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Post–COVID-19 Syndrome Clinical Pathway for the US Veterans Health Administration

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Abstract

The Department of Veterans Health Affairs (VHA) has launched 22 multispecialty post–COVID-19 clinics across the US for the growing number of veterans experiencing long-term sequelae after acute COVID-19 infection. While evidence-based treatments for this syndrome are under investigation, there is a critical need to establish and disseminate clinical pathways (CPWs) based on knowledge and experience gained in those clinics. This VHA CPW is intended to guide primary care clinicians who care for patients experiencing dyspnea and/or cough during post–COVID-19 syndrome (PCS), which includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of acute COVID-19. This effort will help guide and standardize the care of veterans across the VHA, improve health outcomes, and effectively utilize health care resources. This article summarizes our stepwise diagnostic approach for patients presenting with PCS dyspnea and/or cough in primary care; it also highlights teleconsultation and telerehabilitation as opportunities to reach those in rural areas or with transportation barriers and improve reach for specialized services.

Keywords

Primary Health Care; Rehabilitation; Respiration; SARS-CoV-2; Standard of Care

BACKGROUND

As the number of patients who experience long-term sequelae after COVID-19 infection (called long COVID, postacute sequelae of SARS-CoV-2 infection, or post–COVID-19 condition or syndrome PCS) continues to increase, health care systems have had to adapt to meet demands.[1–3] In a recent meta-analysis, the global, pooled post–COVID-19 condition prevalence was estimated to be 0.43 (95% CI: 0.39, 0.46).[4] The mechanisms underlying these persistent symptoms after COVID-19 are poorly understood, and their pathophysiology and treatment options are under investigation. In an effort to rapidly advance PCS characterization, determine its pathophysiology, and develop and test treatments, the US Centers for Disease Control and Prevention, the World Health Organization, and the UK National Institute for Health and Care Excellence recommended establishing multidisciplinary post–COVID-19 assessment clinics.[5,6] As a result, 22 out of 171 Veterans Health Affairs (VHA) sites across the US have launched integrated multidisciplinary clinics. These sites are uniquely structured and use outreach, triaging, and assessment and rehabilitation methods according to their local expertise and resources. The care in clinics consists of comprehensive assessments, treating underlying or uncovered physical and mental health conditions, and providing personalized and holistic rehabilitation care.

Across the majority of VHA sites, veterans are receiving usual care in primary care or specialty care settings. Thus, there is a critical need to establish and disseminate clinical pathways (CPWs) for patients who experience debilitating PCS. This CPW is intended for clinicians who care for patients with PCS, which includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of acute COVID-19 and not attributable to alternative diagnoses.[7] Primary care clinicians diagnose and deliver the first line of care

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for patients with PCS and are therefore at the center of the CPW. This effort will help guide and standardize the care of veterans across the VHA and improve health outcomes and effectively utilize health care resources.

Our team, with expertise in PCS multidisciplinary care, has created the CPW for dyspnea and cough, 2 predominant symptoms during PCS.[3] Although the prevalence of dyspnea in large cohorts has been reported in up to 70% of hospitalized survivors of COVID-19 7 months after discharge[8] and 44.5% of nonhospitalized patients at 1 year,[9] a recent meta-analysis by Chen and colleagues revealed a lower prevalence of 13% at 120 days.[4] However, a range of prevalence has also been reported depending on the studies included. In a systematic review and meta-analysis from 2021, the overall prevalence of dyspnea in survivors of COVID-19 was 37% between 3 weeks and 3 months after discharge.[10] In contrast, another systematic review and meta-analysis from 2022 found that dyspnea was the second most common symptom reported at 3- to 6-month follow-up in 25% of survivors of COVID-19, with a similar proportion still reporting dyspnea at 6 to 9 months, 9 to 12 months, and 12 months or longer follow-up (25%, 21%, and 31%, respectively). [11] Thus, while these reviews provide converging evidence that dyspnea symptoms are a component of the broader PCS symptom profile, prevalence estimates are considerably heterogeneous and affected by a number of factors such as hospitalization status, world region, biological sex, diabetes mellitus diagnosis, disease severity, and overall study quality.[4,11]

Prevalence estimates of PCS cough tend to be lower than those for dyspnea. In a pooled analysis, Song and colleagues found that the estimated prevalence of persistent cough is 18% (95% CI 12%–24%; I^2 = 93%) in 14 studies of hospitalized patients (follow-up duration ranged from 6 weeks to 4 months).[12] The prevalence of cough between 3 weeks and 3 months was similar at 14% in another systematic review and meta-analysis,[10] although only 7% in the study by Chen et al.[4] The dyspnea and/or cough differential diagnosis unique to PCS is outlined in the following sections.

