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COVID-19 Guide for the Rehabilitation Clinician:

A Review of Non-Pulmonary Manifestations and Complications

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Abstract:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – also known as COVID-19 – is primarily known for respiratory illness. While it is clear that patients with moderate to severe cases of COVID-19 will require pulmonary rehabilitation, physiatrists will need to consider effective management plans for COVID-19 survivors with extra-pulmonary involvement. This report will summarize key non-pulmonary considerations to guide rehabilitation clinicians who may be involved in the care of COVID-19 survivors with the best available early evidence.

Key Words: COVID-19; Complications; Manifestations; Rehabilitation

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – also known as COVID-19 – is primarily known for respiratory illness. Infection with the virus triggers a cytokine release storm causing high levels of inflammation, which then results in pulmonary damage characterized by edema, prominent proteinaceous exudates, vascular congestion, and inflammatory clusters with fibrinoid material and multinucleated giant cells and the prominent clinical symptom of hypoxia. One or more storms may occur, causing additional systemic injury[1,2]. While it is clear that patients with moderate to severe cases of COVID-19 will require pulmonary rehabilitation, physiatrists will need to consider effective management plans for COVID-19 survivors with extra-pulmonary involvement.

The COVID-19 literature continues to expand; currently, observational single institution reports and case series with relatively small sample sizes are our primary sources of evidence. This report will summarize key non-pulmonary considerations to provide early guidance to rehabilitation clinicians who may be involved now in the care of COVID-19 survivors with the best available evidence to date.

Neurologic

- SARS-CoV and other human coronaviruses are neuroinvasive and neurotropic. They can also be neurovirulent, causing illnesses like meningitis and encephalitis. Respiratory viruses can enter the central nervous system (CNS) through hematogenous spread, or the peripheral nervous system through axonal transmission. The olfactory nerve, trigeminal nerve or the sensory fibers of the (PNS) vagus nerve are the most common peripheral nerve targets. Similar to mice models, it is possible that SARS-CoV-2 may persist in the CNS, utilizing a theory that supports viral triggers of neurologic diseases such as Multiple Sclerosis[3]. Since SARS-CoV and

SARS-CoV2 have high similarity, SARS-CoV2 may also have the potential to invade the nervous system[4].

- Brain tissue is reported to have angiotensin converting enzyme –2 (ACE-2) receptors. The SARS-CoV-2 uses the SARS-CoV receptor ACE2 for host cell entry at the myocardial cell membrane. Some researchers have proposed access of SARS-COV-2 through the cribriform plate to the brain with the potential of endothelial capillary damage, resulting in hemorrhage within the cerebral tissues. Further confirmatory investigation is needed[5].
- Some patients with severe COVID-19 (78 in a study of 214) have had neurological manifestations including altered consciousness, central nervous system symptoms (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular events and epilepsy), and PNS symptoms (hypogeusia, hyposmia, hypopsia, and neuralgia)[6]. While there are new reports of young healthy patients sustaining strokes due to coagulopathy (https://www.washingtonpost.com/health/2020/04/24/strokes-coronavirus-young-patients/), these data have not yet been published and true incidence of stroke is not yet known.
- An observational series of 58 consecutive patients in France admitted with acute respiratory distress syndrome (ARDS) due to Covid-19, reported agitation and confusion (40/58), dysexecutive syndrome (14 of 39 discharged patients) and corticospinal tract signs (39/58). Two of 13 patients who underwent brain MRI because of unexplained encephalopathic features, had single acute ischemic strokes. Data is lacking to determine which features were specific to SARS-CoV-2 infection[7].

- In a multi-institutional observational series in Italy comprising approximately 1200 patients admitted with COVID-19, five patients were diagnosed with Guillain-Barré syndrome after the onset of disease. Four had positive nasopharyngeal swab for SARS-CoV-2 at onset of disease and one had a negative nasopharyngeal swab but subsequently converted to positive on serologic testing. All the patients had negative real-time polymerase-chain-reaction SARS-CoV-2 assay of the CSF. The findings were generally consistent with an axonal variant of Guillain–Barré syndrome in three of the patients and with a demyelinating process in the remaining two[8].

