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Title: 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)

Short Running Title: Consensus Guidance Statement on Autonomic Dysfunction in PASC

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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)

Key Words: SARS-CoV-2 Sequelae, Long COVID, Post-COVID Syndrome, PASC, autonomic dysfunction, POTS, syncope, orthostatic hypotension, orthostatic intolerance

Introduction

While many people infected with acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recover completely, others are left with long-lasting symptoms that persist for at least 4 weeks, a condition referred to by the National Institutes of Health (NIH) as post-acute sequelae of SARS-CoV-2 infection (PASC). (1) The Centers for Disease Control and Prevention (CDC) define post-COVID conditions as the wide range of health consequences that are present for four or more weeks after infection with SARS-CoV-2, (2) while the World Health Organization (WHO) refers to post-COVID condition as symptoms that persist beyond 12 weeks after an initial infection, last for at least 2 months and cannot be explained by an alternative diagnosis.(3) There are a number of terms found in the literature that describe this condition (e.g., long COVID, persisting symptoms post-COVID, post-acute COVID-19 condition, long-haul COVID, and others), but for the purposes of this statement, the term PASC is used.

PASC can present with a non-specific constellation of signs and symptoms, (4) some of which appear to be autonomic in nature. These include, but are not limited to, orthostatic intolerance, palpitations, tachycardia, syncope, orthostatic hypertension, labile blood pressures, dizziness, fatigue and exercise intolerance. (5) The most common autonomic diagnoses associated with PASC are orthostatic intolerance and postural orthostatic tachycardia syndrome (POTS), which often follow a viral infection. (5) Other common features of PASC which may be related to autonomic dysfunction include cognitive impairment (often called “brain fog”), headache, insomnia, neuropathic pain, gastrointestinal and genitourinary dysfunction and allergic symptoms suggestive of mast cell activation, such as pruritis, urticaria, flushing, angioedema, wheezing, food sensitivities and others. (6) While the mechanisms of post-COVID autonomic dysfunction and PASC in general are being investigated, several possible etiologies have been

proposed including autoimmunity, inflammation, persistent T cell abnormalities, endothelial dysfunction, prothrombotic state, mast cell activation, small fiber neuropathy and others. (5, 7-12)

Data released by the CDC demonstrate that one in five adults (19%) who had COVID in the past still have symptoms of "long COVID," and overall, 1 in 13 adults in the U.S. (7.5%) have "long COVID" symptoms. (13) Estimates in the United Kingdom (UK) suggest that approximately 3% of the UK population is experiencing persistent symptoms 4 weeks after acute infection. (14) Despite the prevalence of prolonged symptoms and emerging data on various manifestations and possible mechanisms, limited guidance exists regarding the assessment and treatment of the broad constellation of symptoms, including autonomic dysfunction, due to PASC. With this in mind, the American Academy of Physical Medicine and Rehabilitation (AAPM&R) Multi-Disciplinary PASC Collaborative (PASC Collaborative) was convened to address the urgent need for interim guidance in the care of patients with PASC. This document is part of a larger series addressing the most common manifestations of PASC, and specifically discusses the assessment and treatment of autonomic dysfunction. Fatigue, cognitive symptoms, respiratory sequalae and cardiovascular complications of PASC are discussed elsewhere. (15-18)

PASC Consensus Guidance Statement Methods

The PASC Collaborative was created, in part, to develop expert recommendations and guidance from established PASC centers with extensive experience in managing patients with PASC. The collaborative is composed of 41 established post-COVID-19 or PASC centers, the first of which were established in April-June 2020. The PASC Collaborative is following an iterative modified Delphi approach to achieve consensus on assessment and treatment recommendations for a series of Consensus Guidance Statements focused on the most prominent PASC symptoms. (15-18) The full description of this process has been published in detail previously. (19)

At present, scientific evidence regarding effective assessment and treatment of PASC is limited, which prevents the creation of evidence-based clinical guidelines. These statements were developed by a diverse team of experts, with patient input, and integrate current experience and expertise with available evidence to provide tools to clinicians treating patients. There is an

intentional focus on health equity as disparities in care and outcomes are critically important to address. Beyond offering recommendations for assessment and treatment based on experience with care of patients presenting with PASC symptoms, the hope is that a broadened understanding of current patient care practices will help identify areas of future research.

We acknowledge that the definition of PASC is evolving, and there are various factors that contribute to a diagnosis. Additionally, PASC is broad and likely encompasses several different subtypes, some of which have overlapping clinical features. As such, the guidance statements developed by the PASC Collaborative are intended for broad audiences that could span primary care clinicians, physical medicine and rehabilitation physicians, and other specialists.

Considerations and Caveats for Implementation

This guidance statement is intended to reflect current practice in patient assessment, testing, and treatment, acknowledging the paucity of data on the diagnosis and treatment of PASC. In addition, we recognize the shortage of autonomic specialists in the U.S. that limit access to specialized autonomic evaluation and testing for many patients. At the time of development of this guidance statement, the early literature focused on patients who were not vaccinated, and the incidence and trajectory of PASC in vaccinated patients with 'breakthrough' cases (including current and emerging variants of the virus) is evolving. The PASC Collaborative considered these issues during the development process, and these guidance statements generally apply to individuals who develop PASC regardless of their vaccination status.

Importantly, the recommendations provided in this guidance statement should not preclude clinical judgment and must be applied in the context of the specific patient, with adjustments for patient preferences, comorbidities, and other factors. As with any treatment plan, clinicians treating individuals with PASC are encouraged to discuss the unknowns and ambiguities of PASC diagnosis, treatment and prognosis, as well as the benefits and risks of any interventions. Additionally, the PASC Collaborative recognizes that patients with autonomic dysfunction due to PASC typically present with a cluster of symptoms and signs that span multiple body systems and may overlap with cardiovascular and pulmonary complications that are not necessarily due

to autonomic dysfunction. These issues and suggested treatments are covered in separate PASC Collaborative guidance statements. (15-18)

Defining Autonomic Dysfunction

In this consensus statement, we use the term "autonomic dysfunction" to refer to any disturbance of the autonomic nervous system, including autonomic symptoms and common autonomic disorders, such as postural orthostatic tachycardia syndrome (POTS), neurocardiogenic syncope (NCS) which is also known as vasovagal syncope, orthostatic hypotension (OH) and inappropriate sinus tachycardia (IST). Orthostatic intolerance (OI) is used when objective tests do not confirm a diagnosis of one of the common autonomic disorders in a clinical setting of autonomic symptoms that are precipitated by an upright position and relieved by recumbency. The diagnostic criteria of POTS, NCS, OH, and IST are outlined in **Table 1**. **Diagnostic Criteria for Common Autonomic Disorders.** (20-22)

{INSERT Table 1: Diagnostic Criteria for Common Autonomic Disorders}

Based on PASC Collaborative discussion and patient feedback during the consensus process, we arrived at assessment and treatment guidance statements that may be utilized by healthcare practitioners when evaluating a patient with PASC-related autonomic dysfunction. We encourage healthcare practitioners to utilize this guidance as early evaluation, diagnosis, and management of autonomic dysfunction may ultimately improve functional impairment and reduce disability in patients with PASC.

Autonomic Dysfunction in Patients with PASC

The autonomic nervous system (ANS) consists of sympathetic, parasympathetic and enteric divisions and is responsible for numerous physiologic functions, including cardiovascular control of heart rate and blood pressure, gastric motility and secretion, bladder function, respiration, temperature control and distribution of blood flow to organs and tissue. The ANS mediates the "flight or fight" response to both external and internal stimuli in order to maintain homeostasis.

