Evaluation & Management of Post-COVID-19 Patients (Long COVID)

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Educational Objectives:
1. Review the initial evaluation of patients presenting with dyspnea after COVID-19 infection
2. Understand common pulmonary findings associated with post-COVID-19 pulmonary impairment
3. Recognize the limitations in evidence-based care and areas of ongoing research in this rapidly evolving field
4. Review the need for a multidisciplinary approach to the evaluation and care of COVID-19 survivors

Scenario 1:
Mr. M is a 45-year-old man who has been referred for evaluation for persistent shortness of breath. He was admitted to the intensive care unit for one week about three months prior to this visit for treatment of acute COVID-19 disease. He required high-flow nasal cannula for respiratory support for several days but was not intubated. He was treated with remdesivir and dexamethasone during his hospitalization. He now complains that despite being quite healthy prior to COVID-19 infection, he is weak and very limited by his breathing. He feels that he can barely walk up a flight of stairs. He is bothered by a persistent cough. He also complains of feeling extremely lethargic and describes having “brain fog,” with memory difficulties and inability to return to work. He is frustrated by the situation and is feeling quite depressed since being discharged from the hospital. He did not have any prior hospitalizations, and his medical history is significant for obesity, hypertension, and diabetes mellitus for which he is on oral metformin.

Question 1: What is your next step for investigating Mr. M’s dyspnea?

Mr. M is struggling with symptoms consistent with post-acute sequelae of SARS-CoV-2 infection (PASC), otherwise known as post-COVID symptoms or “long COVID.” These terms refer to a wide spectrum of symptoms, respiratory and otherwise, that are being observed in survivors of acute COVID-19 infection. By definition, these are symptoms that persist greater than 4 weeks after initial acute infection (1). Of note, post-acute care symptoms, particularly in ICU survivors, are common (2). Acute Respiratory Distress syndrome (ARDS) survivors, in particular, have been known to have respiratory compromise and symptoms that persist long after hospital discharge (3). Whether and why COVID-19 survivors have different or more severe post-acute illness symptoms than comparable ARDS/ICU survivors is an area of ongoing study, as many early studies have methodologic limitations that prevent more comprehensive definitions, generalizations, and work-up and treatment algorithms.
The actual prevalence of PASC is challenging to estimate given rapidly changing data. Depending on the study, the frequency can vary from 5-80%, and include both (a) general complications of acute illness and (b) specific post-acute sequelae of SARS-CoV-2 infection (1, 4, 5). Dyspnea has been noted in some studies to be the most common post-COVID symptom reported (1). There can be many other affected organ systems, however, due to the multi-organ system involvement in the acute phase of illness. These symptoms by some reports are more common in women (4).

The implications of PASC for the health care system are significant given the high rate of healthcare utilization after acute COVID-19 infection. Readmission rates are high, with approximately 9-20% of patients hospitalized for COVID-19 having a readmission within 2 months of discharge (6, 7). However, these studies were conducted during the early parts of the pandemic prior to wide-vaccination.

After an acute COVID-19 illness admission, ideally a patient will have short-term outpatient follow-up to include:

- Medication reconciliation
- Physical exam
- Discussion of clinical course and anticipatory guidance
- Include discussion of mental health / wellness (anxiety/depression/PTSD, especially in patients admitted to the ICU)

In some cases, due to the challenges and limitations of and access to testing options during the early phases of the COVID-19 pandemic, patients may report that they believe that they had COVID-19 but never had a positive test. The illness of COVID-19 is a clinical diagnosis, and so some patients may have had SARS-CoV-2 infection despite never having had a positive nasal PCR test. In these cases, antibody testing can be considered, though it is important to bear in mind that antibody testing can be negative in up to 10-20% of recovered patients (4).

The following table is a partial list of the varied post-COVID symptoms and potential work-up / diagnoses that may be considered.

**Table 1: Commonly reported symptoms among post-COVID-19 patients and possible work-up (adapted from (1, 4))**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Potential Diagnoses</th>
<th>Work-Up</th>
</tr>
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<tbody>
<tr>
<td>Fatigue</td>
<td>Hypothyroidism, Chronic lung disease, Vitamin D or B deficiency, Diabetes mellitus, Chronic thromboembolic disease</td>
<td>Thyroid function testing (TSH, free T4), Cardiac function testing (TTE), Pulmonary function testing, 6-minute walk, Vitamin D levels, Vitamin B12 level, Hemoglobin A1c</td>
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<tr>
<td>Post-exertional malaise (PEM) or lack of endurance</td>
<td>Cardiac evaluation including stress testing, Pulmonary function testing, 6 minute walk testing</td>
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1PEM defined as worsening of symptoms after minor physical or mental exertion, symptoms worse 12-48 hrs after exertion, and can last for days/weeks.
As is evident from this list, the list of symptoms associated with PASC can be extensive. The goal of work-up is to identify organ dysfunction, physical impairments, nutritional deficits, and psychosocial impairments, and then provide targeted therapy as appropriate. This is why many institutions have created “Post-COVID-19” or “Post-ICU” clinics to provide comprehensive care to these patients (8).

