary or permanent “brain fog”	MOCA/MMSE screening, neuropsychological testing
Delirium/encephalopathy	Brain MRI with and without contrast
Unilateral weakness/sensory dysfunction	Brain MRI without contrast
Nerve and muscle pain	EMG/NCS
Headache	None unless red flag symptoms (see Table 2)

Table 2: Suggested imaging studies for the evaluation of headaches with concerning “red flag” symptoms

Signs/symptoms associated with headaches	Testing
Worsens with postural changes Associated with double vision/peripheral vision loss	Brain MRI with and without contrast, brain MRV
Worsens with coughing, sneezing, Valsalva maneuver	Brain MRI without contrast, head and neck MRA
Unrelenting	Brain MRI without contrast
Associated with weakness/numbness, ataxia, altered mental status or other neurological symptoms	Brain MRI without contrast

### Treatment

Because of the wide array of neurologic symptoms. Suggested treatment approaches are outlined in Table 3.

Table 3: Treatment of neurologic symptoms

Clinical manifestations	Treatment
Persistent dizziness/vertigo	Tailor treatment to underlying cause: Vertigo: Meniere's disease, vestibular migraine, BPPV, vestibular neuronitis Dizziness: autonomic dysfunction vs. PPPD
Seizure, seizure-like activity	Tailor treatment to phenotype: Psychogenic nonepileptic seizure (PNES): CBT, supportive care Focal epilepsy: narrow spectrum medication, such as lacosamide or carbamazepine. Generalized epilepsy: broad spectrum medication such as levetiracetam or valproate
Cognitive decline-temporary or permanent, “brain fog”	Supportive care
Delirium/Encephalopathy	Treat source of symptoms (i.e., UTI). Rule out other source (medication, seizure, stroke).
Unilateral weakness/sensory dysfunction	Tailor treatment to underlying cause: Stroke Radiculopathy Peripheral neuropathic Todd's paralysis (paralysis following a seizure)
Nerve and muscle pain	Neuropathic pain: gabapentin or TCA Neuralgic pain: carbamazepine or oxcarbazepine Myofascial pain/musculoskeletal pain: pregabalin or duloxetine

Headache	Tailor treatment to phenotype of headache: Tension-type: TCA or SNRI Migraine-type: TCA, anticonvulsants or beta-blockers
Sleep dysfunction	Tailor treatment to particular dysfunction: Sleep phase disorder: CBT, sleep hygiene, short term course of hypnotic drugs Central vs. obstructive OSA: CPAP vs. oral appliances

**Cardiovascular Symptoms**

COVID-19 infection has variable cardiovascular sequelae. In a recent study, 60% of patients with a history of COVID-19 infection had cardiac inflammation detectable on cardiac MRI. Notably, this finding was independent of chronic comorbidities, duration, or severity of acute COVID-19 infection or time since original diagnosis (Puntmann et al., 2020). In another study, 46% of 26 non-hospitalized college athletes had myocarditis or evidence of prior myocardial injury 12-53 days after acute infection (Rajpal et al., 2020).

During hospitalization for COVID-19, cardiovascular complications are noted in 15-20% of patients. These complications include myocardial injury (10 %), angina (10%), arrhythmias or palpitations (18%), acute heart failure (2%), and acute myocardial infarction (3.5%). Preexisting cardiovascular comorbidities or risk factors were significant predictors of these cardiovascular complications. Inflammation and nonischemic scar are most common among patients recovering from mild or asymptomatic COVID-19, although the true prevalence and clinical implications remain unknown.

All patients with cardiac symptoms should limit exercise until after an evaluation by a physician.

*Evaluation*

**Chest Pain, dyspnea and fatigue**

After hospitalization, chest pain, dyspnea, and fatigue are the most common cardiac symptoms among patients with Long COVID-19. Evaluation of these symptoms is guided by cardiovascular risk factors and the specific pathology identified or suspected. The differential diagnosis and suggested initial diagnostic workup for cardiac symptoms are listed in Table 4.

For patients with symptoms suggestive of obstructive coronary artery disease (dominant symptom of typical or atypical angina), we recommend considering coronary CT angiography, given its high negative predictive value for CAD (both obstructive and nonobstructive) and challenges with interpreting stress echocardiography if regional wall motion abnormalities are present (Ferreira et al., 2018).