(23) There is evidence that the ANS is intimately involved in the process of inflammation as the vagus nerve, which carries the parasympathetic nervous system output, is a major constituent of a neural reflex mechanism—the inflammatory reflex—that controls innate immune responses and inflammation during pathogen invasion and tissue injury. (24) To this end, sympathetic overactivity may be associated with a pro-inflammatory state, while increased parasympathetic activity may have anti-inflammatory properties. (25)

Autonomic symptoms and manifestations, including resting and postural tachycardia and orthostatic intolerance, have been frequently reported by patients after SARS CoV-2 infection. (26, 27) Other common symptoms include dizziness, lightheadedness, palpitations, presyncope, syncope, orthostatic intolerance, exercise intolerance, cognitive dysfunction and fatigue. Gastrointestinal, respiratory, and genitourinary systems are reported as well. (**See Table 2: Clinical Features of Autonomic Disorders).**

{Insert Table 2: Clinical Features of Autonomic Disorders}

New-onset autonomic disorders can develop after a variety of viral and bacterial infections, including influenza, Epstein-Barr virus, and Borrelia burgdorferi. (6, 28) Case reports and series described POTS, OI, NCS, OH, IST and autonomic neuropathy (AN) in patients following SARS-CoV-2 infection, with POTS being the most common autonomic disorder observed. (29-31) OI is commonly diagnosed in patients with symptoms and signs consistent with POTS who do not meet diagnostic criteria for POTS. (32)

There are varying rates of autonomic dysfunction in individuals with PASC; in an international online survey of 802 individuals who had acute infection, 19% of patients reported having received a diagnosis of POTS. (33) Other studies estimate prevalence rates from 25% (34) to upwards of 40-69% in individuals with PASC. (32) Given these data and overlapping symptoms between POTS and PASC, the American Autonomic Society (AAS) called for increased research funding to investigate post-COVID POTS and clinical resources to provide care to patients with new-onset autonomic dysfunction following SARS-CoV-2 infection. (35)

Assessment Recommendations for Autonomic Dysfunction in Patients with PASC

Considering the wide variety of symptoms and signs of autonomic dysfunction, patients with PASC may present a diagnostic challenge. The PASC Collaborative Consensus Guidance Statement assessment recommendations offer an approach to history, physical exam, laboratory tests and diagnostic investigations that can aid with the diagnosis of autonomic dysfunction in patients with PASC (See Table 3: Autonomic Dysfunction in Patients with PASC: Assessment Recommendations).

{INSERT Table 3: Autonomic Dysfunction in Patients with PASC: Assessment Recommendations}

Assessment Recommendations Discussion

Patient History:

Since patients with PASC typically present with a number of symptoms, clinicians should identify the most disabling autonomic signs and symptoms, which include dizziness, lightheadedness, palpitations, tachycardia, presyncope, syncope, orthostatic intolerance, exercise intolerance, cognitive dysfunction and fatigue (Table 2). The onset of these symptoms in relationship to the acute SARS-CoV-2 infection should be recorded due to several possible modes of onset: 1) symptoms may develop as part of the acute SARS-CoV-2 infection and persist after resolution of viral infection; 2) symptoms may develop within the subacute period (days to weeks) of recovery from acute SARS-CoV-2 infection; 3) symptoms may develop with delayed onset, typically within one to three months following acute infection. Review of the course and treatment of acute SARS-CoV-2 infection, hospitalization, current medications with side effects, such as orthostatic intolerance, orthostatic hypotension or resting or postural tachycardia, and personal and family history of autoimmune and autonomic disorders should be obtained.

Initial Evaluation

Orthostatic intolerance is the hallmark of common autonomic disorders. Since dysfunction of the ANS can affect multiple organs and body systems, a thorough history, review of systems, and physical exam are needed to identify whether an autonomic disorder is present and which symptoms it may be causing. From a rehabilitation perspective, it is crucial to also understand how patients' symptoms are affecting their ability to function and participate in home, community, and work activities. Importantly, many patients with PASC present with significant cardiopulmonary symptoms that may include chest pain and shortness of breath and require differentiation between cardiovascular and autonomic diagnostic and therapeutic approaches. If there are abnormalities on electrocardiogram (EKG), cardiac echocardiogram, 24-hour Holter monitor, or noted on cardiovascular exam, or if there is high clinical suspicion for cardiac disease based on history, clinicians should obtain a cardiac evaluation before managing symptoms as an autonomic disorder. In our experience, some patients with post-COVID conditions may have both cardiovascular and autonomic complications and will require dual workup and treatment.

Similarly, some patients with PASC-related autonomic dysfunction may present with symptoms suggestive of anxiety, and while anxiety and other neuropsychiatric manifestations can occur as part of PASC, it is important not to attribute autonomic symptoms to those of generalized anxiety, depression or panic disorder, which can lead to a missed diagnosis and opportunity for treatment of the autonomic disorder. In one study, a survey of patients with POTS unrelated to COVID-19 reported 75% of patients have been misdiagnosed by a physician prior to a diagnosis of POTS. This same study reported that of the survey respondents there were 77% (n=3471)) respondents who encountered a physician who suggested their symptoms were due to a psychiatric or psychological problem before they were diagnosed with POTS. (36)

Many patients with POTS have small fiber neuropathy which has also been found in patients with PASC. (37) A neurologic exam including pinprick and temperature sensation is recommended to help identify small fiber neuropathy. Other potential signs of autonomic dysfunction include abnormal pupillary exam with dilated pupils that are poorly responsive to light, and evidence of acrocyanosis - a purplish-blue discoloration of the lower extremities due, in part, to blood pooling. (38) Acrocyanosis may also occur in patients with Raynaud’s disease,

other connective tissue disorders and erythromelalgia and may sometimes point toward autoimmune etiology. (39) Assessment for joint hypermobility with the Beighton scale may be warranted in some patients with new or pre-existing joint pain or joint hypermobility to identify hypermobility spectrum disorders and hypermobile Ehlers-Danlos syndrome (EDS), which are highly prevalent in patients with POTS and other autonomic disorders. (40) Similarly, flushing, urticaria and dermographism may be present on skin examination of patients with autonomic dysfunction and mast cell hyperactivity, which may accompany POTS, EDS and PASC. (41,42)

A 10-minute stand test, in addition to a thorough examination of the cardiovascular and neurological systems, is recommended. The procedure for a 10-minute stand test is as follows:

1. The patient should lie down quietly for 5 minutes. Obtain the blood pressure and heart rate using a sphygmomanometer on the upper arm.
2. With the patient standing quietly without moving or talking, obtain blood pressure and heart rate using a sphygmomanometer on the upper arm at 3, 5, 7 and 10 minutes of standing.
3. Record patient-reported symptoms throughout the test. (Appendix 1 contains a sample symptom reporting table.)
4. Caution should be exercised for highly symptomatic patients who are unable to safely stand for 10 minutes due to orthostatic intolerance or neuromuscular disorders with impaired mobility.

If the 10-minute stand test confirms a diagnosis of POTS, NCS, OH or OI (see Table 1: Diagnostic Criteria for Common Autonomic Disorders) then no further confirmation via a tilt table test is necessary. If a 10-minute stand test is inconclusive or unremarkable in a patient with suspicion for an autonomic disorder, a tilt table test should be considered (see section on autonomic function tests). Clinicians may take into consideration any available patient generated data from wearable heart rate devices or monitors (Apple watch, FitBit or similar devices) or the patient's self-obtained 10-minute stand test performed at home. These data may help with the diagnosis of an autonomic disorder when an in-office 10-minute stand test is inconclusive. Note that a 10-minute stand test may provide variable results depending on the time of the day, the

patient's symptoms at the time of the appointment, hydration status and other factors. When diagnosis is uncertain, or symptoms are progressing, other cardiovascular, neurologic, gastrointestinal, and genitourinary tests with possible referral to an autonomic specialist may be considered.

It is important to prioritize health equity for persons with pre-existing neurologic and autonomic disorders. Table 4: Health Equity Considerations and Examples in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC): AUTONOMIC DYSFUNCTION provides a summary of what is known about autonomic dysfunction in specific populations and provides clinical considerations for those populations. Autonomic dysfunction is associated with many different conditions that cause disability such as Parkinson's disease, multiple sclerosis, spinal cord injury, traumatic brain injury and diabetes mellitus. (42) Depending on functional status of the individual, modifications may be required for physical exam and autonomic evaluation in the office setting. For example, some patients with impaired mobility, severe orthostatic intolerance or spinal cord injury may be unable to complete a 10-minute stand test, and therefore, modifications and special accommodations in the usual testing protocols may be needed for these patient populations.

