

TABLE 1: Initial evaluation of neurologic sequelae in patients with post-acute sequelae of SARS-CoV-2 infection (PASC).

#	Neurologic Sequelae Initial Evaluation Recommendations
1	<p>Clinicians should conduct a full patient history including a review of predisposing comorbidities, prior neurologic symptoms or disorders, relevant hospitalizations, time course and severity of COVID-19 infection(s), COVID-19 treatments, vaccines/boosters, pertinent family history, and social history.</p> <p>The patient history of present illness should address:</p> <ul style="list-style-type: none"> • Most relevant symptoms that may be neurologic in nature: autonomic symptoms (eg, dizziness, lightheadedness, presyncope, syncope, orthostatic intolerance), headaches (including migraine), exercise intolerance, cognitive dysfunction (e.g., brain fog, processing rate, and memory skills), cognitive fatigue, changes in gait/walking, and pain. • Appropriate review of systems to identify contributions to neurologic symptoms. • The trajectory of neurologic sequelae over time (ie, improving, worsening, or unchanged) to triage need for further workup. • History and review of preexisting, comorbid chronic conditions (eg, pain, psychiatric, renal/endocrine, cardiovascular, neurological, respiratory, etc.) • Time course and severity of COVID-19 infection • Triggers of symptoms, including food, medication(s), activity, and positional changes
2	<p>Clinicians should perform a thorough neurological examination to identify focal neurological deficits.</p>
2a	<p>For those patients identified with new or worsening focal neurologic deficits, an urgent/emergent referral to an emergency department for evaluation is warranted. (The section on Red Flags and corresponding table provides additional information).</p> <p>Determination of need for neuroimaging should be based on individual signs and symptoms. Consider consultation with a neurologist to guide imaging and further testing.</p>
3	<p>Evaluate for medication and supplement use that may impact signs, symptoms, or assessment parameters (i.e., medications with adverse side effects, such as dry mouth, visual changes, dizziness, and/or sleep/sedation). Include review of medications and supplement use and duration of use that have helped, worsened, or had little to no impact on symptoms.</p> <p>Of note, patients with PASC often present on antihistamine, anticholinergic, antidepressant/anxiolytic, and muscle relaxant medications that can contribute to neurologic symptoms.</p>
4	<p>The following basic lab workup should be considered in new patients or for those without a lab workup in the 3 months prior to the visit: complete blood count with differential; chemistries including renal and hepatic function tests, thyroid stimulating hormone, c-reactive protein, erythrocyte sedimentation rate, vitamins B1, B6, B12, and D, magnesium, and hemoglobin A1c (HbA1c).</p> <p>Other laboratory tests, including evaluation for new autoimmune syndromes, may be considered based on the patient history, physical exam, and/or concern for comorbid conditions as outlined in the relevant symptom tables that follow.</p>
5	<p>Assess for history of previous and/or current alcohol and substance use, current diet and exercise habits, physical and cognitive activity levels, and social determinants of health (eg, housing, employment, family, insurance, access to community resources, social stressors, etc.)</p>
6	<p>Assess for changes in basic and instrumental activities of daily living, including participation at work, school, community avocational (ie, hobbies) activities.</p>
7	<p>On initial evaluation, obtain standardized measures of activity performance to compare to normal control values and to guide the initial activity prescription. Repeat the standardized measures of activity performance at follow-up visits to quantify functional changes and guide progression of the activity prescription. Standardized measures may differ by neurologic symptom, refer to specific neurologic symptom assessment and treatment section for recommended standardized measures based on patient presentation.</p>

TABLE 2: Initial treatment options for patients with neurologic sequelae of PASC.

#	Neurologic Sequelae Initial Treatment Recommendations
1	In collaboration with primary care or appropriate specialist treat underlying medical conditions, such as pain, psychiatric, renal/endocrine, cardiovascular, neurological, respiratory, etc., which may be contributing to neurologic symptoms.
2	In collaboration with primary care or appropriate specialist, consider polypharmacy reduction, weaning or deprescribing medications and supplements where medically feasible. Emphasis on medications and supplements with known impact on neurologic symptoms should be considered.
3	For patients who achieve a return to their daily activities, consider recommending regular physical activity as tolerated, which may be effective in improving many neurologic symptoms and also contribute to improved sleep patterns. Patients should be cautioned to avoid rapid escalation of physical and cognitive activities to avoid overuse syndrome triggered by exertion. This approach is recommended to ensure symptoms do not flare and activity is tolerated.
4	For patients with neurologic sequelae affecting gait, mobility, cognitive status or activities of daily living, consider referral to physical medicine and rehabilitation physician and/or allied health professionals (eg, physical therapy, occupational therapy, speech language pathology and social work) for patient-specific recommendations to increase function and independence. To optimize functional outcomes, allied health professionals should preferably be familiar with treating sensorimotor deficits, autonomic dysfunction, and post-exertional fatigue. Suggested approaches are offered in the discussion.
5	Provide counseling, referrals to community resources, and education for risk factor modification in the areas of: <ul style="list-style-type: none">• Alcohol and substance use• Healthy dietary pattern and hydration• Return to activity, as tolerated• Medications and supplements• Sleep hygiene (see sleep section below)• Social determinants of health

TABLE 3: Neurologic red flags.

