**TABLE 1:** Common Long COVID symptoms and differential diagnoses to consider during assessment†

| Symptom Category | Common Symptoms | Differential Diagnoses to Consider (New, Worsening, or Underlying) |
|---|---|---|
| **Physical fatigue**[2]  | • Severe exhaustion after minimal physical, cognitive, or emotional exertion<br>• The sense of being weighed down all day<br>• Post-exertional malaise (PEM)/Post-exertional symptom exacerbation (PESE): "Crashing" after having a "good day" of increased activity level, requiring several days of recovery.[51]<br>• Persistent tiredness or exhaustion after sleep/upon waking | • MCAS[52]<br>• Autoimmune/inflammatory disorders<br>• Cardiopulmonary disorders<br>• Sleep disorders/deprivation<br>• Psychiatric disorders<br>• Medication side effects<br>• Malignancies |
| **Breathing, respiratory**[4]  | • Dyspnea at rest or disproportionate dyspnea with activity<br>• Chest discomfort: pain, tightness, constriction, and/or pressure<br>• Inability to take a full deep breath<br>• New or progressive cough or chest congestion | • Non-pulmonary contributions (e.g., neurologic, cardiovascular, neuromuscular)<br>• Other pulmonary and airway conditions (e.g., asthma) |
| **Cardiovascular**[5]  | • Chest pain, palpitations, or racing heart<br>• Dyspnea, exercise intolerance, fatigue, dizziness<br>• Autonomic dysfunction<br>• Leg swelling, orthopnea | • Complex arrhythmias<br>• Structural heart disease and/or ventricular dysfunction<br>• Coronary heart disease<br>• Myocarditis/pericarditis |
| **Autonomic**[6]  | • Dizziness or lightheadedness with postural changes<br>• Pre-syncopal or syncopal episodes<br>• Any other autonomic symptoms (e.g., racing heart, temperature intolerance, changes to digestion, perspiration) | • Vertigo or other vestibular pathology<br>• Sleep disorders/deprivation<br>• MCAS<br>• Cardiac abnormalities<br>• Small fiber neuropathy<br>• Hypermobility spectrum disorders |
| **Cognitive impairment**[3]  | • Executive function, processing speed, memory, attention, word-finding difficulty (a.k.a., brain fog)<br>• Mental fatigue: Decrease in cognitive ability when participating in tasks requiring sustained attention and executive function<br>• Cognitive symptoms independent of deficits from primary sleep dysfunction (e.g., daytime sleepiness) or lack of motivation | • B12 deficiency<br>• Hypothyroidism<br>• Mood disorders<br>• Sleep disorders/deprivation<br>• ADHD<br>• Underlying infectious etiology (e.g., latent syphilis) |
| **Mental health**[9]  | • Depression, especially anhedonia<br>• Anxiety, including panic<br>• PTSD, which can manifest as grief, survivor's remorse, or suicidal ideation<br>• Psychosis, OCD (less common) | • Cardiorespiratory disorders<br>• Cognitive or sleep disorders<br>• Primary fatigue or dysautonomia<br>• Primary or other secondary causes of mental health symptoms |
| **Neurologic**[8]  | • Neuropathic pain or other sensation (e.g., internal feeling of vibration, change in pain/temperature sensation)<br>• Muscle or joint pain<br>• Headaches<br>• Sleep dysfunction<br>• Focal or diffuse weakness, tremors, or gait changes<br>• Changes in hearing, vision, taste, smell, swallowing (i.e., cranial nerve abnormalities) | • Small fiber neuropathy<br>• Central nervous system lesions (e.g., vasculitis, stroke, demyelinating or neurodegenerative conditions)<br>• Peripheral nervous system lesions (e.g., AIDP, GBS)<br>• Vitamin deficiency (e.g., B1, B6, B12)<br>• Paraneoplastic conditions (e.g., NMDA receptor encephalitis)<br>• Sleep disorders/deprivation |

†Other symptoms not in this table can also be associated with Long COVID, including vision changes and eye redness; tinnitus; smell and taste changes; abdominal pain, bowel habit changes, and heartburn; rashes and hair loss; symptoms of mast cell dysfunction such as with MCAS (e.g., episodic itching, flushing, hives, rhinitis, tachycardia, dyspnea, abdominal pain, diarrhea, and/or headache);[62] and changes in menstrual cycles and fertility.[63]

*Abbreviations:* PEM (post-exertional malaise), PESE (post-exertional symptom exacerbation), MCAS (mast cell activation syndrome), ADHD (attention-deficit/hyperactivity disorder), PTSD (post-traumatic stress disorder), OCD (obsessive-compulsive disorder), AIDP (acute inflammatory demyelinating polyneuropathy), GBS (Guillain-Barré Syndrome), NMDA (N-methyl-D-aspartate).