Parenchymal Lung Disease

Impairments in pulmonary function, specifically reduced diffusing capacity tests and imaging abnormalities such as ground glass opacities (GGO), are common findings in survivors of COVID-19.[13–21] The frequency of computed tomography (CT) scan features suggestive of lung fibrosis have been variously reported at 3 to 6 months, ranging from 1% to 70%.[21–23] In a Spanish cohort, half of the patients with moderate or severe COVID-19 pneumonia developed impaired pulmonary diffusion capacity 6 months after hospital discharge.[20] Other studies have found GGO as the most common imaging abnormalities after COVID-19, with the frequency of abnormalities increasing with the severity of acute COVID-19 illness.[18,21,24–27] In one of the largest cohorts in China, chest CT scans among patients who were hospitalized for COVID-19 and had abnormal CT scans at discharge showed persistent abnormal findings in 25% of study participants at 1 year after COVID-19; 22% had GGO, 13% had subpleural reticular or cystic lesions, and 12% had residual linear opacities. Persistent abnormal findings were more common among those with severe pneumonia and acute respiratory distress syndrome.[28]

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Pulmonary Thromboembolism

Thromboembolism can complicate acute COVID-19 infection. The frequency of thromboembolic disease in PCS is unknown, but differential diagnosis among patients presenting with persistent dyspnea after COVID-19 should include pulmonary embolism and the development of pulmonary vascular disease.[29,30]

Small-Airway Hyperreactivity

Although small-airway hyperreactivity (SAH) is common after respiratory viral infections, its prevalence in PCS remains unknown. In a recent cohort, only 3.9% of patients experiencing dyspnea and/or cough after 4 months of SARS-CoV-2 viral infection were confirmed to have SAH.[31] In a small study of outpatients with mild acute respiratory infection due to COVID-19 (SARS-CoV-2 positive) matched to other causes (SARS-CoV-2 negative), small-airway resistance was significantly higher in cases during infection in comparison to controls; however, the frequency of abnormal oscillometry measures reflecting airway resistance and airway reactance overall were small and were not different between groups at 2-month follow-up.[32] These data suggest that the role of SAH in PCS is minor, unless there is an underlying history of asthma.[33]

Neuromuscular Abnormalities Deconditioning

Recent studies have reported an impaired exercise response at cardiopulmonary exercise testing (CPET) during PCS. These reports suggest the presence of functional limitations in the absence of relevant alterations of ventilatory and gas exchange parameters at CPET. Therefore, deconditioning has been proposed as one of the main mechanisms of reduced peak oxygen uptake and dyspnea in PCS.[34,35]

Phrenic Nerve Mononeuritis

In a cohort in the United Kingdom, 3.2% of patients had a new elevated hemidiaphragm on chest x-ray after COVID-19 pneumonia, persisting for an average of 7 months following COVID-19 diagnosis.[36] This study supports the hypothesis that diaphragmatic weakness may contribute to PCS dyspnea.

Chronic Myocarditis and/or Myocardial Injury

There is a wide spectrum of potential myocardial involvement that may be seen after SARS-CoV-2 infection, although the prevalence in PCS is unknown.[37] It also remains uncertain if myocarditis in PCS results from direct effects of viral penetration of the cardiac structures and intramyocardial viral replication or part of an exacerbated systemic response, such as autoimmune virus-triggered cytokine storm.[38 39] The American College of Cardiology recently published their expert consensus decision.[40]

Breathing Disorders

The prevalence of obstructive sleep apnea during PCS is under investigation. In a small observational study, COVID-19–induced sleep apnea was responsible for PCS symptoms of fatigue, cognitive complaints, and dyspnea.[41] Hyperventilation has also been found in patients with PCS.[42,43] Neurological and psychological conditions can also influence