Neurologic signs/symptoms that may prompt more urgent neurologic assessment	Potential causes	Referral/action
<ul style="list-style-type: none"> ▶ Sudden or progressive weakness 	<p>Acute neurologic condition such as stroke, spinal cord infarct, GBS, myositis/ myopathy, acute neuroimmune syndromes</p>	<p>Referral: consider emergency department (ED) versus neurology depending on time course/urgency. Action: Consider forced vital capacity assessment and neuroimaging as appropriate.</p>
<ul style="list-style-type: none"> ▶ Sudden or progressive sensory changes 	<p>Acute neurologic condition such as stroke, spinal cord infarct, GBS, acute neuroimmune syndromes</p>	<p>Referral: consider ED versus neurology or neurosurgery depending on time course/urgency and associated neurologic signs and symptoms. Action: Consider forced vital capacity assessment and neuroimaging as appropriate.</p>
<ul style="list-style-type: none"> ▶ Unexplained upper motor neuron signs (i.e., pathologic reflexes or spasticity) in the setting of weakness 	<p>Structural cause affecting the brain or spinal cord affecting the brain or spinal cord</p>	<p>Referral: neurology Action: neuroimaging, as appropriate.</p>
<ul style="list-style-type: none"> ▶ Bladder incontinence or retention 	<p>Spinal cord dysfunction</p>	<p>Referral: consider ED versus neurology or neurosurgery depending on time course/urgency and associated neurologic signs and symptoms. Action: bladder scan, urinalysis, urodynamics, voiding diary, timed voiding</p>
<ul style="list-style-type: none"> ▶ Bowel incontinence or retention 		<p>Action: bowel history, review medications, assess rectal sensation/tone</p>
<ul style="list-style-type: none"> ▶ Syncopal episodes or transient loss of consciousness 	<p>Arrhythmia, seizure, severe orthostatic hypotension, or vasovagal syncope</p>	<p>Referral: Referral to neurology or cardiology for consideration for EEG/ arrhythmia monitoring. Action: Determine circumstances of recent events, timing following certain activities, if strenuous, any med changes or abnormalities in cardiac function—time to resolution.</p>

TABLE 3: Neurologic red flags. (continued)

Neurologic signs/symptoms that may prompt more urgent neurologic assessment	Potential causes	Referral/action
<ul style="list-style-type: none"> ▶ Acute neuropsychiatric symptoms/psychosis 	<p>Reduced awareness, visual or auditory hallucinations, encephalopathy</p>	<p>Referral: ED versus neurology depending on time course/urgency. Action: Basic tests of pituitary and adrenal function, thyroid function, and inflammation, review and optimize medications, cognition assessment, evaluate safety.</p>
<ul style="list-style-type: none"> ▶ Headaches—positional, worst headache of life, or associated with focal neurologic signs 	<p>Positional—increased intracranial pressure (or low CSF pressure) Worst headache of life (thunderclap headache)—subarachnoid hemorrhage Headache associated with structural cause affecting the brain or spinal cord</p>	<p>Referral: ED versus neurology depending on time course/urgency. Action: Refer to headache section in this statement.</p>
<ul style="list-style-type: none"> ▶ Cranial nerve abnormalities on physical examination 	<p>Sudden onset cranial nerve deficits or pupillary changes potentially caused by stroke/intracranial bleeding</p>	<p>Referral: ED for urgent neurological evaluation</p>

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram, GBS, Guillain-Barré syndrome.

TABLE 4: Signs, symptoms, and care guidance: cranial nerves.

Loss of smell or taste (cranial nerve: 1, 9, 10)

Signs

- Weight loss/gain
- Dry mucous membranes

Symptoms

- Loss of smell and/or taste
- Altered smell and/or taste
- Dry mouth
- Change in eating habits
- Stress from lack of pleasure in eating

Patient History and Evaluation:

- Assess for tobacco and alcohol use
- When appropriate, assess for other common comorbidities such as:
 - Neurodegenerative conditions
 - Head trauma

Additional Studies to Consider for Differential Diagnosis:

- Consider Sjögren’s antibodies if concerned about potential autoimmune involvement.
- If associated with other cranial nerves, consider magnetic resonance imaging (MRI) brain with or without contrast and lumbar puncture (LP) for encephalitis workup.
- Given the increased clotting risk in post-acute sequelae of SARS-CoV-2 infection (PASC), neuroimaging should be considered prior to any LP to help rule out cerebral venous thrombosis or other central nervous system (CNS) lesion.

Initial Treatment Approach:

- Recommend avoidance of tobacco, alcohol, spicy foods, and foods with extreme temperature
- Consider educating on and recommending smell therapy (eg, Abscent)
- Recommend hydration of at least 64 ounces of fluids a day
- Consider recommending mouth moisturization products (eg, Biotene, Oasis)

Referral Options:

- Consider referral to ear, nose, throat physician (ENT) for abnormalities of smell lasting longer than 3 months,
- Consider referral to a dentist if associated with dry mouth for better dental hygiene.
- If suspicion of Sjögren’s, consider referral to rheumatology for further evaluation.

Resources:

- Smell-Simple steps to recovering your sense of smell after COVID-19 and other viral infections: [Abscent.org](https://www.abscent.org)

TABLE 4: Signs, symptoms, and care guidance: cranial nerves. (continued)

Changes in vision (cranial nerves 3, 4, 6)

Signs

- Papilledema or pallor of optic nerve
- Abnormality in extraocular movements in any direction: out and up, out and down, in and up, in and down
- Inability to accommodate/cross eyes
- Changes to visual acuity
- Changes in color vision
- Changes in visual fields
- Droopy eyes/ptosis
- Nystagmus

Symptoms

- Blurry vision/loss of vision/change in color vision
- Painful eye movements
- Trouble focusing
- Double vision
- Headaches
- Head tilt
- Dry eyes

Patient History and Evaluation:

- Assess for changes in visual acuity, color vision and pupillary changes
- Assess for other common comorbid conditions as appropriate:
 - Diabetes
 - Uncontrolled hypertension
 - Preexisting autoimmune disorders
 - Other disorders with immune dysregulation
- Assess for medications that can worsen symptoms:
 - Oral contraceptives or hormone supplements increase risk of venous sinus thrombosis
 - Anticholinergics such as over-the-counter allergy medications can cause blurry vision or trouble focusing
 - Immunosuppressive treatments can predispose to post viral cranial neuropathies (varicella zoster virus [VZV]/herpes simplex virus [HSV]/Epstein-Barr virus [EBV] reactivation)

Additional Studies to Consider for Differential Diagnosis:

- Consider angiotensin-converting enzyme (ACE) level; serologies for VZV, HSV, EBV PCR (polymerase chain reaction); rapid plasma reagin (RPR); human immunodeficiency virus (HIV); and thyroglobulin and thyroid peroxidase antibodies (TPO and TG Ab).
 - Check vitamin A level if papilledema on exam
- If papilledema on exam consider an urgent referral for head imaging (ideally MRI or magnetic resonance venography, computed tomography is an option if unable to get MRI urgently) for venous sinus thrombosis.
- If optic pallor with painful eye movements and color/acuity changes, order MRI orbit/brain with or without contrast for optic neuritis