**TABLE 2:** Holistic assessment of persons presenting with symptoms suggestive of Long COVID

| Assessment Element | Assessment Details |
|---|---|
| **Symptom identification** | • Common symptoms:<br>o Exaggerated fatigue and diminished energy windows<br>o Cognitive impairment (e.g., brain fog)<br>o Symptom flare 12-48 hours after minimal activity (e.g., PEM/PESE)<br>o Dyspnea, racing heart, dizziness upon standing<br>o Pain/myalgias<br>o Smell and taste alterations<br>• See Table 1 for other possible symptoms |
| **Timeline of symptoms** | • Lasting at least 3 months (continuously or relapsing-remitting)[1]<br>• New or worsened after suspected SARS-CoV-2 infection (supportive but not diagnostic) |
| **Symptom modifiers and triggers** | • Physical and cognitive activities<br>• Social and emotional stressors<br>• Recurrent SARS-CoV-2 infections, vaccines, boosters |
| **Impact on daily functioning and activity levels** | • ADLs, IADLs<br>• Work/school, family, social<br>• Physical and cognitive activity tolerance<br>• Exercise capacity |
| **Potential competing/co-existing diagnoses** | • Pre-existing conditions, symptoms<br>• Other new conditions, relevant hospitalizations<br>• Medication/supplement side effects<br>• Interim life changes |
| **Physical exam** | • Symptom-specific focused exam<br>• 10-minute stand test:†<br>o Record HR and BP after supine for 5 minutes and then after standing for 3, 5, 7, and 10 minutes<br>o Note signs and symptoms (e.g., acrocyanosis, flushing, sweating) |

†Table 1 of the autonomic dysfunction consensus guidance statement outlines diagnostic criteria for POTS, NCS, OH, and IST that incorporate results of the 10-minute stand test.[6]

*Abbreviations:* PEM (post-exertional malaise), PESE (post-exertional symptom exacerbation), ADLs (activities of daily living), IADLs (instrumental activities of daily living), HR (heartrate), BP (blood pressure), POTS (postural orthostatic tachycardia syndrome), NCS (neurocardiogenic syncope), OH (orthostatic hypotension), IST (inappropriate sinus tachycardia).

**TABLE 3:** Labs and procedures *(See Table 1 for differential diagnoses)*

| Symptom Category | Assessment Details |
|---|---|
| **Holistic assessment**<br>(Recommended for all patients) | • To rule out other (potentially treatable) conditions†‡<br>o CBC with diff; CMP; TSH<br>o Also consider: ESR; CRP; CK; vitamins D, B1, and B12 |
| **Physical fatigue**<br>  | • To identify treatable contributors, consider:<br>o Ferritin, iron profile<br>o Testosterone, estradiol[54] |
| **Breathing and respiratory sequelae**<br>  | • If not already performed, consider:<br>o Chest XR<br>• If breathing discomfort not improving ≥ 8 weeks after acute COVID-19 infection, or if new/worsened breathing discomfort later in Long COVID course, consider:<br>o PFTs (FEV1/VC and DLCO)<br>o EKG, echocardiogram<br>• If pulmonary exam, chest XR, or PFT abnormalities, consider:<br>o Non-contrast chest CT |
| **Cardiovascular complications§**<br>  | • If chronic chest pain present and concern for myocarditis, consider:<br>o Troponin (preferably high-sensitivity)<br>• If concern for decompensated heart failure, consider:<br>o BNP (preferably NT-proBNP)<br>• If concern for PE, consider:<br>o D-dimer<br>• If not already performed, consider:<br>o EKG, chest XR<br>o Cardiac MRI (for myocarditis, if chronic chest pain and positive troponin)<br>o Echocardiogram (for heart failure/valve abnormalities)<br>o CT PE protocol (for PE)<br>• If concern for arrhythmia, consider:<br>o Holter monitor for symptoms nearly daily<br>o 14-day monitor for symptoms every few days<br>o Implantable event monitor for infrequent symptoms<br>• If initial work-up is unrevealing and/or to guide activity plan, consider:<br>o Cardiopulmonary stress test |
| **Autonomic dysfunction**<br>  | • If concerned for PE, consider D-dimer<br>• To identify treatable contributors, consider if relevant: ‡<br>o Autoimmune: ANA, RF, Sjogren's Syndrome panel, antiphospholipid antibodies<br>o Iron deficiency: Ferritin, iron profile<br>• If recurrent palpitations, tachycardia, or syncope, consider basic cardiac work-up (See Table 9 [Cardiac table])<br>• If negative 10-minute stand test, consider tilt table test<br>o Tilt table test is not required to diagnose or treat autonomic dysfunction and can cause a symptom flare |
| **Cognitive impairment**<br>  | • To rule out other conditions, consider:<br>o Thiamine, folate, homocysteine, magnesium, RPR, HIV<br>o Neuroimaging based on history, exam, and lab findings |
| **Mental health**<br>  | (See Table 12 for mental health screening tools) |
| **Neurologic sequelae**<br>  | • To rule out other conditions, consider:<br>o HgbA1c, vitamin B6, magnesium, RPR, HIV<br>• Consider neuroimaging based on history, exam, and lab findings<br>o Consider consultation with a neurologist to guide imaging and further testing |

†At this time, no single laboratory finding is definitively diagnostic for confirming or ruling out the diagnosis of Long COVID. However, in some research studies, Long COVID has been associated with low morning cortisol and serotonin levels; EBV reactivation; and high IL-6, TNF-α, and D-dimer levels. Some of these labs are predominantly used in research settings and are not readily available for clinical use. Additionally, sensitivity and specificity values have not been determined, and treatments based on these laboratory findings have not been studied.