In this particular patient’s case, there is concern for significant respiratory or cardiac impairment given that he is having respiratory symptoms. Appropriate work-up might include:

- Pulmonary function tests including spirometry, lung volumes, and DLCO to quantify and categorize impairment
- Six-minute walk test
- Chest radiograph
- CT scan of the chest to assess for parenchymal abnormality
- Serologic testing as in the table above
- Consideration of an echocardiogram
- Consideration of bronchoprovocation testing to assess for reactive airways disease
Scenario 1 (cont.):
Mr. M returns to your office after having undergone the testing described above. His lab values were within normal limits, and echocardiogram showed normal LV and RV size and function without any evidence of valvular abnormalities. His six-minute walk testing shows that he walked 346 meters, desaturating to 92% with ambulation, though he did not drop below 89%. His pulmonary function testing revealed:

- FVC 2.72 L, Z-score 0.80
- FEV1 2.25 L, Z-score 0.71
- FEV1/FVC 0.83, Z-score 0.52
- TLC 4.66 L, Z-score -1.54
- RV 1.74, Z-score -1.65
- DLCO corrected for Hgb 10.01, Z-score 3.58

A chest radiograph showed reticular opacities bilaterally so a CT chest was obtained.

High resolution CT scan of the chest showed the following, with findings such as those highlighted by red arrows seen throughout the lung fields:

![High resolution CT scan of the chest](image)

Question 2: What treatments and evaluations are indicated in this case?

Post-COVID-19 studies from China indicated that at 6 months after acute illness, 6-minute-walk (6MWT) distances were lower than normal in COVID-19 survivors, similar to what had been observed in SARS-CoV-1 and MERS survivors (1, 3). Reduction in diffusing capacity (DLCO) is the most common pulmonary function testing abnormality noted in patients post-COVID-19 with respiratory symptoms, related to the severity of their original illness (9, 10), as has been noted in other post-ARDS patient cohorts (1). Early studies of COVID-19 survivors indicated that about half had abnormalities on their high resolution CT scans of the chest (HRCT), usually ground glass abnormalities (11) [as noted in this patient’s CT scan, see red arrows above], though moderate to severe cases are noted to have fibrotic changes such as reticulation and traction bronchiectasis in up to 65% of survivors (12).
The following CT images are other examples from patients post-COVID-19 infection illustrating areas of ground glass opacities suggestive of organizing pneumonia.

Evidence-based guidance on the treatment of these patients remains an evolving area of study. However, there is some evidence that for patients with organizing pneumonia pattern of post-COVID injury (as indicated by histopathologic diagnosis or compatible clinical and radiologic findings), treatment with corticosteroids can be helpful (13). In a small observational study, patients with organizing pneumonia findings on HRCT (>15% involvement) and pulmonary impairment were offered 0.5 mg/kg prednisolone with a rapid tapering over 3 weeks (13). All treated patients reported improvement in subjective symptoms, and CT scans showed improvement, as well, though the observational nature of the study and its lack of a placebo arm leave the role of steroids uncertain. Additionally, a
separate study indicated that low dose steroids may be as effective as higher dose courses, which may be particularly important for patients who experience significant side effects with steroid therapy and/or have comorbid illnesses affected by it (14).

Pulmonary rehabilitation programs and physical therapy are critical components to patient recovery (1). In a minority of patients, those with severe and prolonged acute illness, there have been cases of lung transplantation, though this is rare (15). There are ongoing studies that aim to address the question of whether those with persistent post-COVID-19 lung fibrosis should be treated with antifibrotics (such as pirfenidone and nintedanib) that are currently utilized in progressive fibrosing interstitial lung diseases (1).

For a patient such as Mr. M, given ground glass opacities throughout his lung fields and his subjective significant respiratory limitation, it would be reasonable to discuss treatment with oral corticosteroids with close monitoring of response to therapy and acknowledgment of potential complications, especially with his comorbid conditions (diabetes and obesity).

**Scenario 1 (cont.):**
Mr. M returns to your office after taking prednisone 40 mg daily tapered over subsequent few weeks. He reports that he is subjectively feeling better, though not quite back to his baseline in terms of his breathing. His cough is improved. He asks what other considerations and evaluation might make sense, as he remains short of breath and unable to go back to work. He notes continued depression, which he feels is due to his persistent dyspnea.

**Question 3: What other evaluations and considerations are warranted?**

Thromboembolic disease: While early in the pandemic, there was a practice of extending DVT chemoprophylaxis to the outpatient setting, no conclusive evidence exists around prolonged chemoprophylaxis or anticoagulation in the outpatient setting. Evaluation for venothromboembolism should include history and physical exam, with appropriate testing if warranted. For any patients who had confirmed thromboembolic disease during their acute illness, the current recommendation is to use direct oral anticoagulants (DOACs) or low molecular weight heparin (LMWH) for anticoagulation for at least 3 months, with further duration to be a topic of shared decision-making (1).