Heart failure symptoms should be evaluated with a transthoracic echocardiogram (TTE). Cardiac MRI can be ordered for clinical suspicion of myocarditis.

**Dysautonomia**

Dysautonomia may be triggered directly by the virus or by an immune-mediated response to COVID-19 infection. The pathology may emerge acutely (Romero-Sanchez et al., 2020) and remain a persistent symptom of Long COVID-19 (Dani et al., 2020). Disruption of the autonomic system results in orthostatic intolerance, which can be divided in three subgroups: postural orthostatic tachycardia syndrome (POTS), orthostatic

hypotension, and vasovagal syncope (Table 4). Symptoms associated with orthostatic intolerance include syncope, dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, headache, dyspnea, chest pain, and neck and shoulder pain. Typically, symptoms are triggered or worsened by upright posture. Thus, a tilt table evaluation can help distinguish between these conditions.

Table 4: Three subgroups of orthostatic intolerance

Condition	Response to head-up tilt table test
<b>Postural orthostatic tachycardia syndrome (POTS)</b>	Heart rate increases (at least 30 beats/min) within first 10 minutes of testing with no change in blood pressure (no hypotension)
<b>Orthostatic hypotension</b>	Blood pressure falls (SBP by 20 mm Hg or more, or DBP by 10 mm Hg or more) with no increase in heart rate
<b>Vasovagal syncope</b>	Blood pressure drops with decrease in heart rate (Abnormal increase in parasympathetic activity)

### Myocarditis

The most feared sequelae include arrhythmia and out-of-hospital cardiac arrest, usually associated with cardiomyopathy (Carfi et al., 2020). Screening for myocarditis can be conducted using a transthoracic echocardiogram. A cardiac MRI (myocarditis protocol) may be obtained to follow up on abnormalities and confirm the diagnosis (Knuuti et al., 2018 and Knuuti et al., 2020). Table 5 outlines suggested differential diagnosis and testing for cardiac symptoms.

Table 5: Differential diagnosis and recommended tests for the evaluation of cardiac symptoms

Symptom	Differential diagnosis	Testing
<b>Chest pain</b>	Chest wall pain, GI source, pericarditis, myocarditis, established CAD, thromboembolic disease, etc.	EKG, ECHO, CTA coronaries
<b>Dyspnea</b>	Residual lung disease, myocardial involvement, pulmonary embolism, angina variant	BNP, EKG, ECHO, Cardiac MRI*
<b>Palpitations</b>	Arrhythmia related to myocardial, pericardial disease or PE, dysautonomia with POTS	EKG, ZIO patch, ECHO
<b>Fatigue</b>	Anemia, hypoxemia, heart failure	EKG, ZIO patch, ECHO
<b>Dysautonomia</b>	Dehydration, autonomic failure, POTS	Autonomic reflex testing

\*If history of myocarditis, cardiomyopathy, reduced LV Function

### Treatment

#### Dyspnea and chest pain

Etiology of chest pain and dyspnea can be multifactorial, and treatment should be guided by clinical evaluation and evidence based guidelines.

#### Dysautonomia

Treatment for dysautonomia includes behavioral modifications and pharmacologic interventions. Patients may be advised to increase salt intake to counteract hypovolemia, wear compression socks to help with

venous return, and increase physical activity to help with deconditioning. Pharmacologic management options include:

- **Fludrocortisone** (steroid): Increase plasma volume and salt retention (up to 0.2 mg per day).
- **Midodrine** (adrenoreceptor agonist): Increase vasoconstriction, improve venous return (up to 10 mg TID).
- **Propranolol** (nonselective beta-blocker): Reduce tachycardia (up to 20 mg TID).
- **Clonidine** (alpha 2 agonist): Can decrease sympathetic activity (0.3 mg bid).
- **Pyridostigmine** (acetylcholinesterase inhibitor): Reduce tachycardia and burden of symptoms (30 mg daily).

If tilt table test is not readily available but clinical suspicion is high, treatment should not be delayed.

### Myocarditis

Treatment for myocarditis includes instructions to restrict physical activity. Medications may include beta blockers. A three-month follow-up cardiac MRI can be obtained to confirm resolution (Knuuti et al., 2018 and Knuuti et al., 2020).