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breathing disorders. Anxiety has been reported as both a new symptom postinfection, as well as a condition exacerbated following COVID-19 infection. In a large cohort, 23% of patients reported anxiety or depression 6 months after acute infection and hospitalization for COVID-19.[44] One-third of patients with COVID-19 were diagnosed with neurological or psychological symptoms, including anxiety, depression, posttraumatic stress disorder, and psychosis within 6 months postinfection.[27]

Post–COVID-19 Chronic Cough

Cough can persist for weeks or months after SARS-CoV-2 infection.[12] The pathophysiology of post–COVID-19 cough might result from the invasion of vagal sensory neurons by SARS-CoV-2 or a neuroinflammatory response, or both, leading to peripheral and central hypersensitivity of cough pathways.[12] Other causes such as SAH, angiotensin-converting enzyme inhibitor therapy, gastroesophageal reflux, and postnasal drip, as well as preexisting lung disease, should be considered. In the clinical management of post–COVID-19 chronic cough, it is essential to exclude pathological or structural causes, such as fibrotic damage to the lung paranchyma[16,20,45] or damage to the airways caused by either SARS-CoV-2 or the treatment provided in critical care.[46–48]

METHODS

A qualitative research study was conducted based on the consensus conference technique among professional experts.[49] This technique consisted of conducting a scientific conference with experts to develop recommendations to address problems related to clinical practice (Figure). Among the main advantages of this technique is its adequate performance with heterogeneous groups, which allows diverse perspectives in multidisciplinary work to be obtained, and its ability to promote consensus among participating experts.

First, a study management team was formed and consisted of representatives of specialties involved in the dyspnea and/or cough patient care process. The management team was responsible for selecting the benchmark clinical practice guidelines, the relevant sources of information, and selecting external experts for the final evaluation of the content. A total of 7 professionals participated in the consensus conferences, with clinical experience in the care of veterans with PCS dyspnea and/or cough (3 pulmonologists, 1 physiatrist/primary care physician, 1 primary care nurse practitioner, 1 pulmonary rehabilitation expert, and 1 research scientist).

The first phase of the study was based on the identification and consensus of the key subpathways in the care process for patients and on the graphical representation of possible care flows. Virtual, moderator-led sessions addressed different issues, in which the individual contributions of the participants and other inputs derived from an open debate were compiled. The issues raised in these meetings focused on the subpathways and elements of the care pathway related to quality and clinical safety in the care of patients with dyspnea and/or cough.

In the second phase, additional experts and the VHA evidence-based guidelines team reviewed the CPW.

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In the third phase, the CPW team will review the new literature annually and publish an alert letter or update this CPW if substantial changes are needed.

RECOMMENDATIONS

Assessments

The sequential evaluation and treatment of patients presenting with persistent dyspnea are depicted in Tables 1 and 2. In summary, the initial encounter of patients with PCS includes a detailed history of underlying and new cardiopulmonary and mental health conditions and a description of the acute COVID-19 illness. A simple, validated instrument to assess and monitor the severity of dyspnea is the modified Medical Research Council dyspnea score (Appendix A in the supplemental material).[50] A thorough physical exam and assessment of chest imaging, pulmonary function, electrocardiogram, and exercise capacity should also be performed. Chest imaging with chest x-ray is important to determine if persistent lung abnormalities are present. Findings of interstitial disease can be better characterized by a chest CT scan. High-resolution chest CT scan with inspiratory and expiratory views detects reticulations, early fibrosis, and SAH.[51] Evaluation for pulmonary embolism should be considered, and diagnosis can be pursued with chest CT angiography or ventilation/perfusion scans. Pulmonary function testing (PFT)—particularly spirometry and assessment of diffusing capacity typically performed 8 weeks or later after acute infection—can determine the presence and severity of abnormalities in airflow and/or gas exchange and can be monitored over time during recovery.