{Insert Table 4: Health Equity Considerations….)

Laboratory Evaluation

Laboratory assessment should include a complete blood count (CBC), a comprehensive metabolic panel (CMP) and thyroid function tests (TFT). (63) Common vitamin and nutritional deficiencies in patients with autonomic symptoms and disorders include iron deficiency without anemia or mild anemia and vitamin B12 deficiency. (64,65) Vitamin B12 and serum ferritin level can be obtained, and supplementation is recommended if deficiencies are noted. Additional tests for consideration include a morning serum cortisol to assess if adrenal insufficiency is contributing to syncope, presyncope, or low blood pressure. In addition, assessing basic markers of inflammation and autoimmunity, (66,67) such as an antinuclear antibodies (ANA), erythrocyte sedimentation rate (ESR), and c-reactive protein (CRP) are recommended in patients with autonomic dysfunction in the setting of PASC.

If the patient is experiencing tachycardia, particularly in conjunction with dyspnea, obtaining a serum D-dimer is recommended to assess for pulmonary embolism, especially if symptoms developed within weeks of their acute SARS-CoV-2 infection, given an association between SARS-CoV-2 and thromboembolic events. (68) Additional laboratory work-up may be considered based on the results of initial laboratory tests, or if there are specific clinical features that warrant further investigation.

Autonomic Function Tests

When an autonomic disorder is suspected and previous testing, including a 10-minute stand test, is unrevealing, a tilt table test should be considered. In situations where the diagnosis is unclear or patients have progressive symptoms or symptoms refractory to treatment, consider referral to an autonomic specialist. Other specialized testing that can be considered (often under the guidance of an autonomic specialist) include a deep breathing test, Valsalva maneuver, quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test and a skin biopsy for evaluation of small fiber neuropathy. (38) It is important to note that access to autonomic specialists and the autonomic laboratories equipped to perform these tests is limited throughout the country, which may present a significant barrier to diagnostic evaluation in patients with suspected autonomic disorders.

Tilt table testing: is recommended in patients presenting with autonomic symptoms with unremarkable in-office 10-minute stand test. Patients are laid in a supine position and then tilted upright to 60-70 degrees for at least 10 minutes while monitoring blood pressure and heart rate using both peripheral arterial volume-clamp measurements, confirmed with an automated cuff sphygmomanometer over the brachial artery, allowing for continuous beat-to-beat assessment during head-up tilt. If possible, all medications that may affect heart rate and blood pressure should be held for at least 4 half-lives prior to the tilt table test to minimize blunting of vital sign responses. A tilt table test can confirm a diagnosis of POTS, NCS, and OH and may also be useful to delineate the etiology of undiagnosed episodes of altered consciousness or awareness and differentiate anoxic reflex syncope from epilepsy and pseudo-seizures. Compared to active standing, which activates skeletal muscles to compress underlying veins and increase venous return, passive head-up tilt testing induces a greater orthostatic stress on the body, and thus is

more sensitive at eliciting orthostatic hypotension, exaggerated postural tachycardia, and neurally mediated hypotension. Tilt testing provides further value in that the clinician can observe real-time beat-to-beat heart rate and blood pressure changes while the patient reports symptoms elicited by the orthostatic challenge. It is thus recommended for evaluation of POTS, NCS, OH and psychogenic pseudosyncope if the initial assessment does not yield a definite or highly likely diagnosis. (69,70)

Deep breathing testing: is performed by having a patient take slow, deep breaths at a rate of 6 breaths/minute in the supine position. This test assesses the integrity of cardiovagal reflexes and the parasympathetic system. Heart rate is monitored with a single-lead EKG and the difference between the heart rate at the end of expiration and the end of inspiration is calculated (maximum-minimum heart rate). An abnormal result is defined as a maximum-minimum heart rate less than the 5^{th} percentile of age- and sex-adjusted normative data, (71) and if present may suggest an autonomic neuropathy. Less than 10% of patients with POTS have been noted to have an abnormal deep breathing test. (28)

Valsalva maneuver: is performed by a forceful attempt of exhalation against a closed airway and assesses cardiovagal responses. Like deep breathing, this test is performed in the supine position to limit the effects of gravitational stress. The patient is coached to forcefully exhale at a pressure of at least 40 mmHg against a closed glottis for 10 seconds using a bugle-type mouthpiece. Blood pressure and heart rate are recorded continuously as during tilt testing. Analysis of the blood pressure response to the Valsalva maneuver evaluates sympathetic adrenergic function, and analysis of the heart rate response evaluates cardiovagal function. There are 4 phases of the Valsalva maneuver, but only late phase II and phase IV are evaluated for integrity of autonomic baroreflex function. Specifically, an increase in blood pressure during late phase II and a blood pressure overshoot in phase IV are expected, both of which represent peripheral vasoconstriction mediated by sympathetic adrenergic outflow. In patients with POTS, the Valsalva test is typically normal, although some patients may exhibit a hyperdynamic blood pressure response consistent with baroreflex hypersensitivity and a hyperadrenergic state. (38)

Quantitative sudomotor axon reflex testing (QSART): assesses the post-ganglionic sudomotor (sweat) function by monitoring the sweat response to peripheral stimulation of sudomotor nerves. It is a diagnostic test for evaluation of small fiber neuropathy. An abnormal QSART has been noted in 33-63% of patients with POTS. (38)

Thermoregulatory sweat testing (TST): assesses the pre- and post-ganglionic sudomotor functions by assessing the sweat response to elevation in core body temperature. It can indicate distinct patterns of sweat loss in neurodegenerative autonomic disorders, such as pure autonomic failure, multiple system atrophy and peripheral autonomic disorders, such as diabetic autonomic neuropathy and autoimmune autonomic ganglionopathy. Abnormal TST is seen in at least half of patients with POTS with a predominantly distal sweat loss pattern. (28, 38)

Skin biopsy: is a minimally invasive in-office procedure using a punch biopsy kit. Obtained from the distal and proximal leg, the skin is evaluated for epidermal nerve fiber and sweat gland densities. Decreased epidermal nerve fiber density and/or decreased sweat gland density are highly prevalent in patients with POTS or PASC. (37)

Cardiac Tests

EKG, echocardiogram and ambulatory cardiac monitoring should be considered for patients presenting with autonomic dysfunction. If history and physical exam are suggestive of or consistent with cardiovascular disorders rather than autonomic dysfunction, we recommend cardiovascular evaluation as per the separately published PASC Collaborative Consensus Guidance Statement on Cardiovascular Complications. (18) In cases of diagnostic uncertainty and given the significant overlap between cardiac and autonomic symptoms, clinicians should have a low threshold for obtaining both cardiovascular and autonomic evaluations.

Activity Performance Measures

Patients who are referred for rehabilitation therapies should be evaluated with objective measures of activity performance. These measures can be used to compare to healthy control values to help understand the degree of physical dysfunction and can help guide the initial activity prescription.

They can then be repeated at follow-up visits to help quantify functional changes and guide progression of activity.

The measures should be individualized to the patient's abilities, including consideration of modifications necessary to accommodate disability due to neurological or other impairment, fatigue with post-exertional malaise, autonomic dysfunction, pregnancy, or other limitations. Potential measures include a 30-second sit-to-stand test, 2-minute step test, and 6-minute walk test. (72-78) Longer testing, such as the 6-minute walk test may be more suited to be performed during a physical therapy evaluation as opposed to a clinic visit for time considerations. It is important to note that these tests may represent significant exertion and could exacerbate post-exertional symptoms. Alternative tests exist for patients requiring more in-depth assessment.