## Pulmonary Symptoms

Cough and shortness of breath are common presenting complaints of COVID-19 (Cheng et al., 2020). These symptoms frequently persist (Tenforde et al., 2020 and Chopra et al., 2020). Complications of acute infection include chronic cough, fibrotic lung disease, bronchiectasis, and pulmonary vascular disease (Fraser et al., 2020).

### Evaluation

#### Cough

As seen in other respiratory infections, a protracted postinfectious cough may last up to eight weeks. This diagnosis should be made after appropriate evaluation with history and pulmonary radiography. Exacerbation of preexisting pulmonary conditions should be considered in the differential.

#### Dyspnea

Progressive dyspnea is not expected and should trigger evaluation. Assessment of concerning persistent or progressive pulmonary symptoms should begin by ruling out superinfection, underlying chronic lung disease, and cardiac causes. Chest imaging may be considered, including two-view chest X-ray to look for new infiltrate or other obvious processes. Additionally, one can consider obtaining chest CT to rule out lung structural changes, pulmonary function tests to evaluate for physiological changes, echocardiogram to evaluate heart function and evidence of pulmonary hypertension, and labs to evaluate for anemia, renal disease, and liver dysfunction. It is most important to look for potentially treatable entities, such as steroid-responsive parenchymal disease, tracheal stenosis in patients recovering from endotracheal intubation, and reversible airflow obstruction.

Table 6: Differential diagnosis and recommended tests for the evaluation of pulmonary symptoms

Symptom	Differential diagnosis	Testing
<b>Dyspnea</b>	Anemia, heart failure, myocarditis, thromboembolic disease, hypoxemia, pulmonary fibrosis, pulmonary vascular disease	CBC BNP, EKG, ECHO, cardiac MRI, D-dimer, ferritin, home pulse oximetry, CT chest, PFTs

<b>Cough</b>	GERD, superinfection, pleuritis	CXR, CT chest
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### Treatment

#### Cough

Treatment options for post-infectious cough include antihistamines for post-nasal drainage, antacids for gastroesophageal reflux disease and bronchodilators for asthma or bronchial reactivity.

#### Dyspnea

Consider home pulse oximetry measurements to reassure patients against hypoxemia for persistent dyspnea. Give patients education about the proper use of the device and instructions to keep a log of readings as well as when to call for help. Readings should be compared to the patient's baseline. Evidence does not suggest that this increases anxiety (Greenhalgh et al., 2020).

Consider supplemental oxygen for patients without underlying pulmonary disease who have pulse oximetry readings below 92% and for those with chronic lung disease below 88%. Table 6 lists initial tests appropriate for the evaluation of dyspnea and cough. Patients acutely receiving supplemental oxygen should be routinely evaluated for continued need. Patients with diagnosed deep vein thrombosis or pulmonary embolism during acute COVID-19 should receive additional follow-up regarding duration and adequacy of anticoagulation.

### Neuropsychiatric Symptoms

Individuals with a prior COVID-19 infection are at increased risk for experiencing neuropsychiatric symptoms weeks or months following the acute infection. While many of these individuals already have preexisting neuropsychiatric diagnoses, at least 20% of individuals have no prior neuropsychiatric diagnosis, according to recent research. These include, but are not limited to, cognitive dysfunction or brain fog, depression, anxiety, insomnia, and symptoms of post-traumatic stress disorder (Taquet et al., 2020).

The underlying pathophysiology is not fully understood. While recent research suggests COVID-19 is capable of infiltrating the central nervous system, there is not a distinct correlation between this infiltration and the presence and/or severity of neuropsychiatric symptoms. Alternatively, a postinfectious inflammatory response causing CNS dysfunction is theorized as a potential mechanism (Matschke et al., 2020).

### Evaluation

Initial evaluations of COVID-19 patients should include basic cognitive screening (ANAM, MOCA – clinician administered), sleep quality screening, basic depression and anxiety screening as well as overall quality of life screening (PHQ-9, GAD-7 and SF-36 surveys completed by patient in advance or with clinician during appointment). Patients who express symptoms concerning for post-traumatic stress disorder may be screened with the PC-PTSD-5 (Primary Care PTSD Screen for DSM-5), which may identify those who may benefit from further evaluation and/or referral to mental health. Screening scores suggesting active symptoms of moderate severity should prompt consideration of a referral for further neuropsychiatric assessment and/or neuropsychological testing. We recommend that all hospitalized patients complete a brief neuropsychological assessment battery (ANAM) relative to discharge.