Initial Treatment Approach:

- Recommend avoidance of medications (eg, anticholinergics or antihistamines) that can worsen symptoms
- If acute herpetic infection is identified, consider antiviral therapy and infectious disease evaluation
- Consider vision rehabilitation by occupational therapist.
- Consider prescription for steroids or immunotherapy if suggestive of autoimmune etiology
- Consider prescription for steroids or referral to emergency department for optic neuritis

TABLE 4: Signs, symptoms, and care guidance: cranial nerves. (continued)

Changes in vision (cranial nerves 3, 4, 6) (continued)

Referral Options:

- Refer to the emergency department if worsening visual acuity, color vision or transient episodes of loss of vision or if weakness of extraocular muscles associated with or without changes in pupil reaction as may be an indication of cerebral aneurysm (red flag).
- Consider referral to neurology or neuro-ophthalmology:
 - If symptoms continue or worsen over time
 - If optic neuritis is identified
- Consider referral to neurology or ophthalmology if papilledema on exam.
- Consider referral to ophthalmology/optometry if there is evidence of visual loss or pupillary changes.
- Refer to optometry for fundoscopy to look for changes consistent with increased intracranial pressure from venous sinus thrombosis or optic neuritis

Resources:

- Eye exam-video by neuro-ophthalmologist: <https://youtu.be/xW6B05a-LTw>

TABLE 4: Signs, symptoms, and care guidance: cranial nerves. (continued)

Dizziness/vertigo/tinnitus/loss of hearing (cranial nerve 8)

Signs

- Impaired midline orientation
- Falls
- Ataxia on finger to nose testing or knee heel testing or truncal ataxia
- Nystagmus

Symptoms

- Unsteady gait
- Poor balance
- Postural dizziness/instability
- Ear ringing
- Ear fullness
- Nausea/vomiting
- Hearing loss
- Being pulled to one side/leaning (impaired midline orientation)

Patient History and Evaluation:

- Evaluate for dysarthria, incoordination, and other sensorimotor deficits in arms or legs or face that may suggest vascular causes like brainstem/cerebellar stroke
- Determine if patient has had recent or persistent upper respiratory, ear infections, or known history of vestibular neuritis, labyrinthitis, benign paroxysmal positional vertigo, Meniere’s disease, migraines, prior strokes, or history of multiple sclerosis
- Consider the following evaluation studies:
 - Bedside hearing test with tuning fork
 - Otoscopy to look for local changes
 - Finger to nose, heel to shin, tandem gait, Romberg test
- Conduct evaluation for nystagmus
- Evaluate for central vs. peripheral vertigo (maneuvers—see resources)
- Assess for other common comorbid conditions: diabetes and uncontrolled hypertension
- Assess for medications that may exacerbate symptoms:
 - Orthostatic dizziness related to medications – antihypertensives, medications for benign prostatic hypertrophy, antidepressants
 - Immunosuppressive treatments – can predispose to postviral cranial neuropathies (VZV/HSV/EBV reactivation)

Additional Studies to Consider for Differential Diagnosis:

- Consider ACE level, serologies for VZV, HSV, EBV PCR, RPR, HIV, TPO, and TG Ab
- Consider ordering MRI brain if physical exam findings suggest central etiology (eg, brainstem/cerebellar stroke)

Initial Treatment Approach:

- Recommend adequate hydration of at least 64 ounces per day
- Recommend use of compression stockings (if postural)
- Consider vestibular rehabilitation with a neurological or vestibular trained physical therapist
- Consider trial of white noise for diagnosis of tinnitus or hearing loss
- Consider referral for hearing aids for diagnosis of tinnitus or hearing loss

TABLE 4: Signs, symptoms, and care guidance: cranial nerves. (continued)

Dizziness/vertigo/tinnitus/loss of hearing (cranial nerve 8) (continued)

Referral Options:

- Refer to ear, nose, throat and/or audiology if sensorineural hearing loss for hearing testing and possible imaging (MRI with/without and internal auditory canal protocol)
- Refer to neurology/autonomic specialist for autonomic evaluation if other symptoms (blood pressure fluctuations/heart rate variability, dryness/abnormal sweating/neuropathic pain). Refer to PASC Multi-Disciplinary collaborative consensus guidance statement on the assessment and treatment of autonomic dysfunction in patients with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)¹³

Resources:

- Dix-Hallpike maneuver: <https://www.youtube.com/watch?v=8RYB2QIO1N4>
- Epley maneuver: <https://www.youtube.com/watch?v=ZqokxZRbJfw&NR=1>
- Performing the Epley maneuver: home: <https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/home-epley-maneuver>
- HINTS exam: <https://www.youtube.com/watch?v=1q-VTKPweuk>
- Brandt-Daroff exercises: https://careguides-videos.med.umich.edu/media/brandt-daroff/1_cqhgjpic/44532291

TABLE 4: Signs, symptoms, and care guidance: cranial nerves. (continued)

Changes in facial expressions, chewing or swallowing (cranial nerves 5, 7, 9, 10, 12)

Signs

- Facial droop
- Inability to smile
- Inability to puff out cheeks
- Inability to stick out tongue
- Inability to elevate palate/absent gag reflex
- Hypophonia/dysphonia
- Weakness of face musculature
- Dysarthria

Symptoms

- Weight loss
- Hard to understand speech
- Coughing/choking while eating or drinking
- Dry mouth
- Nasal regurgitation of food

Patient History and Evaluation:

- Evaluate whether patients are experiencing peripheral (eg, Bell's Palsy) or central (eg, brainstem) cranial nerve damage to better guide management
- Evaluate for constitutional symptoms like fever, weight loss, night sweats for consideration infectious/paraneoplastic/neoplastic etiologies.
- Differentiate dysphagia with solids and/or liquids
- Assess for other common comorbid conditions:
 - o Dry mouth
 - o Uncontrolled hiccups