Initial blood tests should include complete blood count, kidney and liver function tests, B-type natriuretic peptide, high-sensitivity troponin, and thyroid function tests. We recommend referrals for patients with suspected PCS to the relevant specialists or post–COVID-19 services where available if they have signs or symptoms of hypoxemia or oxygen desaturation on exercise, pulmonary parenchymal disease on imaging with decreased diffusing capacity of the lung for carbon monoxide after COVID-19, or suspicion of myocarditis. The American College of Cardiology recently published their clinical pathway for the cardiovascular sequelae of COVID-19.[40] Clinical suspicion of ongoing myocardial injury should be triggered by the presence of an elevated troponin 99th percentile upper-reference limit, reduced left ventricular ejection fraction and/or presence of pericardial effusion on echocardiogram, persistent arrhythmia, persistent dyspnea, reduced exercise capacity, or fatigue.

Assessing exercise capacity is also essential for clinical diagnosis and longitudinal monitoring. Cardiorespiratory fitness, as measured by peak oxygen consumption (Vo_2 peak), is considered a vital clinical sign by the American Heart Association[52] and may be helpful in assessing risk of adverse outcomes and tracking short- to long-term recovery from viral infection in long COVID.[53–55] For instance, according to a postviral risk stratification algorithm proposed by Arena and colleagues, a patient presenting with a Vo_2 peak of <50% predicted a ventilatory equivalency for carbon dioxide slope >45, and exercise-limiting exertional dyspnea may be considered for rehabilitation referral.[54] Therefore, when available, CPET may help characterize physiologic abnormalities in patients with persistent dyspnea and/or poor exercise tolerance that is unexplained by more ubiquitous clinical tools

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such as PFT or CT. However, the 6-minute walk test (6MWT) was selected as a primary tool for assessing exercise capacity because it is simple to implement, has been validated for many cardiopulmonary diseases, and correlates with peak oxygen uptake in CPET.[52,56,57]

PCS clinics are held both in person and/or via telehealth visits. VHA's telehealth systems include video and phone appointments, remote patient monitoring, and the Annie app. VHA regional telehealth hubs for rural veterans and electronic consulations between primary care and subspecialists (pulmonary, cardiology, PCS, or others) improve reach for specialty care.[58,59]

Therapies

Pharmacological treatments of PCS dyspnea and cough are under investigation. Patients with pulmonary fibrosis need to be evaluated by pulmonary subspecialists to receive empiric systemic corticosteroids.[60] Multiple antifibrotic therapies are also undergoing phase 4 clinical trials.[45]

Structured, individualized rehabilitation programs have been recommended in the treatment of PCS dyspnea.[61,62] The American Thoracic Society and the European Respiratory Society statement concluded that pulmonary rehabilitation (PR) can reduce dyspnea, increase exercise capacity, and improve quality of life in individuals with chronic lung disease.[63] A systematic review of PR in survivors of COVID-19 found a similar impact.[64] Referrals to structured rehabilitation can be based on symptom severity, lung function, or exercise capacity abnormalities. Telehealth is a safe option for reaching out to survivors of COVID-19 who are residing in rural or remote areas and expands access to rehabilitation programs. The Michael E. DeBakey Veterans Affairs Medical Center (Houston, TX) has successfully implemented a novel and comprehensive post–COVID-19 telehealth PR program that includes individualized education on disease, comorbidities, and symptoms; pulmonary hygiene and breathing retraining; physical exercise training; psychosocial support; nutritional education; and smoking cessation (Appendix B in the supplemental material). Since 2020, there were 115 veterans enrolled, and 69 have graduated.[65]

Treatment of Dysfunctional Breathing

Complementary and integrative approaches to health offer treatments that focus beyond recovery from the virus and address the whole person from a patient-centered context. In addition to increasing community or family support and using evidence-based mental health treatments, such as cognitive behavioral therapy, heart rate variability biofeedback has been demonstrated to be an effective approach to stress and anxiety management in non–COVID-19 states.[65] Heart rate variability is a measure of beat-to-beat changes in heart rate. When paired with a technology, such as that offered through HeartMath, patients can see changes in heart rhythm patterns that support developing a physiological coherence. Breathing reeducation and myofunctional therapy may be helpful for patients who experience dyspnea in PCS.[65]

