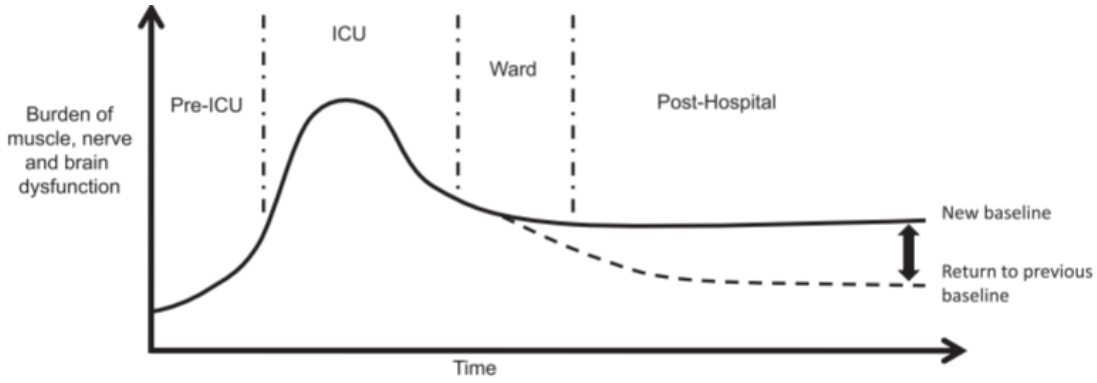
Rehabilitation Clinician's Reference for Covid-Related Rehabilitation

Version 1 – April 20th, 2020

Introduction: Given the novelty of SARS-CoV-2 virus and the recency of COVID-19 illness, long-term effects from symptomatic infection and consequently the best rehab management strategies are unknown. We do know that many patients require hospitalization, ICU level care and may develop complications including acute respiratory failure requiring mechanical ventilator support, ARDS, cardiac injury, and sepsis among other critical conditions. Following discharge from the hospital, we expect many patients may develop varying degrees of alterations in body functions and structures, limitation of activities and participation restrictions across multiple biopsychosocial domains.

In this guide, we aim to provide information for the rehab physician providing care to patients significantly affected by COVID-19. Below, we will provide a brief overview of a variety of rehab-related domains which may be impacted in the subacute to chronic stage. When available, we will report on literature specific to SARS-CoV-2 infection, or otherwise extrapolate from data on similar patient populations (eg SARS, ARDS, Post-Sepsis, Post-ICU Syndrome) for guidance.

Our goal will be to help survivors of critical illness (see adapted Figure) regain as much function as possible (Elizabeth Wilcox et al. 2013).



#Functional Disability:
Following critical illness, weakness and functional limitation is extremely common. Given the recency of COVID19 it is not yet clear what severity and frequency of functional limitations will develop. In post-ICU patients who had at least 7 days of mechanical ventilation (MV), FIM scores performed 7 days post-ICU discharge predicted recovery trajectory at 1 year (Herridge et al. 2016). Patients stratified into four disability groups characterized by age and length of MV. Figures for FIM scores are below:

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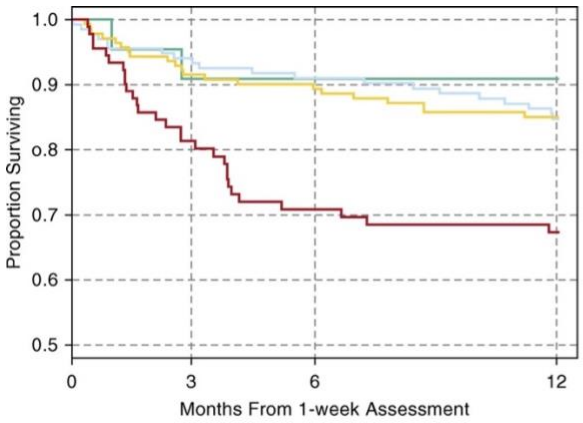