Treatment of Autonomic Dysfunction in Patients with PASC

Currently, evidence-based therapies and clinical guidance available for treatment of autonomic dysfunction specific to patients with PASC are lacking. Therefore, in this consensus guidance statement, we reference therapies that have been utilized for management of POTS, OH, NCS, IST and AN as applicable to PASC and post-COVID autonomic disorders. The therapeutic approach to autonomic disorders consists of non-pharmacologic and pharmacologic treatment modalities that are employed with the goal of reducing symptom severity and functional impairment. The treatment recommendations for autonomic dysfunction in patients with PASC are outlined in Table 5: Treatment Recommendations for Autonomic Dysfunction in Patients with PASC

{Insert Table 5: Treatment Recommendations for Autonomic Dysfunction in Patients with PASC}

Treatment Recommendations Discussion

<u>Non-Pharmacological Treatment Recommendations</u>

As best practices continue to emerge to address the symptoms of PASC-related autonomic dysfunction, non-pharmacological treatment recommendations that have been employed for

treatment of POTS and other autonomic disorders unrelated to COVID-19 may assist in symptom management.

1. *Salt supplementation*: Salt (sodium chloride) supplementation has been utilized as an effective non-pharmacologic therapy in patients with autonomic disorders, likely due to its effect on increasing plasma volume as reducing sympathetic overactivity. (77,79) For individuals with PASC-associated autonomic dysfunction, salt supplementation of 7 to 10 grams (2.8 to 4 milligrams of sodium) per day is recommended. (20,79) Caution should be taken in recommending salt supplementation in those with a history of heart failure, altered renal function or those with episodic or sustained elevated blood pressure. These individuals may require either a recommended daily allowance of sodium at 4 grams per day or mild to moderate increase in salt intake.

2. *Fluid intake*: Water consumption should be increased to at least 3 liters per day. It is recommended that water and salt be consumed together. (77,79) Water without salt is not effective in sustained volume expansion. Another possible option is glucose-salt rehydration solutions although their use has not been confirmed in clinical trials. Increased salt and fluid intake should be started prior to or concurrently with exercise. (20) Caution should be taken in those with a history of cardiovascular or renal disorders.

3. *Compressive garments:* Compression garments are recommended for individuals with autonomic dysfunction to minimize venous pooling and central hypovolemia associated with orthostasis. For individuals with PASC experiencing orthostatic intolerance, waist-high lower body compression garments and/or accompanied by abdominal binders, 20-40 mmHG or 40-60 mmHG in strength, can be trialed. (80,81) If found beneficial, compression garments may be worn during the daytime and removed at night. (82)

4. *Diet*: there is no evidence-based guidance on the dietary approaches to patients with PASC-related autonomic dysfunction. Low-histamine, gluten-free, dairy-free, low Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAP) and plant-based diets have been anecdotally reported to be beneficial. A gluten-free diet

was demonstrated to be beneficial in some patients with POTS. (83) When considering dietary changes, the benefits of a particular diet need to be weighed against the risks, including vitamin or nutrition deficiencies. Diets may be individualized and targeted toward the patient's specific set of symptoms and food sensitivities. A referral to a dietician or nutrition specialist may be considered. (84,85) Small frequent meals with salty snacks instead of 3 large meals may be better tolerated due to a reduction in post-prandial autonomic symptoms and heart rate and blood pressure variability. (86,87)

5. *Counterpressure maneuvers and head of the bed elevation*: Counterpressure maneuvers performed during prolonged sitting or standing may reduce the symptoms of NCS and OI, and head of the bed elevation can be helpful in patients with OH (3 references in the comment). These techniques could offer inexpensive and low-risk treatment modalities aimed at managing orthostatic intolerance and may be useful in some patients with autonomic dysfunction. (88)

Pharmacotherapy

When non-pharmacologic therapy alone is ineffective or insufficient to result in improvement, pharmacologic treatment should be initiated. **Table 6: Pharmacological Treatment Options for Autonomic Dysfunction** summarizes pharmacotherapy options

The choice of pharmacotherapy depends on the clinical presentation and the most disabling symptoms that the patient is experiencing. For example, if the patient exhibits significant postural or resting tachycardia in the absence of significant orthostatic hypotension, a beta blocker, such as propranolol 5 mg to 10 mg twice a day or atenolol 12.5 mg to 25 mg daily, should be considered. (89, 90) The starting dose of a beta blocker should be low since a high dose may result in hypotension, increased dizziness and exacerbation of fatigue. Dosage can be increased according to therapeutic response while considering adverse effects.

If the patient has significant orthostatic intolerance accompanied by low blood pressure, then midodrine 2.5 mg to 5 mg three times a day or fludrocortisone 0.05 mg to 0.1 mg daily should be considered. (89,90) Fludrocortisone requires about 2 weeks of administration to result in symptomatic improvement, while the effect of midodrine can be assessed within a few days after its initiation and dose escalation. Maximum dose of midodrine may be 30-40 mg daily, while low doses of fludrocortisone, up to 0.2 mg daily, are typically used for patients with autonomic disorders. (89,90) As with beta blockers, starting one medication at a time at a low dose and increasing slowly to a maximum therapeutic effect is recommended as patients with POTS and other autonomic disorders can be sensitive to medications and their adverse effects.

Other medications used for autonomic dysfunction, include pyridostigmine, ivabradine, clonidine, modafinil, methylphenidate, methyldopa, or selective serotonin reuptake inhibitors (SSRIs)/serotonin and norepinephrine reuptake inhibitors (SNRIs). (89,90) The choice of medication depends on which clinical symptoms or signs need to be addressed. For example, if the patient has orthostatic intolerance in the setting of normal or elevated blood pressure, pyridostigmine may be utilized. If the patient has labile blood pressure and symptoms of episodic sympathetic overactivity, such as tachycardia, diaphoresis, anxiety and polyuria, clonidine or methyldopa may be tried.

For patients with concurrent depression, anxiety, obsessive-compulsive symptoms or neuropathic pain, a trial of a low dose SSRI or SNRI, such as duloxetine, could be beneficial. (89,90) Bupropion, in particular, has shown some benefit in reducing fatigue in patients with POTS. (89,90) Given significant fatigue and cognitive symptoms (i.e., “brain fog”) in patients with PASC, a trial of modafinil, methylphenidate or other stimulants, can be considered, with caution in patients with POTS or with sleep disturbance since stimulants may worsen tachycardia and

insomnia. In such cases, a low dose of a beta blocker in combination with a stimulant could be employed. In patients who are unable to tolerate beta blockers due to hypotension, fatigue, respiratory disorders or depression, ivabradine can be used to treat tachycardia. (89,90)

Droxidopa is FDA-approved for treatment of neurogenic OH and can be beneficial in patients with post-COVID OH and some patients with POTS. (89,90) Desmopressin 0.1 mg orally can also be utilized in certain cases on an as-needed basis for orthostatic intolerance. Intravenous immunoglobulin therapy can be considered in treatment-refractory patients with severe POTS, small fiber neuropathy, autonomic neuropathy and other autonomic disorders and serologic evidence of autoimmunity (including, but not limited to, elevated serum anti-nuclear antibodies, anti-phospholipid antibodies, sedimentation rate, C-reactive protein and others) or comorbid autoimmune disorders. (91) Additionally, intravenous saline, usually 1-2 liters over 1-2 hours, could be used on as-needed basis for acute exacerbation of POTS or in patients with significant gastrointestinal dysfunction who are unable to maintain oral hydration. (90) Chronic use of intravenous fluids is not recommended due to a risk of infection and thrombosis associated with central intravenous line placement. (90) Non-invasive vagus nerve stimulator, currently under investigation for treatment of POTS, may be considered, given its potential anti-inflammatory effect via activation of the vagus nerve and reduction of pro-inflammatory cytokines. (92,93)