‡Laboratory assessment for MCAS is not necessary prior to an empiric trial of H1 and H2 antihistamines and can be normal even when mast cell dysfunction is present. When laboratory workup is felt to be indicated, it includes: 1) serum tryptase (baseline level several days between any episodes and another level within 4 hours after the start of an episode), and 2) 24-hour urine N-methylhistamine, 11B-Prostglandin F2α, and/or Leukotriene E4 (collection beginning immediately after the start of an episode). (See https://www.aaaai.org/conditions-treatments/related-conditions/mcas).

§Elevated hs-CRP is associated with chronic inflammation and potentially increased risk of cardiovascular complications in Long COVID.[65,66] Checking hs-CRP can be considered in patients who have a history of severe acute COVID-19 infection, other cardiovascular risk factors, and/or persistent cardiovascular symptoms. However, a patient's hs-CRP level, by itself, would not necessarily change cardiovascular management.

*Abbreviations:* CBC with diff (complete blood count with differential), CMP (complete metabolic panel), TSH (thyroid stimulating hormone), ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), CK (creatine kinase), XR (radiograph), PFTs (pulmonary function tests), FEV1 (forced expiratory volume in one second), VC (vital capacity), DLCO (diffusion capacity of the lungs for carbon monoxide), EKG (electrocardiogram), CT (computed tomography), BNP (B-type natriuretic peptide), NT-proBNP (N-terminal pro-BNP), MRI (magnetic resonance image), PE (pulmonary embolism), ANA (antinuclear antibody), RF (rheumatoid factor), PTSD (post-traumatic stress disorder), RPR (rapid plasma reagin), HIV (human immunodeficiency virus), HgbA1c (hemoglobin A1c), AM (morning), EBV Ab (Epstein-Barr Virus antibody), TNF (tumor necrosis factor), MCAS (mast cell activation syndrome), hs-CRP (high-sensitivity C-reactive Protein).

**TABLE 4:** Holistic assessment of persons presenting with symptoms suggestive of Long COVID

| Management Element | Management Details |
|---|---|
| **Validate symptoms, counsel on prognosis** | • "Long COVID is a real condition and fits with your symptoms. Many people experience it – you are not alone."<br>• "Every person is different. Many patients, though not all, improve or fully recover over several months or even years."<br>• "Although we don't have a cure right now, many patients can manage their symptoms and improve their quality of life with the treatment strategies we do have."<br>• "Researchers are learning more about Long COVID every day, and we can work together to make sure you have access to any new treatments that are discovered and are right for you." |
| **Manage symptom triggers** | • Pacing: When returning to physical and cognitive activities that provoke symptoms, "Start low and go slow"[57] (See Figure 1 for return to activity guidance)<br>• Avoid pushing activities to the point of symptom exacerbation<br>o "Respect your symptoms."<br>o "Listen to your body."<br>• Identify appropriate workplace and school accommodations (See Disability section) |
| **Address modifiable risk factors** | • Support a healthy lifestyle with education, counseling, and referrals to community and social support resources[58]<br>o Whole-food plant-predominant nutrition[2, 5, 59]<br>o Stress management (e.g., consider mindfulness, meditation)<br>o Sleep optimization[8]<br>› Address obstructive sleep apnea (OSA) or other sleep disorders, if present<br>› Sleep hygiene<br>› CBT-I, if available†<br>› Over-the-counter sleep aids<br>› Limited or short course of prescription medication<br>o Avoidance of risky alcohol/substance use<br>o Positive social connections<br>› Including in-person or online Long COVID peer support<br>o Regular physical activity as tolerated, without triggering PEM/PESE (See Figure 1 for return to activity guidance)<br>• Use caution if considering a restrictive diet‡<br>o If patient is interested, pursue under nutritionist/dietician guidance<br>• Stay up-to-date on vaccines§<br>• Treat coexisting conditions |
| **Optimize medications** | • Reduce polypharmacy<br>o Previously tolerated medications may flare symptoms<br>• Consider medication trials based on the patient's full symptom constellation (Table 5) |
| **Follow-up** | • If symptoms are significantly impacting daily life, to ensure response to treatment<br>• If titrating medication |
| **Consider referral and/or collaborative treatment** | • To allied health services (e.g., PT, OT, SLP, social work, psychology), if symptoms are significantly impacting daily function or activity levels<br>o Preferable for care team members to have experience treating Long COVID<br>• To specialty medical care if:<br>o Diagnosis is uncertain<br>o Symptoms are severe or new/persistent/worsening despite first-line treatment<br>o Symptoms are out of scope of the treating clinician |

†The Veterans Affairs Insomnia Coach (https://mobile.va.gov/app/insomnia-coach) is freely available from commercial app stores.

‡Some patients with gastrointestinal and mast cell related symptoms have reported benefit from low-histamine, gluten-free, dairy-free, and low Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAP) diets. However, there is a lack of strong evidence of benefit from restrictive diets, and these can cause harm in some cases (e.g., vitamin or nutrient deficiencies).