Cardiovascular complications: Patients who suffered from cardiovascular complications during their acute illness may be at higher risk of longer-term post-COVID cardiac complications, and so echocardiography and Holter monitor evaluation should be considered on a case-by-case basis (1). Additionally, competitive athletes should consider avoiding extreme sports or aerobic activity for 3-6 months after COVID-19 infection due to concern for ongoing damage, though this is based on relatively weak evidence (16).

Underlying illnesses: It is important to review the patient’s medical history thoroughly – not only their COVID-19 illness course, but also to understand other conditions that may have pre-dated their COVID-19 infection and may be worsened afterward, including common pulmonary and non-pulmonary (e.g. cardiac, renal, endocrine) disorders. Some underlying disorders (such as asymptomatic or minimally symptomatic ILD) may have been unmasked by the COVID infection, so review of pre-COVID imaging (if available) is critical (4).
Social support and mental health: Social history is critical– assess social support and resources, as well as risk factors for mental health disease and substance use disorders. Hospitalization and critical illness, along with PASC, may lead to mental health, cognitive, and physical impairments which can be isolating, in addition to disruptive to daily routines, employments, and self-care. Addressing mental health needs directly with pharmacotherapy and counseling, including treatment of substance use, if present, can be instrumental in a patient’s recovery. Post-ICU PTSD is well described in other forms of ICU-survivorship, and has also been reported in COVID survivors (1).

Depending on his level of impairment and symptoms, it would be reasonable to obtain an EKG and echocardiogram, consider stress testing given his CAD risk factors, and screen for depression/anxiety/PTSD, with appropriate referrals for mental health support.

It should also be stressed to him that so-called “objective testing” may not reveal a clear etiology for the symptoms that the patient is experiencing. This is not meant to minimize the impact of such symptoms, but only to clarify that we cannot clearly link symptoms to abnormal testing in all cases. It would be important to acknowledge that the medical community is still learning about how best to evaluate and treat patients with post-COVID-19 symptoms—and that our approaches may evolve as scientific knowledge does.

Scenario 1 (cont.):

Mr. M notes during his visit that he is not vaccinated yet against COVID-19. He is worried about receiving the vaccine based on things he has read on social media – in fact, he is concerned that getting vaccinated will cause his symptoms to recur. He also does not understand why he should require vaccination since he already had COVID-19 and survived. “I have antibodies, don’t I?”

Question 4: Should this patient be vaccinated against COVID-19? What you can tell him about vaccination based on current data.

COVID-19 vaccination should be offered to all eligible patients, regardless of whether they have had prior infection (4). There is no evidence of worsening symptoms of PASC after vaccination (4, 17). It is also important for patients to make sure to remain up to date on yearly influenza vaccination and appropriately scheduled pneumococcal vaccines (4).

It is important to share with the patient that at this time, it is not known how long immunity after infection lasts for COVID-19 survivors, and so up-to-date immunization for all patients is important. This applies to all respiratory viruses for which we have approved vaccines. Vaccination provides a “boost” in immunity for those who have already had the infection (18). Since the initial approval of vaccination for COVID-19, studies have shown that additional or booster doses of the vaccine may be necessary for patients, especially those who are elderly and/or immunosuppressed. Expert opinion on the timing and frequency of booster doses continues to evolve (19).
References:
Pre/Post-Test Questions:

1. Mr. Josephson comes to see you in the office for evaluation after having been discharged from the hospital for COVID-19 infection about 3 months ago. He is having persistent shortness of breath and cough. You review his recent high-resolution CT chest. What is the most common pattern that you might expect to see in a post-COVID patient with persistent respiratory impairment?
   a. Usual interstitial pneumonia pattern
   b. Ground glass opacities
   c. Crazy paving
   d. Pleural effusions

2. You are seeing a patient in the office with findings suggestive of possible post-COVID organizing pneumonia on their CT scan as well as significant pulmonary impairment with an oxygen requirement. What might be a treatment to consider discussing with them?
   a. Inhaled treprostinil
   b. Sildenafil
   c. Prednisone
   d. Nintedanib

3. You are seeing a patient in the office who is hesitant to take the COVID-19 vaccine because he had a mild case of COVID-19 2 months ago, which did not require any medical care. He says that he was told he should wait 9 months before getting vaccinated. What is the most appropriate recommendation and rationale?
   a. Patients who have recovered from COVID-19 infection are immune from future infection and so have no need to be vaccinated.
   b. Patients who have had COVID-19 should wait 9 months before getting vaccinated.
   c. Patients who have survived COVID-19 may have worsened symptoms if they are vaccinated afterward.
   d. Patients can receive vaccination against COVID-19 at any point, though they should wait until after their acute illness subsides and can consider waiting 3 months since symptom onset.