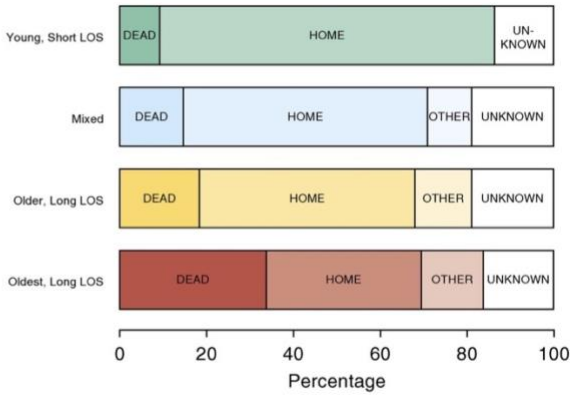

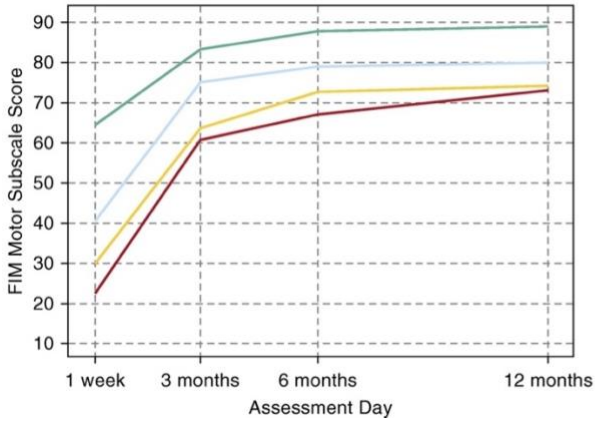

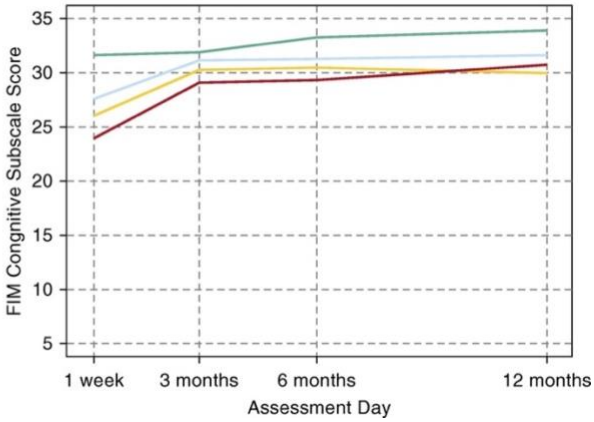

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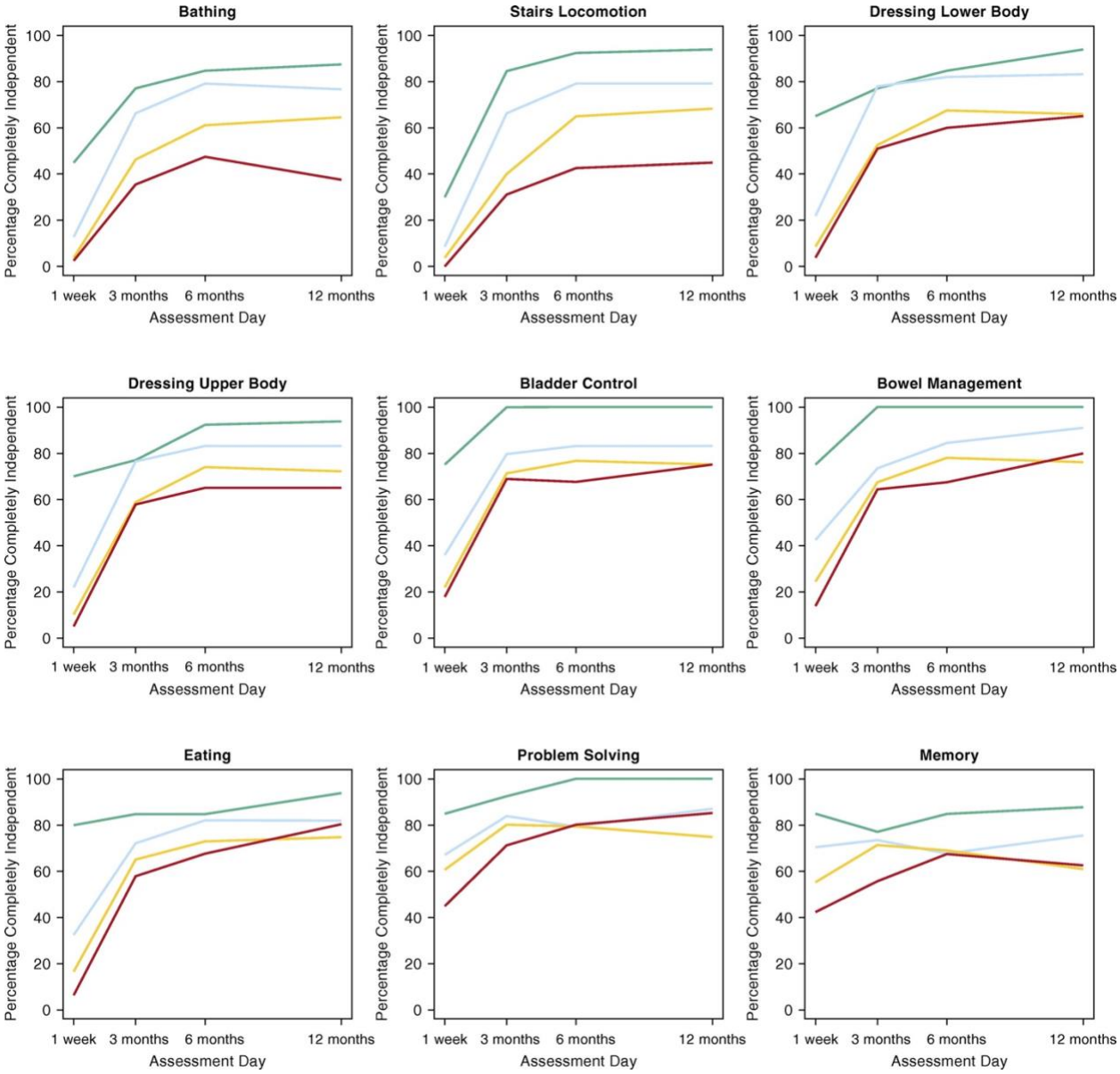