Treatment of common comorbidities associated with autonomic dysfunction, such as migraine headache, neuropathic pain, sleep disturbance, gastrointestinal dysfunction and mast cell hyperactivity-related allergies and food sensitivities may indirectly alleviate autonomic dysfunction by reducing symptom burden caused by the associated comorbidities. Antihistamines, such as loratadine, cetirizine, fexofenadine and famotidine, and mast cell stabilizing agents, such as cromolyn sodium and ketotifen, may be treatment options considering that patients with PASC may display mast cell activation symptoms. (42) Low-dose naltrexone may be considered for treatment of neuropathic pain, chronic joint pain, fatigue and other pain that may occur in patients with PASC-related autonomic dysfunction. (94,95). If pre-diabetes or diabetes is discovered as part of the comprehensive evaluation of PASC, treatment of hyperglycemia should be implemented under the guidance of a primary care physician, Sex differences should be considered in treatment of PASC-related autonomic disorders. In particular, there is a paucity of literature on PASC-related autonomic dysfunction during

pregnancy in individuals with pre-existing or new symptoms. Symptoms of POTS during and after pregnancy are typically variable, and both non-pharmacologic and pharmacologic management may need to be adjusted (e.g., fluid and salt requirements, medications) during pregnancy and afterward if the patient is breastfeeding. (96,97)

Rehabilitation Therapies

Coordination with a multidisciplinary team that includes Physical Medicine and Rehabilitation (PM&R) physicians, occupational therapists, vocational and psychology services can help to create the functional adaptations that allow patient to resume their normal activities and roles while recovering from PASC. If PM&R physicians are available, they are experts in leading multidisciplinary rehabilitation teams and can help to coordinate the care and the variety of interventions needed to treat medically complex patients. Interventions may include the above-mentioned pharmacologic and non-pharmacologic treatments as well as physical and occupational therapy, neuropsychology, nursing, and other specialties. Part of a functional assessment and treatment program includes the assessment of the patient's pre-morbid and current level of function which are then considered in the context of prescribing goal-directed therapy.

Physical therapists knowledgeable about autonomic dysfunction and related diagnoses ensure that patients tolerate and benefit from prescribed activity/exercise-related interventions and help with mobility compensation, including evaluating architectural accommodations, and considerations of wheeled mobility or the use of assistive devices such as rollators or canes. Occupational and physical therapists are instrumental in employing pacing strategies and prescribing adaptative equipment that can improve function and participation levels. For example, ADL adaptations can include items such as long handled reaching devices and other equipment to allow for activities so that bending, stooping, and standing can be reduced for individuals who are challenged by those activities. In coordination with PM&R physicians and therapists, automation and home adaptations can help patients to deal with issues of fatigue by conserving energy, even while the rehabilitation program works to restore endurance.

The entire therapy and physician team working with vocational rehabilitation can help patients to deal with challenges in the workplace (both structural and human resource based) to restore the ability to work with reasonable accommodations in line with the Americans with Disabilities Act (ADA) and allow for return to work. Finally, neuropsychological interventions can help patients deal with the anxiety, depression, and coping mechanisms they may face when encountering a new disability related to PASC. Although traditional approaches to prescribing exercise in individuals with autonomic dysfunction and related diagnoses (e.g., POTS, OI, OH and others) have suggested progressive graded aerobic and resistance-training exercise as a gold standard intervention (78,79,98-101), more recent research into this topic has highlighted significant concerns for the propensity of graded aerobic exercise programs to trigger worsened fatigue, symptom exacerbation and autonomic dysfunction. (102)

Specifically, one of the hallmarks of autonomic dysfunction in PASC is the presence of post exertional symptom exacerbation or post exertional malaise. (33,103,104) Post exertional symptom exacerbation suggests that while an individual may appear to tolerate an intervention during performance of the task, symptoms may flare hours to days following the exercise. (105,106) In one study, 86% of individuals diagnosed with PASC reported physical exertion as a cause for symptom exacerbation. (103) Prior to the initiation of an exercise program, individuals with autonomic dysfunction related to PASC should undergo a comprehensive medical evaluation as described above which should take into account the propensity of physical exertion to lead to symptom exacerbation, and appropriately screen for post-exertional symptoms. (107)

1. *Breathwork exercise:* Sympathetically mediated hypocapnia with orthostasis has been largely reported and is suspected in hypocapnia experienced by individuals with autonomic dysfunction. (108-110) Further, hypocapnia has been reported in individuals with PASC. (111) While the underlying mechanism is under further investigation, structured breathing exercise should be considered to address both autonomic and hyperventilation mediated root causes of hypocapnia. (112)

2. *Symptom titrated physical activity/movement:* The goal of rehabilitation therapy is to promote symptom stabilization, and progress slowly toward improved activity tolerance

without PASC symptom exacerbation. Symptom titrated physical activity progression is recommended as part of a rehabilitation intervention. (113) Rehabilitation therapists should not aim to 'push' patients through symptoms or encourage physical work exceeding a patient's tolerance. For patients with severe symptoms of autonomic dysfunction, post-exertional symptom exacerbation, or those that cannot tolerate upright activities, low intensity activity started in the supine position and slowly progressing to upright activities over time is recommended. (114) A sample rehabilitation program exemplifying this approach to PASC-related dysautonomia rehabilitation is provided below.

3) Functional restoration: One of the major limitations for individuals suffering with PASC and autonomic dysfunction are the overall functional limitations that prevent normal return to activity and life functions. Key among these are limitations of mobility, and inability to resume normal activities of daily living (ADL) and instrumental activities of daily living (IADL). ADL include tasks such as bathing, dressing and eating, and IADL include higher level activities such as shopping, housekeeping, driving and other normal activities of life. A final level of loss of function can be the inability to return to school or work. Restorative or adaptive therapies to allow for vocational recovery are also important considerations.

Sample Rehabilitation Program

Here we provide a sample rehabilitation program that can be trialed with patients experiencing autonomic dysfunction in the setting of PASC. It is important to note that research related to physical rehabilitation in patients with PASC is still in the early stages and other rehabilitation programs may also be appropriate.

Initiate the rehabilitation program with supine based therapeutic movements including symptom titrated active range of motion with focus on open chain activity (for example, heel slides, active range of motion hip adduction, straight leg raises). The term "symptom titration" implies that all interventions are scaled not based on intensity, but rather based on how a patient's symptoms respond to the activity. Tolerance to intervention can be assessed using rate of perceived exertion

(RPE), such as the BORG Scale and visual analog scale (VAS) of patient symptoms. Should the symptom VAS exceed a 3-point change or RPE exceed “fairly light” on the BORG RPE scale from within the session baseline, movement therapy should be stopped. (104,115) Therapeutic exercises should be prescribed on time-based intervals rather than sets/repetitions to allow patients to implement energy conservation strategies and promote symptom titrated activity.

Supine movement should be progressed to upright activity after a minimum of 2 weeks so long as no symptom exacerbation is reported. Should post exertional symptom exacerbation be reported (either within the session or in the hours to days following), interventions should be evaluated for exacerbating factors and the intensity modified/downgraded accordingly. Upright based movement should continue to include open chain movements with the introduction of isometric exercises such as seated hip adduction (squeezing knees together). As active range of motion-based interventions are tolerated, rehabilitation therapists may introduce ambulatory intervals to progress intervention. Heart rate and age predicted heart rate max should not be utilized in the preliminary stages of walking intervals to scale aerobic exercise as traditional metrics of mild-to-moderate intensity exercise may not be tolerated in this cohort. Paced activity should be introduced with adequate rest between intervals. RPE and VAS of primary symptoms should continue to guide symptom titrated activity and intensity of therapy interventions.

The intensity of interval training should be progressed over the course of a minimum of 6 weeks if symptoms remain stable and the patient tolerates. Pacing principles and energy conservation strategies are pivotal to successful participation in rehabilitation therapy and should be continuously reinforced.

As patients continue to tolerate progressive symptom titrated activity, more traditional forms of autonomic therapy can be introduced. Moderate intensity aerobic interventions or similar traditional autonomic rehabilitation protocols (such as use of the Levine protocol) should be considered with the understanding that not all patients will be able to progress this far, and ongoing evaluation of activity tolerance is required. Patients may continue performing symptom titrated movement interventions as tolerated.

Disability Considerations

PASC can be considered a disability under the Americans with Disabilities Act (ADA), section 504 and section 1557, if it substantially limits at least one major life activity. (116) It is imperative that patients with autonomic dysfunction related to PASC have their symptoms and other validated measures documented in the medical record and followed over time. As discussed in this consensus guidance statement, PASC-related autonomic dysfunction should be evaluated with a neurological examination and a 10-minute stand test, as well as a tilt table test and other autonomic function tests, if necessary. These evaluations should be submitted in support of getting disability benefits approved, especially if a patient's autonomic dysfunction is expected to last at least 12 months.