§COVID-19 vaccination is not contraindicated except in cases of preexisting allergy or previous serious adverse reaction.

*Abbreviations:* CBT-I (cognitive behavioral therapy for insomnia), PEM (post-exertional malaise), PESE (post-exertional symptom exacerbation), PT (physical therapy), OT (occupational therapy), SLP (speech-language pathology).

**TABLE 5:** Commonly used medications for Long COVID symptoms†‡§

| Medication | Dose | Indications | Side Effects and Other Considerations |
|---|---|---|---|
| Propranolol | 5-10 mg BID to QID | IST, POTS, OH, NCS, episodic hypertension | Bradycardia, hypotension, fatigue, depression, asthma exacerbation |
| Midodrine | 2.5-10 mg TID to QID | POTS, OH, NCS, hypotension | Supine hypertension, scalp paresthesias, piloerection |
| Fludrocortisone | Start 0.05 mg QD for 1 week, then increase by 0.05 mg QD every week to a max dose of 0.2 mg QD | POTS, OH, NCS, hypotension | Hypokalemia, edema, headache |
| Pyridostigmine | 30-60 mg BID to TID | POTS, OH, AN, GI dysmotility with constipation | Diarrhea, muscle twitching |
| H1 and H2 antihistamines in combination (e.g., cetirizine and famotidine) | Sample regimen:<br>Cetirizine 10 mg daily or Levocetirizine 5mg daily;<br>Famotidine 20 mg daily or bid | MCAS (e.g., itching, flushing, hives, rhinitis, episodic tachycardia, abdominal pain, diarrhea, headache, dyspnea) | Cetirizine: Fatigue, headache, abdominal pain, drowsiness, dizziness, dry mucous membranes.<br><br>Famotidine: Headache, dizziness, constipation, diarrhea. |
| Low-dose naltrexone (60-62) | Sample regimen:<br>Start 1 mg QD for 4 weeks, then increase by 1 mg QD every 4 weeks to a max dose of 4.5 mg QD being studied | Fatigue, PEM/PESE, headache | Often requires compounding.<br><br>Diarrhea and nausea |
| Methylphenidate | 5-10 mg BID to TID | POTS, OH, NCS, brain fog, fatigue | Headache, tachycardia, insomnia, PEM/PESE exacerbation if over-exerts during drug's duration of action |
| Amantadine | 100 mg QD to BID | Fatigue, brain fog | Contraindicated for ESRD<br>Abrupt discontinuation can cause withdrawal symptoms<br>Dry mouth, OH, neuropsychiatric symptoms, livedo reticularis, nausea, abdominal pain |
| Duloxetine | 20-60 mg QD | Depression (especially if coexisting neuropathic pain), OH, NCS | Hypertension, nausea, Increased perspiration |
| Fluoxetine | 10-40 mg QD | Anxiety (especially if predominant symptom), depression, NCS | Anxiety, insomnia, nausea |
| Bupropion | 75-150 mg QD to BID | Depression (especially if neurovegetative symptoms), fatigue, hypersomnolence, POTS, NCS | Anxiety, insomnia, nausea, decreased seizure threshold |
| Gabapentin | 100-300 mg QHS to TID, then increase 100-300 mg every week | Neuropathic pain, poor sleep quality | Needs renal dosing.<br>Brain fog, sleepiness, dizziness, nausea |
| COVID-19 vaccine[63-67] | Annual booster | Lower risk of subsequent COVID infection sequelae and reduce the severity and duration of PASC | Vaccine reaction or worsening of symptoms |

†Supplements including branched-chain amino acids, omega-3 fatty acids, vitamin B12, vitamin B2 (riboflavin), vitamin C, vitamin D, magnesium, L-Carnitine, Coenzyme Q10, ginseng, Echinacea, and many others have been suggested to alleviate chronic fatigue and pain due to other causes such as multiple sclerosis, fibromyalgia, and myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS).[78-80]

‡Given the current state of evidence, medication utilization in Long COVID generally follows standard practice regarding indications and dosing, with extra attention to: 1) starting doses low and ramping up slowly, 2) prioritizing patient preference, 3) using caution with medications that may worsen some Long COVID symptoms while improving others, and 4) tapering off if no noticeable benefit.

§The National Institutes of Health (NIH) Researching COVID to Enhance Recovery (RECOVER) initiative is investigating the effectiveness of the following medications for Long COVID: nirmatrelvir-ritonavir (Paxlovid) at 300 mg nirmatrelvir (two 150 mg tabs) + 100 mg ritonavir (one 100 mg tab) BID for 15-25 days; ivabradine and gamunex-C intravenous immunoglobulin (IVIG) for POTS; modafinil and solriamfetol for hypersomnia; and melatonin for complex sleep disturbances.

Abbreviations: PEM (post-exertional malaise), PESE (post-exertional symptom exacerbation), IST (inappropriate sinus tachycardia), POTS (postural orthostatic tachycardia syndrome), OH (orthostatic hypotension), NCS (neurocardiogenic syncope), AN (autonomic neuropathy), QD (once daily), BID (twice daily), TID (three times daily), QID (four times daily), QHS (nightly).