Extrapolating from previous coronavirus outbreaks, it is unlikely that there is a unitary factor that can account for the cognitive impairment in COVID-19 patients. Rather, there is an interaction between illness-related factors (e.g., severity), medical and psychiatric comorbidities, hospital admission, ICU admission and treatment factors, and premorbid variables (Hopkins & Jackson, 2006). If cognitive impairment is present at hospital discharge, improvements in neuropsychological status are likely for most patients in the first year



and are likely to plateau after this milestone. Latent onset of neuropsychological symptoms has been demonstrated in ARDS (9%) that were not present at hospital discharge. Probable cognitive sequelae include reduced speed of processing, attention, executive functions, learning and memory. Language and visuospatial abilities are largely spared (Rabinovitz, Jaywant, & Fridman, 2020; Riordan et al., 2020).

Table 7 lists differential diagnoses and testing appropriate for common neuropsychiatric sequelae. Neuropsychiatric testing and psychiatric evaluation may be appropriate.

*Table 7: Differential diagnosis and recommended tests for the evaluation of neuropsychiatric symptoms*

Symptom	Differential diagnosis	Testing
<b>Cognitive dysfunction</b>	Premorbid cognitive disorder (e.g., dementia), secondary impact from insomnia, fatigue, depression, neurologic injury from acute illness (e.g., stroke)	ANAM  MOCA, MMSE, Mini-Cog for geriatric patients
<b>Depression</b>	Premorbid mood disorder (e.g., major depressive disorder, bipolar disorder), secondary impact from neurologic injury from acute illness (e.g., stroke), persistent depressive disorder, depressed mood associated with comorbid substance use disorder or anxiety disorder	PHQ-9, HAM-D (inpatient), GDS short form for geriatric patient
<b>Anxiety</b>	Premorbid anxiety disorder (e.g., generalized anxiety disorder, social anxiety disorder, specific phobia, obsessive compulsive disorder), anxiety associated with comorbid substance use disorder or post-traumatic stress disorder	GAD-7, HAM-A (inpatient)
<b>Insomnia</b>	Premorbid sleep disorder, hypersomnolence disorder, circadian rhythm sleep-wake disorders, substance/medication-induced sleep disorder	ISI, ESS

### *Treatment*

Neuropsychological treatments vary by the treating provider but have generally include cognitive rehabilitation, psychotherapy, and CBT-I (gold standard psychological intervention for sleep disturbances). The Institute of Medicine defines cognitive rehabilitation as the following: “Cognitive rehabilitation attempts to enhance functioning and independence in patients with cognitive impairments as a result of brain damage or disease, most commonly following TBI or stroke.” (IOM, 2011, p. 76). Interventions are modular and multifaceted, and can include compensatory strategies, safety planning, cognitive remediation/retraining, establishing routines, and optimizing a healthy lifestyle, including psychotherapy. A healthy lifestyle (including mental health) and a support network can be paramount for rehabilitation success. Thus, treatment of psychiatric conditions and sleep health are often included in cognitive rehabilitation protocols and can address not only cognitive sequelae, but also commonly comorbid symptoms, such as headache and fatigue. Speech language pathologists also commonly provide cognitive rehabilitation, but with less focus on psychological factors.

Treatment for anxiety and depression will depend on the severity of the symptoms and their impact on the patient’s current social and occupational functioning. Ensuring a patient has adequate social support and addressing major psychosocial stressors (e.g., financial, work-related, interpersonal, substance use) are key

to identifying barriers to symptom management and recovery. This can often be accomplished by basic counseling or referral to psychotherapy for individual, group, or family therapy sessions. If symptoms are moderate to severe, a proper safety assessment for imminent risk of danger to self or others is critical to determine potential need for a higher level of care, like inpatient management. Medication management may be necessary. Selective serotonin reuptake inhibitors (SSRIs) are the first line of treatment for symptoms of depression and anxiety. These include sertraline, fluoxetine, escitalopram, citalopram, paroxetine, and others. The extent of management of these types of medications in primary care should depend on the prescriber’s degree of familiarity and comfort with them. Anything outside the scope of typical practice should prompt a referral to a mental health prescriber.