Worker's compensation companies and disability insurers need to acknowledge the disability that can occur when workers have PASC-related autonomic dysfunction. Employers are required to provide reasonable accommodations to employees with disabilities. Individuals with PASC-related autonomic dysfunction may need their clinical team's assistance with requesting special accommodations from their employer. These accommodations may include flexible work schedule, periodic rest breaks, remote work, seated or reclining workstations, accessible parking, ability to have fluids at the workstation, and use of a fan at a workstation. This list is not an exhaustive list of accommodations for individuals with PASC-related autonomic dysfunction; other reasonable accommodations may be needed to address specific symptoms that may be interfering with the employee's ability to work.

Summary

Individuals with PASC commonly present with symptoms of autonomic dysfunction and should undergo a clinical evaluation for autonomic disorders. A comprehensive treatment program including non-pharmacologic, pharmacologic and rehabilitative interventions is often needed to manage autonomic dysfunction and improve functional status. This guidance statement is designed to help clinicians currently treating individuals with PASC-related autonomic disorders by presenting evidence-based recommendations as well as recommendations based on the collective experience of the PASC Collaborative.

Future Directions

While COVID vaccines may decrease the risk of PASC, breakthrough cases of COVID and subsequent PASC have been reported in fully vaccinated individuals, as well as observed in clinical practice. (117,118) Importantly, a number of patients with PASC experience temporary or permanent improvement in symptoms after immunization with COVID vaccines. (119-121) In an early post-vaccination study to assess changes in the trajectory of Long Covid symptoms in adults infected with SARS-CoV-2, the incidence of symptoms decreased after both the first and second vaccination doses. This study suggests that vaccination may reduce the burden of both SARS-CoV-2 and PASC in adults. (122) In contrast, a retrospective cohort study did not find COVID vaccines to be protective against PASC in breakthrough cases. (123) While further studies are needed to determine whether COVID vaccines decrease the incidence of PASC in vaccinated individuals after breakthrough infection, vaccination remains one of the most important public health measures to mitigate the pandemic.

These PASC Collaborative guidance statements are preliminary. Studies that investigate autonomic dysfunction in patients with post-COVID symptoms are needed in order to determine what subset of patients with PASC have autonomic dysfunction. At this time, it is unknown whether post-COVID autonomic disorders are similar to those that can arise after other viral infections or whether these represent a distinct phenotype unique to SARS-CoV-2 virus. Future studies are also needed to determine the biomarkers as well as appropriate diagnostic, prognostic and therapeutic approaches to patients with post-COVID autonomic dysfunction. Specialized rehabilitation programs, non-pharmacologic management, including individualized dietary and exercise regimens, and pharmacologic treatment, including immunotherapy, require further investigation in clinical trials. As new studies emerge, the PASC Collaborative may require a re-evaluation of the assessment and treatment clinical recommendations in order to provide the most up-to-date evidence-based patient care for individuals with PASC.

{Insert Health Equity Statement}

Health Equity Statement

The American Academy of Physical Medicine and Rehabilitation (AAPM&R) recognizes the need to support equitable access to rehabilitation care for individuals with Post-Acute Sequelae of SARS CoV-2 infection (PASC). The AAPM&R states that equitable access to care includes: (1) timely and local patient access to multidisciplinary care; (2) addressing inequities in the United States health system that result in diminished access to sustained quality care because of structural racism or socioeconomic factors; and, (3) strengthened safety-net care, including disability evaluation and benefits. (124)

Each of the AAPM&R's PASC guidance statements were produced by a diverse and multidisciplinary team of subject matter experts with patient input. Although an in-depth discussion of health equity issues is beyond the scope of the PASC guidance statements, each one highlights health equity concerns and refers readers to other publications and resources. The term "health equity" has many different definitions, and they generally focus on ensuring that every person is able to achieve the highest level of health and function. For example, the Centers for Disease Control and Prevention (CDC) defines health equity as the opportunity for people to fulfill their full health potential and states that people should not be disadvantaged from achieving their potential because of social position or other socially determined circumstances. (125) The Centers for Medicare and Medicaid Services (CMS) uses the definition established in Executive Order 13985, issued on January 25, 2021 that states equity is "the consistent and systematic fair, just, and impartial treatment of all individuals, including individuals who belong to underserved communities who have been denied such treatment, such as Black, Latino, and Indigenous and Native American persons, Asian Americans and Pacific Islanders and other persons of color; members of religious minorities; lesbian, gay, bisexual, transgender, and queer (LGBTQ+) persons; persons with disabilities; persons who live in rural areas; and persons otherwise adversely affected by persistent poverty or inequality." (126) There are many root causes for health disparities, some of which fall under the categories within social determinants of health (SDOH). Examples of SDOH include but are not limited to socioeconomic status, neighborhood, availability and access to healthy food, and access to a high-quality education.

In addition to advocating for equitable access to rehabilitation care for all persons with PASC, the AAPM&R supports four "Principles of Inclusion and Engagement" which include: (1) valuing diverse group composition (a diverse group is more representative of AAPM&R's membership and volunteers may be selected as a member of a particular community to enhance diversity of thought and experiences); (2) mutual respect (cultivating a receptive space for differing opinions and viewpoints); (3) talent and skill-based selection for leadership opportunities (ensuring that broad criteria of diversity of experience, talent and knowledge are incorporated and removing barriers to involvement that support an equitable environment); and, (4) comprehensive collaboration (building community among various member constituent and bringing together different perspectives). (127) Readers of the PASC guidance statements are encouraged to consider the recommendations through the lens of health equity in order to improve access to rehabilitation care for all individuals with PASC.

Tables

Table 1. Diagnostic Criteria for Common Autonomic Disorders

Autonomic Disorder	Diagnostic Criteria
POTS (20)	1. Sustained HR increase ≥30 bpm within 10 minutes for adults (≥40 bpm for adolescents 12-19 years of age) of standing or on TTT 2. Absence of OH 3. Symptoms of orthostatic intolerance for ≥6 months 4. Exclusion of other causes of postural tachycardia, such as dehydration, medication side effect and other medical conditions
NCS (20)	1. Transient loss of consciousness typically preceded by prodromal symptoms and signs, such as pallor, diaphoresis, nausea, abdominal discomfort, yawning, sighing, and hyperventilation. That may occur up to 60 sec prior to loss of consciousness. 2. A sudden fall in blood pressure, heart rate and cerebral hypoperfusion on standing or on TTT
OH (21)	Sustained drop in blood pressure ≥20/10 mmHG within 3 minutes of standing or on TTT
IST (22)	1. Average sinus HR exceeding 90 bpm over 24 hours or HR while awake and at rest ≥100 bpm 2. Palpitations and other distressing symptoms associated with sinus tachycardia

Legend: POTS – postural orthostatic tachycardia syndrome; NCS – neurocardiogenic syncope; OH – orthostatic hypotension; IST – inappropriate sinus tachycardia; HR-heart rate; bpm – beats per minute, TTT – tilt table test

Table 2: Clinical Features of Autonomic Disorders

Review of Systems	Clinical features
Cardiovascular	• Orthostatic intolerance • Postural tachycardia • Orthostatic hypotension • Postprandial hypotension • Exercise intolerance • Syncope • Presyncope • Palpitations • Chest pain, pressure or discomfort
Neurologic	• Dizziness or lightheadedness • Cognitive dysfunction (a.k.a. “brain fog”) • Paresthesia • Generalized weakness • Neuropathic pain • Headache, including migraine
Respiratory	• Shortness of breath • Hyperventilation
Gastrointestinal	• Nausea • Dysphagia • Acid reflux • Early satiety • Abdominal fullness, distension or pain • Gastric and intestinal dysmotility • Diarrhea or constipation
Genitourinary	• Urinary frequency, urgency or hesitancy • Incomplete bladder emptying • Urinary retention • Overactive bladder • Polyuria • Nocturia • Interstitial cystitis • Erectile dysfunction • Vaginal dryness • Pelvic pain
Thermoregulatory	• Hypohydrosis • Hyperhidrosis • Anhidrosis • Gustatory sweating • Heat intolerance • Cold intolerance
Pupillomotor	• Blurred vision • Light sensitivity • Dilated pupils