**TABLE 6:** The clinician's role in facilitating return to work for a person with Long COVID

| Task | Task Details |
|---|---|
| **Evaluation** | • Ask about work requirements<br>• Evaluate function via physical examination, diagnostic testing, and collaboration with a multidisciplinary team, as necessary (e.g., neuropsychology, physical therapy, occupational therapy, speech and language pathology, etc.) |
| **Assessment** | • Identify work limitations<br>• Identify appropriate accommodations, which may include:<br>o Remote work<br>o Reduced hours<br>o Flexible work schedule (e.g., alternating workdays)<br>o Frequent/periodic rest breaks<br>o Permission for self-pacing<br>o Gradual return to work (e.g., progressively increased hours)<br>o Limiting lifting, standing, and/or walking<br>o Limiting tasks that divide attention<br>o Limiting overstimulating environments<br>o Quiet work environment<br>o Seated or reclining workstation<br>o Ability to have fluids at the workstation<br>o Accessible parking |
| **Action** | • Establish expectations with the patient<br>• Complete relevant paperwork and document:<br>o Diagnosis/disability (Use ICD-10 code U09.9)<br>o Major life activities affected<br>o Work activities affected<br>o Recommended accommodations<br>o Follow-up plan<br>• Re-evaluate and modify accordingly |

*Abbreviations:* PEM (post-exertional malaise), PESE (post-exertional symptom exacerbation), IST (inappropriate sinus tachycardia), POTS (postural orthostatic tachycardia syndrome), OH (orthostatic hypotension), NCS (neurocardiogenic syncope), AN (autonomic neuropathy), QD (once daily), BID (twice daily), TID (three times daily), QID (four times daily), QHS (nightly).

**TABLE 7:** Symptom-specific assessment and management considerations for physical fatigue in Long COVID

| Assessment Element | Assessment Details |
|---|---|
| **History**  | • Differentiate between:<br>o Fatigue<br>o PEM/PESE† (i.e., exaggerated worsening of symptoms after exertion)<br>o Exercise intolerance‡ (i.e., difficulty beginning or continuing physical activity)<br>• If PEM/PESE present, inquire about other ME/CFS symptoms§[15,51]<br>• If suspicious for MCAS, inquire about other symptoms of mastocytosis (e.g., episodic itching, flushing, hives, runny nose, red eyes, rapid heartrate, lightheadedness/fainting, shortness of breath, abdominal pain, nausea, diarrhea, headache)[80]<br>• Use a validated tool to assess and trend severity (e.g., Fatigue Severity Scale)[74]<br>• Assess for sleep, mood, diet, and/or medication considerations as modifiable contributors to fatigue |
| **Physical exam** | • Is the patient:<br>o Seated and conversing? Lying down?<br>o Participating in the interview independently or with assistance?<br>o Tolerating the interview/encounter?<br>• If concern for autonomic dysfunction, see Table 10 [Autonomic Table] |
| **Treatment Element** | **Treatment Details** |
| **Non-pharmacologic management** | • Discuss energy conservation strategies:<br>o "The 4 P's" for essential tasks: Pacing, Planning, Prioritizing, Positioning<br>o "The 3 D's" for non-essential tasks: Delete, Defer, Delegate<br>• Treat coexisting orthostatic intolerance, if present (See Table 10 [Autonomic Table])<br>o Orthostatic stress can worsen fatigue<br>• Begin an individualized and structured, titrated return to activity program (See Figure 1)<br>• Consider cognitive behavioral therapy (to address cognitive and behavioral factors that can perpetuate fatigue)[75] |
| **Pharmacologic management** | • Consider weaning/de-prescribing sedating and anticholinergic medications<br>• See Table 5 for commonly used medications for Long COVID |
| **Referral, as needed** | • To immunology, if concern for MCAS and history is suggestive of anaphylaxis |

†Post-exertional malaise (PEM) / post-exertional symptom exacerbation (PESE) is "the worsening of symptoms following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks." [61] It is a diagnostic criterion for ME/CFS.[19]

‡Exercise intolerance can be caused by cardiovascular, pulmonary, myopathic, motor neuron, and other conditions.

§ME/CFS is characterized by the reduced ability to "engage in pre-illness levels of activity," PEM/PESE, unrefreshing sleep, and cognitive impairment and/or orthostatic intolerance. Other symptoms may be present, as well.[19, 61, 88]

¶Fatigue can be present even if a patient appears to tolerate the encounter without difficulty, for instance due to relapsing/remitting symptoms or onset of PEM/PESE after the encounter.

*Abbreviations:* PEM (post-exertional malaise), PESE (post-exertional symptom exacerbation), ME/CFS (myalgic encephalomyelitis / chronic fatigue syndrome), MCAS (mast cell activation syndrome).