Treatment for post-traumatic stress disorder that is most efficacious includes individual, manualized trauma-focused psychotherapy. These have a primary component of exposure and/or cognitive restructuring and may include prolonged exposure (PE), cognitive processing therapy (CPT), and eye movement desensitization and reprocessing (EMDR). When this is not readily available or not preferred, pharmacotherapy or individual nontrauma-focused psychotherapy may be used. There is moderate evidence of monotherapy with sertraline, paroxetine, fluoxetine and venlafaxine.

## Sleep Disorders

Chronic sleep difficulties are common symptoms reported with COVID-19 (Huang et al., 2021). Hypersomnia, insomnia, and obstructive sleep disordered breathing are the most common sleep disorders reported. Narcolepsy has been reported in other post-viral conditions. Central sleep disordered breathing should be ruled out in cases of heart failure or if neurological involvement is present.

### Evaluation

We recommend evaluation of underlying preexisting sleep disorders that will exacerbate symptomatology. Screening for sleep disordered breathing should be considered with clinical presentation of symptoms of fragmentation of sleep, hypersomnia, or other symptoms of apnea, such as gasping arousals and snoring. Viral syndromes can interfere with ventilatory control leading to a diagnosis of central sleep apnea, which has rarely been reported. A score of three or greater on the STOPBANG questionnaire indicates a high pretest probability for obstructive sleep apnea, and the patient should be referred for diagnostic evaluation for home apnea testing, an in-lab polysomnography, or referral to a sleep medicine specialist. A score of 10 or greater of the Epworth sleepiness scale indicates pathological hypersomnolence.

Table 8: Evaluation of sleep dysfunction

Symptom	Testing
<b>Sleep dysfunction</b>	Home apnea test or PSG, MSLT, actigraphy depending on specific clinical presentation

### Treatment

If sleep disordered breathing is identified, then treatment with positive airway pressure or oral appliance therapy may be helpful. Stimulants or wakefulness-promoting agents can be helpful in some cases with hypersomnia. Short term hypnotics may be considered with close clinical follow up as long as other etiologies for fragmentation of sleep are ruled out. Melatonin at low doses may be tried two hours before desired bedtime to secure the circadian rhythm.

Chronic insomnia is best treated with cognitive behavioral therapy for insomnia (CBT-I) to address underlying behavioral patterns. CBT-I can be provided in person or with apps, such as CBTi-Coach. The main

tenets of CBT-I use behavioral strategies, such as stimulus control, sleep restriction, and relaxation therapy, and eliminating negative thought patterns to treat insomnia.

## Gastrointestinal Symptoms

Prevalence of gastrointestinal symptoms are as follows: diarrhea (7.7%), nausea/vomiting (7.8%), abdominal pain (3.6%) (Sultan et al., 2020). There are no reports of gastrointestinal symptoms being the only presenting symptom of COVID-19, but it may be the first/primary presenting symptom of COVID-19. Gastrointestinal symptoms and involvement are associated with a more severe disease course (Ouali et al., 2020).

Stool with a positive COVID-19 PCR test is more common in patients with gastrointestinal symptoms (70%) than in those without (17%). However, it will stay positive (in up to 70%) for two to three weeks and possibly longer (Cheung et al., 2020), even after respiratory samples are negative for COVID-19. This is further prolonged in patients using steroids. Gastrointestinal involvement is likely related to the presence of ACE2 receptors throughout the gastrointestinal tract; the COVID-19 nucleocapsid protein has been found in gastric, duodenal and rectal cells.

The liver is also often involved in COVID-19 infection, with elevated serum liver biochemistries in hospitalized patients ranging from 14%-83% (Fix et al., 2020). Typically, these patients have only modest elevations in bilirubin and AST/ALT 1-2x ULN. Predictors of worse peak liver tests are severity of COVID-19, age, male gender, body mass index, diabetes mellitus, medications (e.g., lopinavir/ritonavir, hydroxychloroquine, remdesivir, tocilizumab) and inflammatory markers (IL-6, ferritin). Due to the prevalence of ACE2 receptors in biliary and hepatic epithelial cells, the liver is a common target of COVID-19. Particles of COVID-19 have been found in hepatocytes even without other typical markers of viral infection. Liver histology is nonspecific but has included macrovesicular steatosis, microvesicular steatosis, acute hepatitis (lobular inflammation), mild portal inflammation and focal necrosis.