Secretomotor	• Dry eyes • Dry mouth
Constitutional	• Fatigue • Sleep disturbance • Loss of appetite • Weight loss or gain • Pallor • Flushing • Diaphoresis • Myalgia

Table 3: Autonomic Dysfunction in Patients with PASC: Assessment Recommendations

#	Autonomic Dysfunction Assessment Statement
1	Clinicians should conduct a full patient history including a review of predisposing comorbidities, prior autonomic symptoms or disorders, relevant hospitalizations, and timeline of symptom evolution. The patient history should address: • Most disabling symptoms/signs that may be autonomic in nature: dizziness, lightheadedness, palpitations, presyncope, syncope, orthostatic intolerance, exercise intolerance, cognitive dysfunction and fatigue. (See Table 2) • Medication history: evaluate for medications that may impact symptoms, signs or assessment parameters (i.e., medications with side effects, such as orthostatic intolerance, orthostatic hypotension or resting or postural tachycardia; these may include anti-hypertensive, anti-cholinergic and stimulant medications.) • Social history of previous and current substance use, current diet, fluid and salt intake, exercise routine, if any, employment status and psychological stressors. • Family history of autonomic, autoimmune and post-COVID complications.
2	Clinicians should characterize symptoms including onset (new acute or chronic), frequency, intensity, aggravating and alleviating factors and impact on function and activities.
3	Clinicians should conduct a neurologic exam, including sensory exam to look for signs of small fiber neuropathy (particularly the loss of pinprick or temperature sensation). To evaluate for autonomic dysfunction, clinicians should perform a 10-minute stand test recording heart rate and blood pressure while supine and after standing 3 minutes, 5 minutes, 7 minutes and 10 minutes. Consider obtaining a tilt table test in symptomatic individuals with a negative 10-minute stand test.
4	Recommended initial laboratory tests in individuals with suspected autonomic dysfunction including: CBC, CMP, TFT, vitamin B12, ferritin, morning cortisol, ANA, ESR, CRP • Consider obtaining a D-dimer to assess for pulmonary embolism in the appropriate clinical setting.
5	Clinicians should consider obtaining a pulse oximetry at rest and with exertion/activity to rule out persistent hypoxemia, EKG, Echocardiogram and ambulatory cardiac monitoring with: • Holter monitor for palpitations and tachycardia occurring daily • Cardiac event monitor for recurrent palpitations, tachycardia or syncope occurring less than daily Further cardiac evaluation may be warranted as per the PASC Collaborative Cardiovascular Complications Consensus Guidance Statement. (18)
6	Where diagnosis is uncertain or symptoms are progressing, consider a referral to an autonomic specialist for more detailed assessment including autonomic function tests such as Valsalva maneuver, deep breathing test, quantitative sudomotor axon reflex test (QSART) and a skin biopsy for evaluation of small fiber neuropathy.
7	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.

Legend: CBC – Complete Blood Count, CMP – Comprehensive Metabolic Profile, TFT – Thyroid Function Tests, ANA – Antinuclear Antibody, ESR * Erythrocyte Sedimentation Rate, CRP – C-Reactive Protein

Table 4: Health Equity Considerations and Examples in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC): AUTONOMIC DYSFUNCTION

Category	Comment	What is Known	Clinical Considerations
Disability *Example: People with certain conditions that cause disability and autonomic dysfunction*	Individuals with pre-existing autonomic disorders require special consideration in the workup and management of autonomic dysfunction in PASC.	The impact of PASC-related autonomic dysfunction should be considered early and often in individuals with possible baseline autonomic dysregulation. Autonomic dysfunction is known to occur in many different conditions that cause disability (e.g., Parkinson's disease, multiple sclerosis, spinal cord injury [SCI], traumatic brain injury, and diabetes mellitus). (42) As an example, autonomic dysreflexia is a well-documented complication of SCI and can be a medical emergency warranting urgent attention. In SCI, autonomic dysfunction may be affected by the level and/or severity of the initial injury. (43)	Depending on functional status, modifications may be required for a 10-minute stand test in the office setting (e.g., some patients with SCI may be unable to perform supine to sitting to standing orthostatic maneuvers). Thus, modifications in usual testing protocols may be needed for this population. The treatment of autonomic disorders in people with underlying SCI also requires careful consideration. (44,45) For example, increasing fluids may affect bladder protocols such as frequency of intermittent catheterization. Exercise and activity prescriptions should take into account paralysis, autonomic symptoms, and other considerations (e.g., underlying heterotopic ossification or rotator cuff dysfunction). People with SCI and other patients who have complicated medical conditions combined with autonomic dysfunction may require longer visits and more health care personnel (e.g., PM&R physicians, nurses, physical therapists, psychologists, social workers) to deliver optimal care. (35)
Obesity *Example: People diagnosed as overweight/obese*	Individuals who are overweight may have more severe COVID-19 acute infection and sequelae.	Individuals who are overweight are at higher risk for COVID-19 infections and associated morbidity and mortality. (46) Although research is still emerging, obesity may be a risk factor for PASC. (47) While the effect of excess weight on	Although it is unknown whether obesity is a risk factor for PASC-related autonomic dysfunction, it is important to recognize that individuals who are overweight and experiencing autonomic symptoms may need special consideration from a rehabilitation perspective. For example, addressing weight loss

		PASC-related autonomic function is not currently known, obesity does have documented effects on sympathetic nervous system activity. (48,49)	strategies can be done within their system of care and considering their own social determinants of health (SDOH). Identifying and treating sleep apnea, which is associated with obesity, is an important component of enhancing autonomic regulation and improving symptoms of fatigue. (49) Physical activity should be cautiously and appropriately prescribed to take into account obesity as a comorbidity.
Racial / Ethnic Minority Groups *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)*	Individuals who identify with historically, socially, or economically marginalized groups may be at higher risk for COVID-19 related morbidity and mortality.	Throughout the pandemic, it has been documented that people who identify with racial/ethnic minority groups may be a higher risk for acute COVID-19 infection and more severe disease. (50) PASC-related sequelae have been reported to increase with more severe acute infection (5) and with more baseline comorbidities; race may also be a factor, though research is still emerging. (51) Race is among the factors that have been reported to affect heart rate variability, including with Postural Orthostatic Tachycardia Syndrome (POTS). (52) For example, while a majority of patients with POTS are young White/Caucasian women, a diagnosis of POTS should not be missed in patients who identify with other races or in male patients. (53)	While the incidence of autonomic dysregulation in various populations of PASC is still unknown, rehabilitation clinicians should be aware that patients who identify with historically, socially, or economically marginalized groups may experience disparities in diagnosis and treatment. The impact of SDOH should also factor into evaluation and management strategies to manage autonomic disorders. Vigilance about recognizing autonomic dysfunction is important. Educating clinicians and patients about how to access specialized care when needed is vital. The impact of PASC-related autonomic dysfunction should be considered in persons from all racial/ethnic minority groups and efforts to improve symptoms, function and participation should be a priority.
Biologic Sex *Example: Pregnancy*	Sex differences should be considered for both the diagnosis	Patients with POTS tend to present with a constellation of symptoms and the diagnosis is much more common in female adults (compared to male adults),	Among the medical community, there is limited awareness and recognition of autonomic conditions, inclusive of but not limited to POTS. POTS is a common autonomic disorder that is ideally managed