**TABLE 8:** Symptom-specific assessment and management considerations for breathing discomfort and respiratory sequelae in patients with Long COVID

| Assessment Element | Assessment Details |
|---|---|
| **History**  | • Pulmonary history of acute COVID-19 course:<br>o Desaturation? Supplemental $O_2$? ICU? Mechanical ventilation?<br>• Document character and severity of breathing discomfort<br>o At rest or with exertion? Relieved with rest? Chest tightness or air hunger?<br>• Assess for non-pulmonary contributors that could also limit activity (e.g., fatigue, PEM/PESE, autonomic, neurologic, cardiovascular, neuromuscular) |
| **Physical exam** | • Vital signs:<br>o HR, RR, BP, POx (on room air, at rest, and while walking at a pace/duration tolerated by the patient)<br>• Cardiopulmonary exam:<br>o Assess for crackles, use of accessory breathing muscles, peripheral edema, acrocyanosis<br>o Assess for JVD, split P2, peripheral edema<br>• Peripheral vascular perfusion and skin integrity |
| **Treatment Element** | **Treatment Details** |
| **Non-pharmacologic management** | • Pulmonary rehabilitation (PR) [80-82]<br>o Covered by Medicare and many other insurance plans for COVID-19 related pulmonary disorders<br>o At-home PR programs are covered by some insurance plans<br>o Use caution if coexisting PEM/PESE, and modify program accordingly<br>• If symptoms are improving or supervised rehabilitation is not available:<br>o Breathing techniques and self-monitored paced physical activity (See Figure 1)<br>o Consider self-directed educational resources or online programs<br>o For patients with phone-based or wearable activity trackers, use data to track progress of therapy<br>• If chronic productive cough, difficulty clearing airway secretions, or bronchiectasis:<br>o Airway clearance techniques, and consider prescribing an airway clearing device[83]<br>• If requires home oxygen (to maximize mobility, quality of life, and participation in rehabilitation):<br>o Portable oxygen device, when possible<br>• Consider a home peak flow meter to track progress and quantify the impact of respiratory infection or another setback |
| **Pharmacologic management** | • If evidence of impaired pulmonary function, consider oral corticosteroids, inhaled bronchodilators, and inhaled corticosteroids<br>o Not for isolated breathing discomfort |
| **Referral, as needed** | • To pulmonary medicine, if:<br>o Breathing discomfort is progressing or limiting activity<br>o Productive cough and/or difficulty clearing airway, persistent and unexplained pulmonary exam abnormalities, new or worsened $O_2$ desaturation with activity, or new or worsened PFT or imaging abnormalities<br>• To pulmonary rehabilitation (PR), if:<br>o Recent diagnosis of a qualifying condition (i.e., history of Long COVID with abnormal PFTs or exercise test, interstitial disease on imaging, functional limitations and associated dyspnea from oxygen desaturation with exertion or at rest)<br>o If pulmonary rehabilitation is unavailable, consider PT with supplemental oxygen for conditioning and OT for ADL training<br>• For patients with mild limitations such that insurance may not cover PR, PT, or OT, consider a gentle return-to-activity program in a gym with a certified athletic trainer (See Figure 1 for return to activity guidance)<br>• To otolaryngology, if abnormal upper airway breath sounds or voice changes (e.g., stridor, hoarseness, unexplained episodic breathing discomfort, especially if history of endotracheal intubation and/or tracheostomy) |

*Abbreviations:* $O_2$ (oxygen), ICU (intensive care unit), PEM (post-exertional malaise), PESE (post-exertional symptom exacerbation), HR (heartrate), RR (respiratory rate), BP (blood pressure), POx (pulse oximetry), JVD (jugular venous distension), PR (pulmonary rehabilitation), PFT (pulmonary function test), PT (physical therapy), OT (occupational therapy), ADL (activities of daily living).

**TABLE 9:** Symptom-specific assessment and management considerations for cardiovascular symptoms in Long COVID

| Assessment Element | Assessment Details |
|---|---|
| **History**  | • Cardiac details of acute COVID-19 course:<br>o Cardiac event (e.g., arrhythmia)?<br>o Ventilator, ECMO, etc.? |
| **Physical exam** | • Vital signs:<br>o HR, RR, BP, POx<br>• Cardiopulmonary exam:<br>o Heart/lung auscultation<br>o Check peripheral pulses for bruits<br>o Assess for volume overload<br>• Chest wall palpation |
| **Treatment Element** | **Treatment Details** |
| **Non-pharmacologic management** | • Follow existing guidelines for return-to-activity and participation in cardiac rehabilitation (See Figure 1)[88,89] |
| **Pharmacologic management** | • Review cardioactive medications<br>o If felt to be contributing to any Long COVID symptoms, discuss with cardiologist for consideration of effective dose or medication alternatives<br>o High-dose beta blockers can worsen fatigue and dizziness<br>o Diuretics can worsen orthostasis<br>o Statins can worsen myalgias<br>• See Table 5 for commonly used medications for Long COVID |
| **Referral, as needed** | • To cardiac rehabilitation, if recent diagnosis of a qualifying condition:<br>o Stable angina, MI, systolic heart failure with LVEF ≤ 35%<br>o Percutaneous coronary intervention (angioplasty or stent)<br>o Cardiac surgery (coronary artery bypass, cardiac valve repair/replacement, heart transplant)<br>• To cardiology, if new or worsened cardiovascular disease; complex arrhythmia; structural heart disease; or myocardial, pericardial, and/or ventricular dysfunction |

*Abbreviations:* ECMO (extracorporeal membrane oxygenation), HR (heartrate), RR (respiratory rate), BP (blood pressure), POx (pulse oximetry), MI (myocardial infarction), LVEF (left ventricular ejection fraction).