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PCS Cough Treatment

Treatment recommendations for chronic cough are based on existing guidelines and managing underlying lung disease (asthma and/or chronic obstructive pulmonary disease) or upper airway cough.[66] The Swiss COVID Lung Study group and Swiss Society for Pulmonology have published COVID-19–specific pulmonary guidelines.[60] Inhaled corticosteroids (ICS) are safe and a 4- to 6-week trial is recommended for the treatment of PCS cough. The suggestion to use antimuscarinic drugs, such as tiotropium, to control COVID-19 cough is based on the ability to decrease cough sensitivity in acute viral upper respiratory tract infections. In chronic refractory or unexplained cough, gabapentin and pregabalin, which are neuromodulators, have been shown to be effective and might be useful in COVID-19, although data in PCS is lacking.[60]

Small-Airway Hyperreactivity

Empiric therapy with bronchodilators and/or ICS for a limited trial of 4 to 6 weeks may be an option to treat PCS SAH, if no improvement in SAH physiology needs to be explored with PFTs (spirometry and possibly methacholine challenge).[60]

CONCLUSIONS

In a rapidly changing evidence base of the characterization, diagnosis, and management of PCS, a CPW helps to guide clinicians in the evaluation and treatment of patients with persistent dyspnea and/or cough beyond 12 weeks post–COVID-19 infection. Although the general guidelines for the evaluation and management of patients experiencing chronic dyspnea and/or cough are based on those previously described in the literature, our approach highlights the specific conditions seen in PCS dyspnea and/or cough and utilizes the resources available within the VHA care system. This CPW will be updated as new evidence-based management options become available.

Based on the state of the evidence, diagnosing VHA patients with PCS should involve a thorough medical history, physical examination, radiographic assessment, pulmonary function evaluation, and exercise capacity evaluation. However, it is important to consider the setting, availability, and resources needed to carry out workups. For instance, technical expertise and equipment required for tools such as CPET and full PFT are not readily available at every VHA facility. Therefore, more accessible tools such as the 6MWT[68] or bedside spirometry may provide an alternative means for profiling the exercise capacity or pulmonary function of patients with exertional dyspnea.

Therapies of PCS dyspnea and/or cough are still under investigation. Nevertheless, we argue that individualized rehabilitation programs are a cornerstone of PCS treatment and highlight the VHA's experience with an established telehealth PR program. However, it is still unclear which patients benefit from structured rehabilitation programs vs self-guided exercise. Several other key areas require further investigation in PCS dyspnea and/or cough, including the natural history of parenchymal lung abnormalities and lung function repercussions, the prevalence of pulmonary embolism and myocarditis, and all pharmacological treatments for cardiopulmonary sequelae of PCS.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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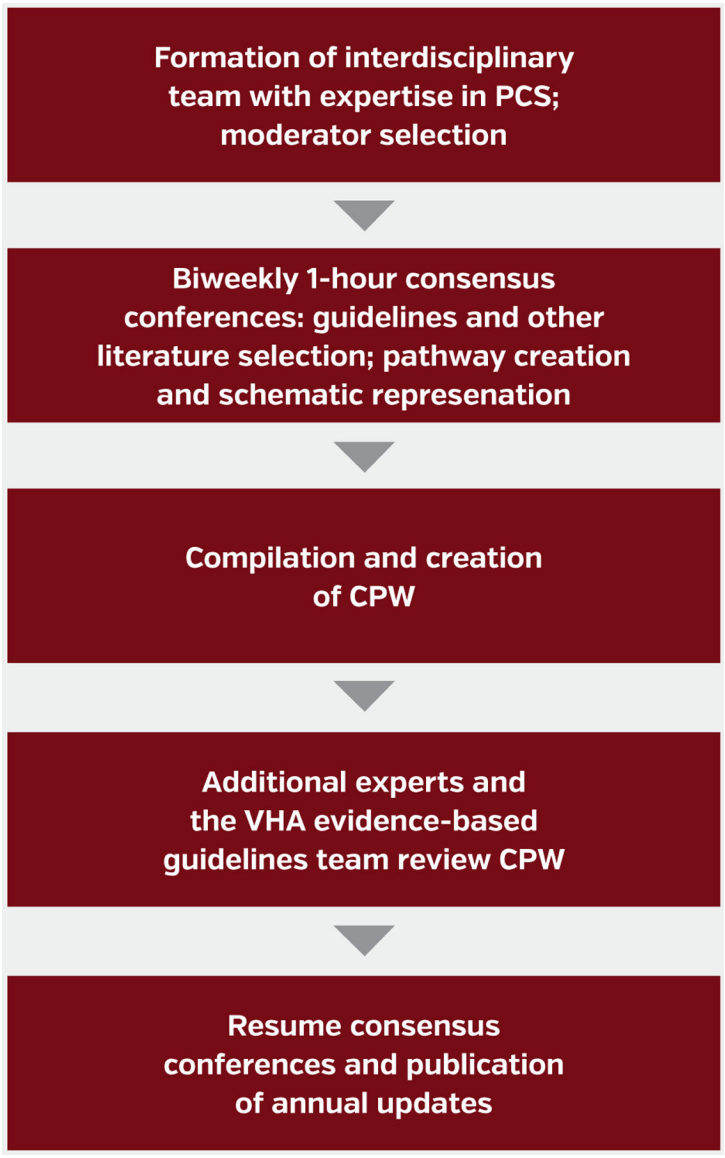