Hematologic

- A case series of 3 patients with confirmed SARS-CoV-2 described positive antiphospholipid antibodies and subsequent multiple cerebral infarctions. One patient also had evidence of ischemia in lower limbs and several digits of the hand[9].
- A Netherlands report evaluated thrombotic complications in 184 ICU patents with COVID-19 infection in which the incidence was found to be 31%. Pulmonary embolism was the most frequent thromboembolic complication[10].

Musculoskeletal

- Skeletal muscle injury has been seen in 17 out of 214 patients with severe COVID-19 disease, characterized by elevated creatinine kinase and lactate dehydrogenase[6]. Prolonged immobility in the intensive care unit could be the etiologic cause of these symptoms.
- Additionally, there is a case report of a patient hospitalized for COVID-19 who, on day 9 of hospitalization, presented with pain and weakness in lower limbs with

positive tenderness. Myoglobin, creatinine kinase and lactate dehydrogenase were elevated along with liver enzymes, suggesting rhabdomyolysis. No confirmation of pathology consistent with rhabdomyolysis was available[11].

Ocular

- In a meta-analysis with three studies including 1167 patients, it was reported the overall rate of conjunctivitis at admission to the hospital was 1.1% (3% and 0.7% in severe and non-severe COVID-19 patients), respectively[12].
- There was a single case report of bilateral acute conjunctivitis and positive reverse transcription-polymerase chain reaction (RT-PCR) SARS-CoV-2 in conjunctival swabs, with swabs remaining positive for 17 days[13].

Cardiovascular

- ACE-2 is expressed in the cardiovascular system during severe infections. Patients with underlying cardiovascular disease can be especially susceptible to the pro-arrhythmic effects, with co-existing fever, electrolyte disturbances, stress and the use of antiviral drugs. Aggressive antipyretic treatment and electrocardiogram (ECG) monitoring is recommended in some patients[14].
- There is an additional case report of a patient with positive SARS-CoV-2 with acute myopericarditis, with signs and symptoms of heart failure a week after upper respiratory tract symptoms began[15].
- While the mechanism of cardiac injury is not fully described, several mechanisms have been proposed, including immune inflammatory response, viral invasion to

cardiomyocytes, severe hypoxia and oxidative stress with myocardial injury from increased myocardial oxygen demand[16].

- There is one case series of patients (n=3) who showed decompensation of underlying heart failure, ST segment elevation, and cardiogenic shock concurrent with COVID-19[17].
- Like patients with exacerbations of COPD and/or community acquired pneumonia, survivors of COVID will likely be at high risk of cardiovascular events and mortality, especially in the 30 days following the resolution of the acute phase of the virus[18].
- In a single-center series in China involving 138 patients with COVID-19 pneumonia, 10 were found with laboratory evidence of acute myocardial injury via significantly higher cardiac biomarkers CK-MB (creatine kinase myocardial band) and hs-cTnI (high sensitivity cardiac troponin I)[19].

Gastrointestinal

- Earlier studies of SARS indicated that the gastrointestinal tract tropism of SARS coronavirus (SARS-CoV) was verified by the viral detection in biopsy specimens and stool even in discharged patients. The increased gastrointestinal wall permeability with virus infection and subsequent enteric symptoms like diarrhea due to invaded enterocytes malabsorption suggest that the digestive system might be vulnerable to COVID-19 infection[20].
- Chai et al.[21] showed that specific ACE-2 expression in cholangiocytes may cause liver damage after COVID-19 infection. The liver abnormalities of COVID-19 patients may not be due to hepatocyte damage, but rather cholangiocyte dysfunction,

and with systemic illnesses, there may be non-specific elevations of liver enzymes as well.