There is scarce literature on gastrointestinal and liver symptoms in Long COVID-19, but acute symptoms may persist. Management is similar to that of chronic symptoms in patients without COVID-19 and is detailed in Table 9. If no alarm symptoms are present, initial focus is on supportive measures, with progressive workup as warranted based on duration and severity of symptoms.

### Evaluation

If workup (as in table 9) has not revealed an alternative etiology, treatment should be focused on management of symptoms. This includes managing stressors by providing behavioral health support (psychotherapy, cognitive behavioral therapy) and using complementary alternative therapies, such as yoga, acupuncture, and massage. In select cases, supportive medications (anti-diarrheal, anti-nausea, etc.) can be used as well.

If primarily watery diarrhea, first-line response should focus on supportive measures with adequate hydration and nutrition. In select instances, patient can trial anti-diarrheal medication (loperamide), but generally recommend ruling out infectious etiology before use. If diarrhea persists for more than two to four weeks, we recommend a full infectious workup (stool cultures, C. diff, O&P, giardia) as well as checking inflammatory markers (fecal-calprotectin and CRP), TSH and celiac panel. Review of potential culprit medications, supplements, and diet (i.e., artificial sugars) are often revealing. In immunocompromised patients, providers should also consider evaluation for Cyclospora, Isospora, Cryptosporidium, microsporidium (if CD4 <100). In persistent cases, colonoscopy and upper endoscopy may be helpful.

Bloody diarrhea or steatorrhea should prompt more urgent infectious workup. Bloody diarrhea should be checked for stool culture as well as Yersinia and Aeromonas. A fecal fat test can confirm diagnosis of steatorrhea and target workup for giardia/parasites as well as pancreatic/biliary/small bowel etiologies.

In patients with nausea/vomiting or abdominal pain, triage is dictated by severity of symptoms. Severe symptoms require immediate evaluation, including consideration of central nervous system etiologies. Mild/moderate symptoms can be treated supportively if patient is able to take in sufficient nutrition/hydration. Review medications (NSAIDs) and stressors for potential culprits. Persistent symptoms require further evaluation. If symptoms are consistent with gastroesophageal reflux disease (GERD) or dyspepsia, can trial H2 receptor antagonist (H2RA) or proton-pump inhibitor for eight weeks. H2RAs (specifically famotidine) have been associated with decreased COVID-19 infection and decreased risk of death in hospitalized patients. H2RAs may have particular benefit for symptoms mediated by COVID-19-induced mast cell activation. In dyspeptic cases, provider can also consider checking H. pylori and treating if positive. In some cases, workup may include abdominal imaging and/or endoscopy.

Management of persistent elevations in liver enzymes is also dictated by severity and pattern of elevation. Borderline levels can be monitored to see if self-resolve or worsen. Low level elevations (<5x ULN) should receive a basic workup (see Table 9), and if unrevealing, can be monitored as well. Higher elevations (>10x ULN) should receive more extensive workup in conjunction with a hepatology consult.

Table 9: Differential diagnosis and recommended tests for the evaluation of gastrointestinal symptoms