Additional Studies to Consider for Differential Diagnosis:

- Consider MRI brain with/without contrast for multiple lower cranial neuropathies or stroke or uncontrolled hiccups for possible CNS demyelinating disease like neuromyelitis optica.
- Consider evaluation for myasthenia gravis if signs or symptoms are worse with activity (fatigable) or if acetylcholine receptor antibodies are negative, proceed to nerve conduction study (NCS) or electromyography (EMG).
- Conduct a dysphagia evaluation via instrumental swallow assessment such as Video Swallow or Fiberoptic Endoscopic Evaluation of Swallowing

Initial Treatment Approach:

- Recommend oral moisturizing or lubricating agents that contain carboxymethylcellulose, such as Biotene Oral Moisturizing gel or saliva substitutes with xylitol, such as Mouth Kote or Oasis mouth spray

Referral Options:

- Refer to ED for urgent evaluation if sudden onset or progressive symptoms and risk of aspiration are high.
- Refer to speech therapy for dysphagia evaluation and treatment, including Video Swallow or Fiberoptic Endoscopic Evaluation of Swallowing

Resources:

- Additional information on Bell's Palsy: <https://www.aanem.org/Patients/Muscle-and-Nerve-Disorders/Bell-s-Palsy>

TABLE 5: Warning signals to raise suspicion of secondary causes of headache using the mnemonic SNOOP4 (recreated with permission from Dr. David Dodick).³³

Letter	Warning Signal	Features	Differential diagnosis
▶ S	Systemic symptoms	Fever, night sweats, chills, weight loss, jaw claudication	Metastases, giant cell arteritis, infection (central nervous system, systemic)
	Secondary diseases	Cancer, immunosuppression, chronic infection human immunodeficiency virus (HIV), tuberculosis	
▶ N	Neurologic symptoms/signs	Confusion, focal neurologic symptoms/signs, diplopia, transient visual obscurations, pulsatile tinnitus	Mass lesion, structural lesion, stroke, hydrocephalus
▶ O	Onset	Thunderclap	RCVS, stroke, subarachnoid hemorrhage, cerebral venous sinus thrombosis, arterial dissection, pituitary apoplexy, idiopathic intracranial hypertension
▶ O	Older (age > 50 years)	New onset, persistent/progressive headache	Mass lesion, giant cell arteritis
▶ P1	Positional	Orthostatic, recumbent, or worsens with change in position	Low intracranial pressure (CSF leak), mass lesion, cerebral venous sinus thrombosis, sinus pathology
▶ P2	Prior history	New onset or change to persistent/daily headache	Mass lesion, infection (central nervous system, systemic)
▶ P3	Pregnancy/postpartum	New onset during pregnancy	Cerebral venous sinus thrombosis preeclampsia, RCVS, pituitary lesion, stroke
▶ P4	Precipitated by Valsalva	Cough, sneeze, bending, straining	Intracranial/posterior fossa mass, Chiari malformation

Abbreviations: CSF, cerebrospinal fluid; RCVS, reversible cerebral vasoconstriction syndrome.

TABLE 6: Headaches.

Patient History and Evaluation:

- Assess for new, ongoing, and persistent symptoms including onset, duration, intensity, and location (does it move around or stay in one spot).
- Obtain detailed headache history including the features and co-occurring symptoms to determine if the headache is due to a primary headache disorder (like migraine or tension-type, etc.) or if it is due to a secondary cause (space-occupying lesions, infections, vascular disorders, structural abnormalities). Refer to Table 5: Warning Signals to Raise Suspicion of Secondary Causes or Headache Using the Mnemonic SNOOP433
 - Obtain a family history of neurological conditions including migraines or other headache disorders.
 - Determine if history of trauma
 - Determine if patient able to recall date of onset of persistent headache
 - Determine if family history of aneurysm or brain cancer
- Complete a full medication review including vitamins and supplements to ascertain if they might be contributing to headaches. Assess if headache is nonresponsive to over-the-counter medications.
 - Also evaluate how prior trials of headache medications/doses affected the headache
- Obtain sleep and exercise history
- Obtain history of substance use, including caffeine, alcohol, and other drugs, to assess frequency and duration. Alcohol and drug use can interfere with sleep and response to treatment.
- Evaluate for contributing comorbidities:
 - sleep disturbances like insomnia or sleep apnea (refer to sleep section),
 - anxiety and depression,
 - postural orthostatic tachycardia syndrome (POTS)

Additional Studies to Consider for Differential Diagnosis:

- Human immunodeficiency virus (HIV) testing should be considered in patients with suspected infection or refractory chronic daily headache pattern. Lyme antibody testing may be important in endemic regions.
- Prolactin and cortisol should be obtained if concern for a pituitary lesion.
- A lumbar puncture may be indicated to evaluate opening pressure, rule out infections or subarachnoid hemorrhage, evaluate for granulomatous pathology, neuroimmune conditions or meningeal carcinomatosis.

Initial Treatment Approach:

- Recommend lifestyle modifications; a useful strategy for the treatment of migraine and tension type headache using lifestyle modifications can be remembered using the mnemonic SEEDS (sleep, exercise, eat, diary, stress).³⁵
- Recommend counseling on the negative effects of medication overuse (including acetaminophen and ibuprofen) (>3x/week) and how it can cause rebound headaches.
- Recommend counseling for alcohol and drug use effects
- Patients with PASC-related headache may benefit from a multidisciplinary approach to treatment that includes both pharmacologic and nonpharmacologic approaches.³²
- Consider over-the-counter supplements for prophylaxis (eg, magnesium, melatonin, coenzyme Q10, riboflavin, feverfew) can be beneficial.
- Nonpharmacologic therapies (acupuncture, relaxation therapies with deep breathing exercises, biofeedback) may be beneficial for those patients with sensitivity, resistance, or inability to tolerate medication. Ideas for relaxation strategies include:
 - gentle stretching
 - ergonomics—positioning at work, headset,
 - trigger point injections
 - nerve blocks
 - neuromodulation devices

TABLE 6: Headaches. (continued)

Consider the following treatment and referral approaches based on headache phenotype

Migraine

- Headaches that meet the International Classification for Headache Disorders third edition (ICHD-3) diagnostic criteria for migraine can be treated acutely with acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), triptans, ergotamines, ditans, or gepants.
- Consider preventative treatment of episodic migraine if indicated³²
- Consider referral for botulinum toxins for chronic migraine management

Moderate–severe headache

- Abortive regimens should not be overused. Avoid regular intake for greater than or equal to 10 days per month for more than 3 months of ergotamines, triptans, opioids, or combination-analgesic medications or greater than or equal to 15 days per month of NSAIDs or acetaminophen.³⁴

Tension type headache

- Headaches meeting the ICHD-3 criteria for tension type headache can be treated with acetaminophen, aspirin, or NSAIDs.