**TABLE 10:** Symptom-specific assessment and management considerations for autonomic dysfunction in patients with Long COVID

| Assessment Element | Assessment Details |
|---|---|
| **History**  | • Current diet, fluid, and salt intake<br>• Medication use that may impact symptoms, HR, or BP (e.g., antihypertensives, anticholinergics, stimulants)<br>• Previous/current substance use<br>• History of multifocal joint pain, subluxations, and/or dislocations (suggestive of joint hypermobility syndrome) |
| **Physical exam** | • Sensory exam (especially pinprick and temperature), to evaluate for small fiber neuropathy<br>• Beighton Hypermobility Scale |
| **Treatment Element** | **Treatment Details** |
| **Non-pharmacologic management** | • Increase oral intake to 2.5-3.5L of fluid and 2.8-4g of sodium (i.e., 7-10g of salt) daily<br>• Compression garments (waist-high stockings and/or abdominal binder)<br>• Physical counterpressure maneuvers to mitigate orthostatic intolerance (e.g., stand with legs crossed, sit in knee-chest position)[91]<br>• Personalized autonomic rehabilitation program<br>o May start with supine core strengthening or recumbent activities (e.g., recumbent biking, swimming)<br>o Dysautonomia International: Exercises for Dysautonomia Patients: https://dysautonomiainternational.org/page.php?ID=43 |
| **Pharmacologic management** | • Consider weaning/de-prescribing medications or substances that can worsen orthostatic intolerance, tachycardia, and hypotension<br>• See Table 5 for commonly used medications for Long COVID<br>o See the autonomic dysfunction consensus guidance statement for additional medication options<br>• Medication management should be strongly and promptly considered if symptoms are severe or persistent after a trial of non-pharmacologic measures<br>• Consider IV fluids during symptom flare, sparingly and as needed |
| **Referral, as needed** | • To autonomic specialist, if:<br>o Non-pharmacologic and first-line pharmacologic management does not ameliorate symptoms<br>o Frequent syncope<br>o Additional autonomic function assessment is warranted (e.g., Valsalva maneuver, deep breathing test, QSART, skin biopsy for evaluation of small fiber neuropathy)<br>• Directories of autonomic specialists:<br>o https://americanautonomicsociety.org/physician-directory/<br>o http://dysautonomiainternational.org/page.php?ID=14<br>• To general cardiologist, if autonomic specialist is unavailable and management is outside the scope of the treating clinician |

*Abbreviations:* HR (heartrate), BP (blood pressure), IV (intravenous), QSART (quantitative sudomotor axon reflex test).

**TABLE 11:** Symptom-specific assessment and management for cognitive symptoms in Long COVID

| Assessment Element | Assessment Details |
|---|---|
| **History**  | • Pre-existing conditions with cognitive symptoms (e.g., ADHD, learning disabilities, mild cognitive impairment)<br>• Obtain collateral history from loved ones and care providers, as needed |
| **Physical exam** | • Document objective severity of cognitive deficits:†<br>o Brief tools: MoCA[92], MMSE<br>o Resource permitting: Neuro-QOL™, NIH Toolbox Cognition Battery<br>• Rule out signs of general medical abnormalities or focal neurological deficits |
| **Treatment Element** | **Treatment Details** |
| **Non-pharmacologic management** | • Optimize restorative sleep (See Table 4)<br>• For patients who achieve a return to ADLs, see Figure 1 for return to activity guidance |
| **Pharmacologic management** | • Consider weaning/de-prescribing medications that may lead to sedation, confusion, and possible cognitive decline (e.g. anticholinergic, antidepressant, antipsychotic, benzodiazepine, non-benzodiazepine sedative hypnotic, benzodiazepine receptor agonist hypnotic, and skeletal muscle relaxant medications)<br>• See Table 5 for commonly used medications for Long COVID |
| **Referral, as needed** | • To OT or SLP, if cognitive symptoms are affecting daily function<br>• To neuropsychology, if need to assess capacity for return to cognitively demanding work and/or to assess eligibility for vocational rehabilitation |

†This list of screening tools is revised compared to the original cognitive symptoms consensus guidance statement. The tools in this list reflect those which are most sensitive to detect patterns of cognitive impairment that are typically seen in Long COVID.

*Abbreviations:* ADHD (attention-deficit/hyperactivity disorder), MoCA (Montreal Cognitive Assessment), MMSE (mini mental state examination), Neuro-QOL™ (Quality of Life in Neurological Disorders), NIH (National Institutes of Health), OT (occupational therapy), SLP (speech and language pathology).