- In a large cohort including 1099 patients from 552 hospitals in 31 provinces or provincial municipalities and of those with available results of liver enzymes, patients with more severe disease had abnormal liver aminotransferase levels than did patients with non-severe disease[22].
- In 52 patients with COVID-19 pneumonia, the incidence was 33% for heart injury (abnormal LDH or CK), 29% for liver injury (any abnormality in AST, ALT, GGT or ALP), 17% for pancreatic injury, 8% for renal injury (abnormal creatinine), and 2% for diarrhea. There is potential for mild pancreatic injury patterns in patients with COVID-19 pneumonia, and these may be related to direct viral involvement of the pancreas or from secondary enzyme abnormalities in the context of severe illness without substantial pancreatic injury. These patients also had abnormal blood glucose[23] with implications for patients with pre-existing diabetes mellitus.
- In a retrospective study with 206 patients with mild COVID-19, nearly one-quarter (48) had digestive symptoms only, 69 displayed both digestive and respiratory symptoms, and 89 had respiratory symptoms only. Of the patients with digestive symptoms (117), 67 had diarrhea, the study found[24].
- Viral RNA can be detected in the stool of 81.8% (54/66) of cases, even with negative results for throat swabs. Compared to SARS, patients with COVID-19 experienced diarrhea, nausea, vomiting and/or abdominal discomfort less often before respiratory symptoms. However, feces as a potential contagious source of viral RNA can last even after viral clearance in the respiratory tract. It is strongly recommended that all

recovered COVID-19 patients disinfect and clean their toilets until 17 - 20 days after negative blood tests and respiratory disorder recovery[25].

Dermatologic

- From collected data in 88 COVID-19 patients in Italy, 18 (20.4%) developed skin manifestations including 8 at the onset of disease and 10 after hospitalization. Manifestations included erythematous rash, urticarial and chickenpox-like vesicles. Lesions seemed to heal within a few days[26].

It will be imperative for continued data to be collected on these patients during the recovery and rehabilitation stage in order to sort acute reactions to sepsis from intrinsic actions of the novel coronavirus. Additionally, many of these patients will be experiencing symptoms related to stress disorders, anxiety, or depression. It is highly likely that many of these patients will be cared for on inpatient rehabilitation units and as outpatients in physical medicine and rehabilitation clinics and early establishment of registries to document symptom clusters and recovery trajectories will inform rehabilitation management during the next year.

This brief report can serve as a guide for the rehabilitation clinician in different scenarios we have considered including: 1) Determining screening criteria for admission to the post-acute setting with the knowledge that there can be many extra-pulmonary symptoms and viral shedding can occur outside of the respiratory system. According to the CDC "SARS-CoV-2 can cause asymptomatic, pre-symptomatic, and minimally symptomatic infections, leading to viral shedding that may result in transmission to others who are particularly vulnerable to severe disease and death"[27]. In consideration of this, identifying any of the clinical findings discussed in

this report during the pre-admission assessment in a patient with no documented respiratory symptoms leading to acute care hospital, along with clinical judgement, can prompt testing prior to admission and also justify medical complexity for admission to an inpatient rehab facility (IRF). Even though viral shedding in stool has been identified even after throat swabs are negative[25], at this time the CDC reports that the risk of infection through stool is low[28]. Until more studies are available, standard precautions should be exercised during toileting activities. 2) Increase clinical awareness and guide need for COVID-19 testing in patients in IRF and skilled nursing facility (SNF) settings when only non-respiratory symptoms are present. Screening tests used in existing studies, presented in Table 1, could serve as guidance for further diagnostic investigation depending on the sign or symptom. 3) Inform of risks of other medical complications that may arise requiring monitoring and management in the post-acute inpatient and outpatient settings. In particular, the elevated potential for cardiac arrhythmias may require additional monitoring as patients begin participation in aerobic reconditioning. Laboratory monitoring for improvement after end-organ injury (i.e. liver, pancreas, cardiac) might also be warranted during an IRF stay.

As mentioned previously, in most cases, available data cannot confirm that SARS-CoV-2 infection directly relates to these findings, so caution should be exercised when considering implementation of this information into clinical practice. Current data are preliminary and no practice-based guidelines are available. However, the best currently available evidence can help guide treatment decisions in conjunction with clinical expertise and patient preferences. Rehabilitation clinicians should implement an Evidence Based Physiatry approach to clinical care, combining their individual clinical expertise with evolving external evidence while engaging patients in the decision-making process[29].