Symptom	Differential diagnosis	Testing
<b>Diarrhea</b>	Medications, infection, ischemia, inflammatory, dysmotility, malabsorption/  maldigestion, food intolerance, irritable bowel syndrome	Supportive measures initially (ensure adequate hydration, OTC anti-diarrheal). If prolonged >2-4 weeks – stool cx, c. diff, O&P, giardia, fecal calprotectin, TSH, celiac markers.
<b>Nausea/vomiting</b>	Medications, infection, GERD, gastroparesis, obstruction, CNS, functional	Review medication usage, treat GERD if present (can trial short-term PPI), consider CNS causes, review stressors. If persists, may need endoscopy.
<b>Abdominal pain</b>	Medications, infection, GERD, peptic ulcer disease, obstruction, constipation, gastroparesis, gynecologic	CBC, CMP, lipase. Consider abdominal US or CT AP depending on severity.
<b>Abnormal liver biochemistries</b>	Medications, viral hepatitis, autoimmune hepatitis, shock liver/ischemia, alcohol, biliary obstruction, hemolysis, Gilbert's syndrome	Direct bilirubin and GGT may help initially. Then depends on presenting pattern, but if mild (<5x ULN), HBV panel, HCV Ab, transferrin sat, TSH, ultrasound liver, then can monitor labs. If severe (>10x ULN), tox screen, HAV Ab, HBsAg, HbcAb, HCV Ab, HCV RNA, EBV DNA, CMV DNA, HDV, HEV, SPEP, ANA, anti-SM, anti-LK, ceruloplasmin, creatine kinase, doppler US.

### Treatment

Treatment focuses on managing stressors by providing behavioral health support (psychotherapy, cognitive behavioral therapy) and using complementary alternative therapies such as yoga, acupuncture, and massage. In refractory cases, supportive medications (anti-diarrheal, anti-nausea, etc.) can be used but their

efficacy may be limited. H2 blockers may be used for the treatment of abdominal pain/peptic ulcer disease due to the potential for anti-COVID-19 activity.

## Considerations for Older Adults

Older adults may experience a higher burden of disease from COVID-19 due to underlying conditions and comorbidities. Long COVID-19 symptoms such as fatigue and brain fog may exacerbate underlying cognitive impairment, sarcopenia, frailty, fall risk, and other geriatric conditions.

### Evaluation

For older adults, initial visits should focus on assessment of activities of daily living (ADLs/IADLs) and mobility (using a test such as the Timed Up and Go). Depression is common and the Geriatrics Depression Scale should be utilized, as it is more sensitive than the PHQ9 in older people. Cognitive function can be assessed with the Mini-Cog or MOCA test.

It is also important to assess older adults for social isolation and loneliness. Many older adults are feeling isolated due to COVID-19. If an older adult has recovered from COVID-19, he or she may feel even more isolated. Patients may not understand when it is “safe” again to be with close contacts, such as a spouse, if they are still feeling poorly.

We also encourage you to have a discussion of goals and values to guide advance care planning. Consider using the [Serious Illness Conversation Guide](#).

### Treatment

In addition to symptom-specific treatments outlined elsewhere, there are some specific considerations for older adults. Polypharmacy should be addressed, drug-drug interactions identified, and medications that could compromise cognitive function and mobility discontinued. High risk medications include benzodiazepines, “Z-drugs” for sleep, anticholinergics and opioids, among others.

Older adults may also derive particular benefit from meditative exercise practices, such as tai chi. This martial art practice reduces falls and improves sleep, cognition, and symptoms in chronic fatigue syndrome and may be valuable for Long COVID-19. There is no research to back this up yet, but it is a very safe exercise (can start sitting, and gradually move to standing) and may prove helpful for Long COVID-19. Options for virtual tai chi: ([standing](#)) and ([sitting](#)).

## Phases of Rehabilitation

After ruling out medical complications which would preclude exercise, a graded return to activity under the supervision of a physical therapist is recommended. The phases of rehabilitation are outlined in Table 10.

Table 10: Phases of rehabilitation

	Goals	Modality	Level of Effort
<b>Phase 1: Getting started</b>	Introduction of exercise and stabilization of symptoms	Supine/recumbent exercises, such as bridges, straight leg raises, supine hip abduction, etc.	< 2/10 on RPE (rating of perceived exertion scale)
<b>Phase 2: Graded aerobic</b>	Introduction of a walking program to begin aerobic exercise, continued	Interval walking and strengthening exercises; intervals can be very short (1	< 2/10 on RPE (rating of perceived exertion scale)

<b>exercise walking</b>	symptom stabilization, autonomic regulation	minute initially with rest, then repeat) and should gradually progress over weeks	
<b>Phase 3: Submaximal exercise</b>	Progression to higher intensity aerobic exercise (i.e., Levine Protocol, which is typically used for aerobic exercise guidance for patients with POTS)	Swimming, recumbent bicycle/stepper, upright bike, elliptical, treadmill, walking	Variable, should be based on target heart rates, ranges from RPE 2-8

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