**TABLE 12:** Symptom-specific assessment and management considerations for mental health symptoms in patients with Long COVID

| Assessment Element | Assessment Details |
|---|---|
| **History**  | • Differentiate/ask whether symptoms are related to a DSM-V disorder versus other underlying cause<br>o E.g., is lack of interest due to fatigue versus anhedonia (i.e., low mood and reduced pleasure in previously enjoyable things)?<br>o E.g., are palpitations due to dysautonomia versus panic/anxiety?<br>• If symptoms are impacting function or quality of life, assess severity using validated instruments such as:†<br>o PHQ-9‡ or PHQ-2 (Depression)<br>o GAD-7 (Anxiety)<br>o PCL-5 (PTSD)<br>• If mental health symptoms present, perform suicide risk screening<br>o E.g., C-SSRS<br>• Medications that may impact mental health signs or symptoms (e.g., anti-arrhythmic, diuretic, or autonomic medications)<br>• Other potential symptom triggers:<br>o Pain, sleep dysfunction, physical/cognitive symptoms<br>o Menstrual cycle, alcohol or drug use<br>• Therapeutic response and possible adverse effects to prior treatments tried (patient-directed and prescribed)<br>• Existing social, emotional, and logistical support |
| **Physical exam** | • Symptom-specific focused exam to evaluate for physical sequelae of Long COVID which could be masquerading as, or exacerbating, mental health symptoms<br>o E.g., 10-minute stand test to assess for signs of dysautonomia that could be masquerading as panic disorder (e.g., palpitations, tachycardia) |
| **Treatment Element** | **Treatment Details** |
| **Non-pharmacologic management** | • Largely mirrors mental health treatment in the absence of Long COVID<br>o Validate experience, create a therapeutic alliance<br>o Psychotherapy (e.g., supportive, cognitive behavioral, group, or exposure therapy)<br>» If dysautonomia is present, use caution with exposure therapy (for PTSD)<br>o Free apps available by the VA (https://www.veteranshealthlibrary.va.gov/HealthyLiving/Stress/)<br>• Treat coexisting pain, sleep disorders (including poor sleep hygiene and insomnia), and neurologic symptoms, if present<br>• Mental health symptoms can be worsened by (and can worsen) other Long COVID symptoms |
| **Pharmacologic management** | • Consider psychotropic medication management based on symptoms and severity, per standard approaches outside the Long COVID setting<br>• Consider weaning/de-prescribing anti-hypertensive and sedating medications (e.g. benzodiazepines, sleep-promoting medications)<br>• See Table 5 for commonly used medications for Long COVID |
| **Referral, as needed** | • To emergency department, if expresses thoughts of harm to self or others, with a plan, means, and intent<br>• To mental health specialist, if symptoms of psychosis, significant PTSD, passive suicidal ideation, or active substance addiction<br>o E.g., social worker, therapist, counselor, neuropsychologist, clinical psychologist, and/or psychiatrist |

†These instruments have not been validated specifically in the Long COVID population.

‡For patients with a high PHQ-9 score, clinicians should obtain additional history to identify whether the high score is attributable to anhedonia (which would suggest true depressive symptoms) versus fatigue or other physical sequelae of Long COVID (in which case, a diagnosis of depression should not be given).

*Abbreviations:* DSM-V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), PHQ (Patient Health Questionnaire), GAD (generalized anxiety disorder), PCL-5 (PTSD Checklist for DSM-V), PTSD (post-traumatic stress disorder), C-SSRS (Columbia-Suicide Severity Rating Scale), VA (United States Department of Veterans Affairs).

**TABLE 13:** Symptom-specific assessment and management considerations for neurologic sequelae of Long COVID

| Assessment Element | Assessment Details |
|---|---|
| **History**  | • Time course of neurologic symptoms<br>• Acute versus chronic<br>• Static versus progressive<br>• Medication/supplement use that may impact signs, symptoms, or assessment parameters (e.g., anticholinergic medications) |
| **Physical exam** | • Thorough neurological examination to identify focal neurological deficits, as indicated based on the patient's reported symptoms and associated differential diagnosis<br>o Cognition, attention/concentration, expressive and receptive speech<br>o Cranial nerves, strength, sensation, reflexes, coordination, gait<br>• If concern for cognitive impairment, see Table 11 [Cognitive Table] |
| **Treatment Element** | **Treatment Details** |
| **Non-pharmacologic management** | • For patients who achieve a return to ADLs, see Figure 1 for return to activity guidance.<br>• For patients with headaches, consider ergonomic optimization, gentle stretching, deep breathing exercises, and acupuncture |
| **Pharmacologic management** | • Consider weaning/de-prescribing antihistamine, anticholinergic, antidepressant/anxiolytic, and muscle relaxant medications<br>• For rebound headaches due to regular overuse of abortive headache medications (including acetaminophen and NSAIDs), reduce use of these medications to < 3 times weekly<br>• See Table 5 for commonly used medications for Long COVID |
| **Referral, as needed** | • To emergency department, if new or worsening focal neurologic deficits<br>• To physiatry or neurology, if chronic focal neurologic sequelae affecting gait, mobility, cognitive status, and/or activities of daily living<br>• To neuroimmunology, if laboratory abnormalities concerning for neuroimmune dysregulation or paraneoplastic conditions (e.g. abnormal lymphocyte or immunoglobulin levels, paraneoplastic autoantibodies)[8] |

*Abbreviations:* ADLs (activities of daily living), NSAIDs (non-steroidal anti-inflammatory drugs), MRI (magnetic resonance image).