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Table 1. Summary of Potential Non-Pulmonary Manifestations and Complications of COVID-19 (continued)					
Neurologic	Altered consciousness, headache, dizziness, ataxia, acute cerebrovascular events, epilepsy, hypogeusia, hyposmia, hypopsia, neuralgia	78/214 (36%)	Retrospective study	▪ History and Exam ▪ Head CT	Mao et al[6]
	Agitation and confusion Dysexecutive syndrome Corticospinal tract signs	40/48 (83%) 14/39 (36%) 39/58 (67%)	Observational series	▪ The Confusion and Assessment Method for the ICU ▪ Richmond Agitation and Sedation Scale ▪ Physical Exam	Helms et al[7]
	Guillain-Barré Syndrome	5/~1200 (0.4%)	Observational series	▪ History and Exam ▪ CSF analysis ▪ MRI ▪ Antiganglioside Antibodies ▪ Electrophysiological studies	Toscaso et al[8]
Hematologic	Positive antiphospholipid antibodies, lower limb ischemia, hand digit ischemia	3	Case series	▪ Prothrombin/partial thromboplastin time ▪ D-dimer ▪ Fibrinogen ▪ Antiphospholipid antibodies	Zhang et al[9]
	Pulmonary embolism, other venous thromboembolic events, arterial thrombotic events (ischemic stroke)	31/184 (17%)	Observational series	▪ CT pulmonary angiography ▪ Ultrasonography ▪ CT head	Klok et al[10]
Musculoskeletal	Rhabdomyolysis	17/214 (8%)	Retrospective case series	▪ Creatinine kinase ▪ Lactate dehydrogenase ▪ Myoglobin ▪ C-reactive protein	Li et al[6]
		1	Case report	▪ Creatinine kinase ▪ Lactate dehydrogenase ▪ Liver enzymes	Jin et al[11]
Ocular	Conjunctivitis	13/1167 (1%)	Meta-analysis	▪ Physical Exam ▪ Conjunctival swab	Loffredo et al[12]
		1	Case report	▪ Conjunctival swab	Chen et al[13]

Body System	Clinical Findings	No. (%)	Study Design	Screening Tests Used	Reference
Cardiovascular	Myopericarditis and heart failure	1	Case report	▪ Electrocardiography ▪ HS-troponin T ▪ NT-proBNP ▪ Cardiac MRI	Inciardi et al[15]
	Decompensation of underlying heart failure, ST segment elevation, cardiogenic shock	3	Case series	▪ Electrocardiography ▪ Troponin I ▪ Transthoracic echocardiography ▪ Chest radiography	Fried et al[17]
	Acute cardiac injury	10/138 (7.2%)	Case series	▪ CK-MB ▪ hs-CTnI	Wang et al[26]
Gastrointestinal	Abnormal AST Abnormal ALT	168/757 (22.2%) 158/741 (21.3)	Cohort study	▪ Aspartate aminotransferase ▪ Alanine aminotransferase	Guan et al[21]
	Liver injury (AST, ALT, GGT or ALP abnormality) Pancreatic injury Diarrhea	15/52 (29%) 9/52 (17%) 1/52 (2%)	Retrospective study	▪ AST ▪ ALT ▪ GGT ▪ ALP ▪ Amylase ▪ Lipase	Wang et al[22]
	Digestive symptoms (Decreased appetite, vomiting, diarrhea, abdominal pain)	117/206	Retrospective study	▪ History and Exam	Han et al[23]
Dermatologic	Erythematous rash Widespread urticaria Chickenpox-like vesicles	18/88 (20.4%)	Case series	▪ History and Exam	Recalcati[25]

* CT denotes computed tomography, ICU intensive care unit, CSF cerebrospinal fluid, MRI magnetic resonance imaging, HS high sensitivity, NT N-terminal, B-type natriuretic peptide, CK-MB creatine kinase myocardial band, hs-cTnI high sensitivity cardiac troponin I, AST aspartate aminotransferase, ALT alanine aminotransferase, GGT gamma-glutamyl transpeptidase, ALP alkaline phosphatase