	and treatment of PASC-related autonomic disorders.	typically occurring during childbearing years. (54) There is a paucity of literature on PASC-related autonomic dysfunction during pregnancy in individuals with pre-existing or new symptoms. However, it is known that both pregnancy and COVID-19 infection may affect autonomic regulation. (54,55) One survey study of patients with POTS showed challenges with diagnosis and multiple comorbidities. (56) In this study, female patients with POTS were impacted more regarding challenges with diagnosis, symptom burden, and quality of life. There was significant diagnostic delay of POTS, including 2 years longer in female than male patients.	by physicians and rehabilitation clinicians who recognize the heterogeneity of the syndrome and implement a tailored treatment approach. (57) Enhancing clinical education may reduce diagnostic delays as well as improve access to care and outcomes. Clinicians should be aware of implicit (unconscious) sex-related bias as this may add to the challenges for female patients with POTS or another autonomic related dysfunction; importantly, a misdiagnosis with psychiatric or psychological disorders is common. (58) In pregnant individuals, rehabilitation interventions such as exercise prescriptions, should be carefully prescribed and based on an individual's ability to tolerate the exercise and the safety of the prescribed intervention for that person. Symptoms of POTS during pregnancy cannot be consistently predicted and may (perhaps counterintuitively) be worse in the first trimester whereas pregnancy related weight gain, pain, and balance problems (all of which may affect exercise prescriptions) may be more significant in the last trimester. (54) Diagnostic testing using radiation (e.g., chest x-ray or computed tomography) to rule out other conditions is usually contraindicated. Similarly, medications may be contraindicated during pregnancy (and in individuals who are breastfeeding) and therefore, caution is advised.
Insurance *Example: Individuals who are*	Insurance coverage, or lack thereof, should be considered when	Autonomic disorders, including but not limited to POTS, are challenging to diagnose. This means that patients often undergo multiple evaluations and	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,

uninsured, underinsured, or cannot afford access to recommended healthcare services	devising a treatment plan addressing autonomic-related issues in PASC. Encouraging patient engagement and addressing psychosocial factors may improve adherence with treatment recommendations.	extensive medical testing. (57) For patients who are uninsured or underinsured, the cost of securing a diagnosis and undergoing appropriate treatment may not be feasible. Financial hardships associated with COVID-19 acute infections and PASC-related sequelae are being increasingly documented. (58)	may be limited by the cost of copayments and deductibles, even in patients who have medical insurance. Individuals with post-COVID POTS and other autonomic disorders may need to be referred to an autonomic specialty clinic as guided by the assessment recommendation statements (Table 3). (5) Social services or community groups may assist persons with finding local support. During the pandemic, there has been a broadening of insurance coverage for telemedicine services, including telephone visits and virtual visits online—leading to greater use of and access to these services. Telerehabilitation is evolving, (59) and patients have reported relatively high rates of satisfaction with physiatry (60) and therapy visits. (61) Physicians should consider advocating on behalf of their patients who require immunotherapy to maintain their functional status by actively engaging in the appeal process when insurance deny coverage of this important therapy. (62)

Legend: This table is included to provide additional information for clinicians who are treating patients for PASC-related autonomic dysfunction. 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 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 (e.g., those who identify with more than one underrepresented or marginalized group), often face enhanced levels of bias and discrimination.

Table 5: Treatment Recommendations for Autonomic Dysfunction in Patients with PASC

#	Autonomic Dysfunction in PASC Treatment Recommendations
1	For individuals diagnosed with autonomic dysfunction, provide education on etiology and management including identification of exacerbating and remitting factors.
2	For individuals presenting with autonomic dysfunction and no evidence of post-COVID cardiovascular complications or other contraindications such as congestive heart failure, pericarditis, myocarditis, coronary artery disease or hypertension, start non-pharmacologic management including: • Increased fluid/salt intake: >3 liters of fluid and > 10 grams of salt (4 milligrams of sodium) daily • Compression garments (waist-high stockings and/or abdominal binder) • Lifestyle management to include recognizing and avoiding symptom triggers and physical counterpressure maneuvers to mitigate orthostatic intolerance • Patient education, psychological support and coping skills • Consideration of discontinuation of medications or substances that may cause or exacerbate orthostatic intolerance, tachycardia or hypotension.
3	For individuals with severe or persistent symptoms after a trial of non-pharmacologic measures, consider pharmacologic interventions. • First-line medications: low-dose beta blockers (e.g. propranolol or atenolol); fludrocortisone; midodrine • Second-line medications: pyridostigmine; ivabradine; clonidine; methyldopa; modafinil, methylphenidate; selective serotonin reuptake inhibitors (SSRIs); serotonin and norepinephrine reuptake inhibitors (SNRIs); bupropion; droxidopa
4	Individuals with autonomic dysfunction may benefit from personalized autonomic rehabilitation program interventions to reduce fatigue and gradually improve exertional tolerance. This may start with activities in a supine or sitting position. The intensity of rehabilitation activities should be carefully titrated to avoid post-exertional symptomatic exacerbation. See: Multi-Disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Fatigue in Post-Acute Sequelae of SARS-CoV-2 infection (PASC) Patients (17)
5	Consider referring individuals experiencing treatment-refractory or progressive symptoms to an autonomic specialist. https://americanautonomicsociety.org/physician-directory/ http://dysautonomiainternational.org/page.php?ID=14

Table 6: Pharmacological Treatment Options for Autonomic Dysfunction (85,86)

Medication	Dose	Indications	Side Effects/Precautions
1st Line			
Propranolol Atenolol	5-10 mg BID to QID 12.5-25 mg QD to BID	POTS, IST, OH, NCS, episodic hypertension	Bradycardia, hypotension, fatigue, depression, asthma exacerbation
Fludrocortisone	0.05 - 0.2 mg QD	NCS, OH, POTS, hypotension	Hypokalemia, edema, headache
Midodrine	2.5 - 10 mg TID to QID	NCS, OH, POTS, hypotension	Scalp paresthesia, piloerection, supine hypertension
2nd Line			
Pyridostigmine	30-60 mg BID to TID	POTS, OH, AN, GI dysmotility with constipation	Diarrhea, muscle twitching
Ivabradine	2.5-7.5 mg BID	POTS, IST	Visual disturbance, headache, hypertension
Methylphenidate	5-10 mg BID to TID	NCS, OH, POTS, cognitive dysfunction, fatigue	Insomnia, headache, tachycardia
Modafinil	50-200 QD to BID	Cognitive dysfunction, hypersomnolence, fatigue	Tachycardia, insomnia
Clonidine	0.05 – 0.2 mg QD to TID or long-acting patch	POTS, episodic hypertension and/or tachycardia, anxiety	Hypotension, fatigue, brain fog
Methyldopa	125-250 mg BID	POTS, episodic hypertension and/or tachycardia, anxiety	Hypotension, fatigue, brain fog
Fluoxetine	10-40 mg QD	NCS, anxiety/depression	Anxiety, insomnia, nausea
Bupropion	75 -150 mg QD to BID	POTS, NCS, fatigue, depression, hypersomnia	Nausea, anxiety, insomnia, decreased seizure threshold
Duloxetine	20-60 mg QD	NCS, OH, neuropathic pain, depression	Nausea, hypertension, Increased perspiration
Droxidopa	100-600 mg TID	FDA-approved for neurogenic OH; NCS and POTS in some cases	Headache, hypertension, tachycardia, nausea
Other			
Desmopressin	0.1-0.2 mg QD prn	POTS, OH	Hyponatremia, edema

IV saline	1-2 L IV over 1-4 hours prn	Decompensation of POTS, NCS, OH with dehydration, infection or GI dysmotility disorder	Avoid chronic frequent use that can lead to placement of central catheters, which can cause thrombosis and infection
IVIG	1-2 gm/kg/month IV weekly to every 4 weeks	Severe, treatment-refractory POTS, SFN, and AN with positive autoimmune markers	Flu-like symptoms, headache, aseptic meningitis
Legend: QD: once daily; BID: twice daily, TID: three times daily; QID: four times daily; POTS: postural orthostatic tachycardia syndrome; NCS: neurocardiogenic syncope; OH: orthostatic hypotension; IST: inappropriate sinus tachycardia; SFN: small fiber neuropathy; AN: autonomic neuropathy; GI: gastrointestinal; prn: as-needed; IV: intravenous; IVIG: intravenous immunoglobulin; mg: milligram; gm: gram; kg: kilogram; FDA: Food and Drug Administration.			

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