Figure.

Consensus conference technique used to develop clinical pathway recommendations. Abbreviations: CPW, clinical pathway; PCS, post–COVID-19 syndrome; VHA, Veterans Health Affairs.

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Table 1.

Proposed process for sequential evaluation and treatment of patients presenting with post–COVID-19 syndrome dyspnea or cough

	Recommended		Optional	
History				
History of Present Illness	**1**	When symptoms started	**1**	When acute illness resolved
	2	When/how diagnosed	**2**	Treatments (Y/N)
	3	Current supplemental oxygen use (Y/N)	**a.**	Azithromycin
	4	Vaccination status	**b.**	Corticosteroids
	5	Booster	**c.**	Monoclonal antibody
			d.	Convalescent plasma
			e.	Remdesivir
			f.	Nirmatrelvir/Ritonavir
			g.	Tocilizumab
			3	Hospitalization
			a.	ICU stay (Y/N)
			b.	Mechanical ventilation (Y/N)
			c.	High-flow nasal oxygen or noninvasive ventilation (Y/N)
			d.	Duration (days)
Past Medical History	History of pulmonary/cardiac disease		**1**	Pulmonary (asthma, COPD, ILD, OSA)
			2	Cardiac (CAD, CHF)
			3	Mental Health (PTSD, GAD, MDD)
			4	Other (Obesity)
Current Symptoms				
Dyspnea	At rest			
	On exertion			
Cough	Dry/productive			
	Nocturnal			
Negatives	Chest pain			
	Leg edema			
	Palpitations			

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Recommended	**Optional**
PND/orthopnea	

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GAD, generalized anxiety disorder; ICU, intensive care unit; ILD, interstitial lung disease; MDD, major depressive disorder; OSA, obstructive sleep apnea; PND, paroxysmal nocturnal dyspnea; PTSD, posttraumatic stress disorder.

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Table 2.

Proposed process for diagnosis of patients presenting with post–COVID-19 syndrome dyspnea or cough

I. Bedside tests	**1**	Vital signs including pulse oximetry
	2	12-lead (EKG) if not one on file since COVID-19
	3	Orthostatic measurement
	4	6-minute walk test (when feasible)
II. Labs	**1**	Complete blood count
	2	Complete metabolic panel
	3	High-sensitivity troponin
	4	BNP
III. Additional tests	**1**	2-view CXR
		a. If abnormal, then high-resolution noncontrast chest CT
	2	If hypoxemic, then full PFTs with lung volumes and diffusion capacity
	3	Ventilation/Perfusion scan if prior pulmonary embolism with residual dyspnea or significantly reduced diffusing capacity
	4	Consider pulmonary referral when worsening hypoxemia or dyspnea and when pulmonary fibrosis is detected
	5	TTE (if ↑ BNP/troponin or abnormal EKG)
		a. If abnormal TTE, then cardiology consult
	6	If arrhythmia on EKG, order Holter monitor
		a. If abnormal, then cardiology e-consult
	7	If troponin abnormal → Cardiology consult (TTE with possible CMR)
	8	If exertional chest pain or EKG ischemic changes, consider further cardiac testing

Abbreviations: BNP, B-natriuretic peptide; CMR, cardiovascular magnetic resonance imaging; CT, computed tomography; CXR, chest x-ray; EKG, electrocardiogram; PFT, pulmonary function test; TTE, transthoracic echocardiogram.

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