Referral Options:

- A neurology referral should be considered if the clinician is unsure of the diagnosis/etiology of the headache and/or if headaches are refractory to treatment or progressively worsening)

Resources:

- Advocacy for Migraine Relief: Strategic Planning to Eliminate the Burden³⁶

TABLE 7: Sleep disturbances.

Signs

- Restless legs
- Observed apneic episodes
- Hypertension
- Arrhythmias
- Impaired cognition
- Metabolic dysfunction: glucose intolerance
- Pain (muscle, headaches, nerve)
- Sudden sleep/drop attacks
- Insomnia regardless of attempts at behavioral approaches

Symptoms

- Poor sleep
- Wakes frequently or wakes early
- Non-restorative/unrefreshing sleep
- 'Tired' on waking
- Snoring
- Frequent urination at night
- Bad dreams/nightmares
- Easily falls asleep during the day
- Pain
- Night sweats
- Cognitive symptoms especially attention, processing speed, memory and executive function
- Behavioral symptoms: irritability, anxiety, depression and mood lability
- Headaches

Patient History and Evaluation:

- Obtain a sleep history to include review of:
 - Pre- and post-COVID quantity and quality of sleep, difficulty with sleep initiation, maintenance, or early waking.
 - Presence of daytime naps and/or drowsiness.
 - Impact on cognition (attention, concentration, memory, decision making)
 - Severity: patients should be advised to monitor sleep patterns through the use of a sleep diary for at least 2 weeks and document specific sleep and wake habits over the specified a period of time.
- Review reports of sleep disruptions: nightmares (suggestive of post-traumatic stress disorder [PTSD]) sleep apnea, restless leg syndrome, presence of pain (muscle cramps; neuropathic pain). Abnormal parasomnias (sleep walking, talking), or drop attacks during day, both of which may suggest presence of autonomic or autoimmune disturbances
- Assess for other factors affecting sleep:
 - Routine exercise, or any physical activity limited by exertional fatigue
 - Presence of polypharmacy (>4 medications)
 - Excessive caffeine intake
 - Initiation of new supplements
 - Increased alcohol use
 - Anxiety
- Evaluate current sleep routine including use of sleep aids (apps, white noise machines), sleep medication, blue light, or behavioral strategies
- Actigraphy can be considered as an additional objective measurement tool.
- Review medications that may cause insomnia: alcohol, antidepressants, beta-blockers, caffeine, chemotherapy drugs, cold and allergy medications containing pseudoephedrine, diuretics, illicit drugs, such as cocaine and other stimulants, nicotine, stimulant laxatives
- Assess sleep characteristics. The following screening tools can be used: Epworth Sleepiness Scale (ESS), Stanford Sleepiness Scale, PROMIS Sleep, Sleep Scale Survey, Insomnia Severity Index
- Screen for Sleep Apnea: STOP-BANG questionnaire

TABLE 7: Sleep disturbances. (continued)

Initial Treatment Approach:

- The first line approach for insomnia should include cognitive behavioral therapy (CBT) for insomnia, whenever it is available.
- Manage underlying conditions that may impact sleep: asthma, heart failure, hyperthyroidism, acid reflux, anxiety
- Educate on behavioral strategies: Creating a sleep routine, avoiding stimulants, stopping electronic screens for at least an hour prior to bedtime, Journaling thoughts before bedtime, relaxation techniques
- Consider short-term use of over the counter medications and aids: melatonin, doxylamine succinate (Unisom SleepTabs), chamomile tea
- Consider pharmacology when over the counter medications and aids and behavioral strategies have not proven successful: Consider trazodone, zolpidem (Ambien), eszopiclone (Lunesta), zaleplon (Sonata), doxepin (Silenor), ramelteon (Rozerem), suvorexant (Belsomra), temazepam (Restoril). These medications must be used with caution in the older population and patients should be advised regarding potential for habituation to these medications over time.
- Clinician prescription of medication can be guided by the presence of other symptoms. The following medications often have side effects and should be used cautiously.
 - o Headaches: gabapentin
 - o Muscle aches or spasms: tizanidine or baclofen
 - o Anorexia: mirtazapine
 - o Pain: amitriptyline, gabapentin
 - o Anxiety: gabapentin
 - o Psychiatric disorders: quetiapine

Referral Options:

- Refer to pulmonology, sleep medicine for polysomnogram; closer follow-up or to adjust medications
- Refer to psychology, social work, or psychiatry for CBT, anxiety, or PTSD management

Resources:

- Veterans Affairs Insomnia Coach: <https://mobile.va.gov/app/insomnia-coach>
- American Academy of Sleep Medicine: <http://www.sleepeducation.org/>
- American Sleep Apnea Association: <http://www.sleepapnea.org/>
- Circadian Sleep Disorders Network: <http://www.circadiansleepdisorders.org/>
- Narcolepsy Network: <http://narcolepsynetwork.org/>
- Restless Legs Syndrome Foundation: <https://www.rls.org/>
- Wake Up Narcolepsy: <http://www.wakeupnarcolepsy.org/>

TABLE 8: Health equity considerations and examples in post-acute sequelae of SARS-CoV-2 infection (PASC): neurologic sequelae.

Category	Comment	What is known	Clinical considerations
<p>▶ Racial/Ethnic Minority Groups</p> <p><i>Example: People who identify as Black (including African-American), American-Indian/Alaska Native, Pacific Islander, Asian-American, and Mixed Race, and/or Latino/Hispanic (ethnicity)</i></p>	<p>Individuals who identify with groups that have been historically, socially, or economically marginalized may be at higher risk for COVID-19 related morbidity and mortality.</p>	<p>Historically marginalized racial/ethnic minority groups have higher rates of COVID-19 infection and lower rates of access to health care services.⁴³ It is well documented that many of these disparities are affected by social determinants of health (SDOH).⁴⁴ In a study of provision of physical and occupational therapy services for those hospitalized with COVID-19 in the University of Colorado Health System, therapy sessions were significantly reduced for patients with Hispanic ethnicity.⁴⁵ The Household Pulse Survey from June 2022, showed nearly 9% of Hispanic adults having Long COVID, which was higher than non-Hispanic White (7.5%), Black (6.8%), and non-Hispanic Asian (3.7%) adults.⁴⁶</p>	<p>Individuals from racial/ethnic minority groups have been reported to have lower referral rates to neurologic rehabilitation than people classified as White/Caucasian.^{47,48} All individuals with neurologic impairment and symptomatology such as tremor, vestibular dysfunction, cognitive complaints, or paresis should be considered for specialized neurorehabilitation programs. Referrals should occur in a timely manner. Treating physicians should determine what type of rehabilitation interventions and/or programs will be most beneficial as well as considering other factors such as cost and accessibility. Every effort should be made to close gaps in health disparities and ensure optimal care for people who identify with racial/ethnic minority groups.</p>
<p>▶ Biologic Sex</p> <p><i>Example: Female adults</i></p>	<p>Many studies have documented sexrelated disparities affecting female adults with neurologic conditions. Knowledge of areas of potential bias are important for clinicians to recognize and intentionally counteract to provide equitable health care.</p>	<p>Biologically female adults have some differences in neurologic symptoms and diagnoses. For example, hormone levels (eg, estrogen) are related to both migraine and stroke in female adults.</p> <p>A meta-analysis showed that nonpregnant women were at a higher risk of having symptoms such as headache, myalgia, fever, diarrhea and anosmia as primary symptoms of COVID-19 compared to pregnant women.⁴⁹ The study also noted that pregnant women were more likely to be admitted to the intensive care unit and receive mechanical ventilation compared to non-pregnant women.⁴⁹ One report summarizing the COVID-19 literature to date stated, “Current evidence suggests that severity and mortality of COVID-19 is higher in men than in women, whereas women might be at increased risk of COVID-19 reinfection and development of long COVID.”⁵⁰ Another study found that female adults were more symptomatic for both acute infection and PASC than male adults.⁵¹ Further research is needed to better understand gender-related differences in PASC.</p>	<p>Sex-related disparities have been reported and female adults may be underdiagnosed and undertreated in neurologic conditions. For example, a systematic review concluded that women have worse stroke outcomes than men and this may be due to misdiagnosis and undertreatment.⁵² Thus, it is important for clinicians to be aware of the potential for underdiagnosis, misdiagnosis, and undertreatment and ensure that people, including female adults, receive optimal care. Individuals with underlying and/or new PASC-related neurologic symptoms or diagnoses should be considered for multidisciplinary rehabilitation services and referred in a timely manner. Pregnant women with baseline neurologic conditions and/or PASC-related conditions should be treated by clinicians who have expertise in this population as there are often contraindications with testing and treatment interventions that must be adhered to in order to protect the mother and fetus. Primary care providers and other specialists (eg, neurologists, rehabilitation medicine physicians) should determine what type of rehabilitation interventions and/or programs will be most beneficial as well as considering other factors such as cost and availability.</p>

TABLE 8: Health equity considerations and examples in post-acute sequelae of SARS-CoV-2 infection (PASC): neurologic sequelae. (continued)

Category	Comment	What is known	Clinical considerations
<p>► Age</p> <p><i>Example: Children compared to older individuals</i></p>	<p>Age should be considered in PASC-related health conditions as this may affect clinical decision making.</p>	<p>Many clinical trials, including rehabilitation studies, have gaps in the inclusion of people across the age continuum, particularly children and older individuals. Thus, clinicians should be aware that while PASC-related care needs will outpace the research for everyone, studies to guide the care of children and older individuals may be particularly slow to evolve.</p> <p>A recent cross-sectional study with age-matched controls showed SARS-CoV-2-positive adolescent participants in the case group had greater odds of having at least one long COVID symptom lasting at least 2 months compared with the control group. In addition, the case group reported 16 or more sick days (18.2% vs. 11.6%; $p < .0001$) and 16 or more days of school absence (10.5% vs. 8.2%; $p < .0001$) compared to the control group.⁵³</p> <p>A review in patients with type 2 diabetes mellitus and PASC highlighted issues related to older individuals.⁵⁴ The report explained that in diabetes, neuropathy and myopathy contribute to muscle atrophy and sarcopenia. In addition, acute COVID-19 infection, hospitalization, protein deficiency, and corticosteroid therapy often cause rapid onset of sarcopenia in severe COVID-19 infections. Acute COVID-19 infection may also contribute to new or worsening neurologic issues.</p>	<p>In older patients with type 2 diabetes mellitus, good control of blood sugar and other comorbidities, supervised physical activity and exercise, and optimal nutrition may be helpful in reducing and managing PASC symptoms.⁵⁴ Since older individuals may have low skeletal muscle mass with baseline sarcopenia, following infection they may become weaker than premorbidly. Clinicians should be vigilant about recognizing new or worsening neurologic or cardiovascular issues with activity and/or exercise. For older individuals who have an upcoming surgery, prehabilitation may help to support optimal outcomes.⁵⁵ Virtual visits for telerehabilitation may enhance access to care for older individuals.</p> <p>Recognition of PASC-related conditions in skilled nursing facilities is a factor that should be considered for individuals from that specific living setting. Larger number of beds and location in an area with high COVID-19 prevalence were the strongest and most consistent predictors of facilities having more COVID-19 cases and deaths.⁵⁶ This multicenter cohort study showed that delirium was the sixth most common of all presenting symptoms and signs of acute COVID-19 infection, and factors associated with delirium were age older than 75 years, living in a nursing home or assisted living, vision impairment, hearing impairment, stroke, and Parkinson disease.⁵⁷</p> <p>Though the studies in children are evolving, long COVID is recognized and should be considered at all ages. Expedited referrals to a multi-disciplinary PASC clinics should be considered for children when symptoms continue and to pediatric neurologists, pediatric rehabilitation medicine physicians, and other rehabilitation specialists when there are neurologic symptoms and sequelae.</p>

TABLE 8: Health equity considerations and examples in post-acute sequelae of SARS-CoV-2 infection (PASC): neurologic sequelae. (continued)

Category	Comment	What is known	Clinical considerations
<p>▶ Disability</p> <p><i>Example: People with certain conditions that cause disability and neurologic dysfunction</i></p>	<p>Individuals with baseline disability require special consideration in the workup and management of neurologic conditions in PASC. Further attention may be given for individuals with special needs and additional comorbidities.</p>	<p>People with disability due to spinal cord injury (SCI), stroke, multiple sclerosis (MS) and other common rehabilitation conditions have baseline neurologic dysfunction and may be at higher risk for COVID-19 acute infection and/or more severe disease. The incidence of PASC-related neurologic sequelae has yet to be fully explored in patient populations with pre-existing disability. However, clinicians should be aware of the overlapping issues of pre-morbid conditions associated with disability, risk of COVID-19 infection, severity of acute infection, and PASC sequelae. For example, patients with MS may be on disease modifying therapy (DMT), and both the MS and the DMT may put them at higher risk for COVID-19 acute infections as well as more severe course, though in a recent systematic review these were not consistent findings.⁵⁸ The review included more than 80 reports involving 2493 MS patients and 37 Neuromyelitis Optica Spectrum Disorder patients with COVID-19. Older age, higher expanded disability status scale (EDSS) scores, cardiac comorbidities, and obesity were independent risk factors for severe COVID-19. A systematic review of persons living with SCI showed similar clinical presentation, and low intensive care unit admission, but increased mortality for this population.⁵⁹</p>	<p>The impact of PASC-related neurologic dysfunction should be considered in individuals with baseline comorbidities that involve disability. Neurologic assessments should be tailored to the individual. Treating clinicians such as primary care providers, neurologists, and rehabilitation physicians should determine what type of rehabilitation will be most helpful and accessible. People with disability may benefit from addressing issues related to social determinants of health such as travel-related access to care. They may require and benefit from telehealth visits or access to community or other available travel resources.^{60,61} Consideration of the types of rehabilitation as well as the benefits, cost, and availability may vary, depending on a variety of factors. For safety purposes, patients may need to be cleared by a cardiologist prior to starting an exercise program. For those patients with SCI, a referral to a SCI-trained professional with experience in ventilation and pulmonary management of these patients may be indicated.⁶² Safety precautions should be clearly documented and adhered to. Monitoring vital signs and pulse oximetry is important as is a patient’s perceived exertion. Exercise and activity prescriptions, medications, injections, and other interventions aimed at supporting rehabilitation and enhanced function should be tailored to the individual and prescribed by clinicians who are experienced in caring for medically complex patients.</p>
<p>▶ Obesity</p> <p><i>Example: People who are diagnosed as overweight/obese</i></p>	<p>Obesity may not only increase the incidence and mortality associated with acute COVID-19 infection, but also development of PASC-related symptoms.</p>	<p>Obesity is an important risk factor for the development of severe COVID-19 infection and mortality.⁶³ Moderate and severe obesity (body mass index [BMI] ≥ 35 kg/m²) are associated with a greater risk of PASC.⁶³ Obesity has been thought to accelerate immunosenescence due to greater gene expression of inflammatory markers and oxidative stress.⁶⁴ In one study, PASC symptoms were characterized by fatigue, headache, dyspnea and anosmia and these were more likely with increasing age, increased BMI and female gender.⁶⁵ High BMI and previous pulmonary disease could be risk factors for development of PASC in exposed health care workers.⁶⁶</p>	<p>Recognize that obesity as a comorbidity can increase a patient’s risk for PASC and neurologic complications. Overweight individuals also face weight-related stigmatization. Furthermore, criteria for obesity using BMI may not be accurate for people with paralysis, who have lower ratios of fat to lean muscle mass. Addressing weight loss strategies can be done within patients’ system of care and in consideration with their own SDOH.</p> <p>Exercise and physical activity should be appropriately prescribed and consider obesity as a comorbidity. Furthermore, avoiding stigmatization should be embraced to promote physical activity in this population.⁶⁷</p>

TABLE 8: Health equity considerations and examples in post-acute sequelae of SARS-CoV-2 infection (PASC): neurologic sequelae. (continued)

Category	Comment	What is known	Clinical considerations
<p>▶ Insurance</p> <p><i>Example: Individuals who are uninsured, underinsured, or cannot afford access to recommended health care services</i></p>	<p>Insurance coverage, or lack thereof, should be considered when devising a treatment plan addressing health issues in PASC. Encouraging patient engagement and addressing psychosocial factors may improve adherence with treatment recommendations.</p>	<p>States with the highest rates of the uninsured will have widening disparities in health outcomes among racial/ethnic minority and low-income populations, worsening for those persons with PASC.⁶⁸ There may be lower participation in rehabilitation due to factors such as older age and reduced mobility or driving ability as well as social determinants of health such as being unemployed, having a low education level or lower income.⁶⁹ Access to telehealth services may be helpful for health care access to individuals with challenges with transportation, distance, and/or mobility.^{70,71}</p>	<p>Clinicians should be aware of the cost of diagnostic and treatment interventions. Consider the value of diagnostic testing to rule in/out various conditions. Treatment interventions, such as physical therapy, may be limited by the cost of copayments and deductibles, even in patients who have medical insurance. Social services or community groups may assist persons with finding local support inclusive of free therapy services. While access to telehealth services may facilitate care for some people, technology poses significant challenges for others. For example, individuals may have difficulty downloading, installing, and using new technology software or applications, a limited number of available digital devices, insufficient internet speed and bandwidth to manage audio and visual data, and poor quality of the camera and/or microphone on the device thus affecting the quality and diagnostic accuracy.⁷²</p> <p>Insurance coverage for telemedicine services, including telephone visits and virtual visits online, has expanded during the pandemic—leading to greater use of these services, though coverage for these services is changing. Telerehabilitation is often feasible, cost-effective, and may improve function in neurologic conditions as well as PASC.^{73,74}</p>

Note: This table is included to provide additional information for clinicians who are treating patients for PASC-related neurologic sequelae. This is not intended to be a comprehensive list, but rather to provide clinical examples as they relate to health equity, health disparities, and social determinants of health. The literature demonstrates that all marginalized groups face socioeconomic barriers and access to care barriers, though these may or may not be barriers for a specific individual patient. People with intersectional identities (eg, those who identify with more than one underrepresented or marginalized group), often face enhanced levels of bias and discrimination.

TABLE 9: Neuropathy/neuropathic pain.

Signs

- Weakness
- Gait instability
- Sensory testing abnormalities
- Muscle atrophy
- Change in mobility

Symptoms

- Numbness
- Sensory changes
- Nerve pain
- Burning
- Tingling
- Vibration
- Sharp shooting pain
- Hypersensitivity to touch
- Temperature instability with hot/cold feeling
- Phantom pain or sensations/itching
- Falls

Patient History and Evaluation:

- Assess for a personal history of diabetes, chemotherapy, alcohol use, autoimmune disorders, peripheral nerve injury or compression
- Assess for prolonged hospital stay, hospital stay including intensive care unit stay and/or prone positioning
- Manual muscle testing, with a focus on pattern of weakness (ie, proximal versus distal vs. focal vs. nerve distribution vs. dermatome)
- Sensory testing including light touch, pinprick vibration, proprioception, temperature
- Muscle stretch reflex testing
- Gait assessment, tandem gait
- Postural stability and alignment, dynamic balance (sitting or standing)

Additional Studies to Consider for Differential Diagnosis:

- Consider creatine phosphokinase, ferritin level, HIV and rapid plasma reagin, serum protein electrophoresis with immunofixation, methylmalonic acid may be considered in specific populations.
- Consider electromyography/nerve conduction studies (EMG/NCS) testing to identify and classify focal or diffuse neuropathy (motor/sensory, axonal/demyelinating)
- Consider small fiber neuropathy skin biopsy for intraepidermal nerve fiber density (may be done by neurology and trained internal medicine or dermatology clinicians)
- Magnetic resonance imaging imaging of spine can be considered in selected cases based on EMG/NCS or for presence of cord involvement (sensory level, bowel/bladder changes, increased reflexes) or look for root enhancement in polyradiculoneuropathy (chronic or acute inflammatory demyelinating polyneuropathy) (Refer to Table 3: Red Flags)

Initial Treatment Approach:

- Consider use of pain management strategies for neuropathic pain (gabapentin, Lyrica, Cymbalta, Nortriptyline, topical capsaicin, dry needling, heat, ultrasound)⁸²
- Consider use of "Evidence-based pain medicine for primary care physicians" as an evidence-based resource for pain management.⁸³

Referral Options:

- Refer to neurology for significant neuropathy, progressive weakness, or worsening gait instability
- Refer to pain management for severe symptoms that do not respond to first-line medication therapy
- Refer to orthotist for joint protection or stabilization; compression garments
- Refer to physical therapy for strengthening, balance retraining, gait training, stretching (muscular and neural tension), Aquatic therapy and patient education on pain.
- Refer to occupational therapy for desensitization, functional skills training including safety and compensatory strategies for sensory changes, stretching (muscular and neural tension), and patient education on pain.
- Refer to speech language pathology/therapy for focal exercises for facial or cervical muscles, dysphagia therapy, voice.

TABLE 10: Muscular pain, muscle weakness, tremor.

History and Physical Examination:

- Assess for prolonged hospital stay, hospital stay including intensive care unit stay; duration of hospitalization/bed rest
- Determine exposure to paralytics or steroid use
- Assess past medical history for previous neuromuscular pain/involvement or injury
- Perform range of motion assessments for all major joints; note contracture presence
- Conduct manual muscle testing, with a focus on pattern of weakness (ie, proximal versus distal; focal vs. diffuse nerve distribution; dermatome vs. myotome)
- Conduct sensory testing including light touch, pinprick vibration, proprioception, temperature
- Conduct muscles stretch reflex testing and a gait assessment (tandem gait)
- Assess for presence of fasciculations (muscle fiber twitching) or entire muscle contraction or tremors
- Conduct a tremor assessment (resting versus action versus postural; unilateral/bilateral)
- Assess for focal or generalized atrophy

Additional Studies to Consider for Differential Diagnosis:

- Consider creatine kinase (CK), ANA, lactate dehydrogenase, protein electrophoresis and immunofixation, aldolase, rheumatoid factor/anticitrullinated peptide antibodies and myasthenia gravis profile
- Consider myositis panel if CK is elevated or EMG demonstrates evidence of myositis
- Consider EMG/NCS testing: identify and classify myopathy
- Consider an order for magnetic resonance imaging (MRI) muscle to evaluate for myositis
- Consider MRI of the brain if abnormalities noted like resting tremor or involvement of muscles of the face/swallowing or speech (RED FLAGS)

Initial Treatment Options and Referrals:

- Refer to neurology for significant myopathy, progressive weakness, or worsening gait instability
- Refer to rheumatology for inflammatory myopathy or consideration for rheumatologic conditions
- Refer to orthotist for joint protection or stabilization, improved functional safety; night-time splinting and positioning (as needed)
- Refer to pain management for treatment strategies for myalgias
- Refer to physical therapy for strengthening, stretching (muscular and neural tension), balance retraining, gait training, aquatic therapy, adjunct therapies such as yoga or sports
- Refer to occupational therapy for strengthening, stretching (muscular and neural tension), pacing strategies, functional skills training including safety and compensatory strategies for pain, tremor and activities of daily living, myofascial pain techniques
- Refer to speech language pathology/therapy to perform focal exercises for facial or cervical muscles, dysphagia therapy, voice.