#Pulmonary:

Given the nature of the SARS-CoV-2 virus, pulmonary conditions dominate with 82% of patients reporting cough and 31% with dyspnea (Chen et al. 2020). Numbers from China indicate 14% develop severe disease, marked by dyspnea, hypoxia, or >50 percent lung involvement on imaging, and 5% develop critical disease (Wu and McGoogan 2020). Most patients who require mechanical ventilation have ARDS, which is characterized by non-cardiogenic pulmonary edema with alveolar collapse affecting gas exchange. In Wuhan, 41% of 201 hospitalized patients developed ARDS and those affected were more likely to be older than 65 and have pre-existing comorbid health problems (Wu et al. n.d.). The long-term pulmonary sequelae of COVID19 is unknown so we extrapolate from SARS and ARDS literature.

Pulmonary function at 1-year in SARS survivors are normal in 63%, mildly reduced in 32% and moderately impaired in 5% with abnormalities characterized by restrictive patterns and reduced

DLCO (Ong et al. 2005). In a 15-year follow up study (Zhang et al. 2020) no post-SARS patients had restrictive ventilation dysfunction, 2% had obstructive dysfunction, 35% had reduced DLCO. Patients with ARDS commonly experience increased mortality and morbidity in the months and years after hospital discharge, with one study demonstrating as high as 15-20% of patients who survive acute hospitalizations will die within 1 year, though this is mainly due to underlying comorbidities. Studies are mixed it terms of pulmonary outcome for ARDS. In most patients, lung volumes and PFTs normalize by six months and DLCO should normalize by five years. Formal outpatient rehabilitation may reduce 10-year mortality (Chen; 2019), improve PFTs, HRQoL, and exercise capacity (Hsieh et al. 2018).

#Cardiac:
Cardiac complications during acute illness including arrhythmias, acute cardiac injury, and shock are reported in 17%, 7%, and 9% of patients, respectively (Wang et al. 2020b). In addition, 33% of 21 patients admitted to the ICU in the US developed cardiomyopathy though higher prevalence may be related to the cohort's older age (Arentz et al. 2020). Patients with cardiac injury have higher mortality and rate of complications including ARDS, AKI, electrolyte disturbances, hypoproteinemia, and coagulation disorders than those without (Shi et al. 2020).

#Swallowing:
Approximately 3.2% of patients with COVID19 require intubation and invasive ventilation. Following extubation in a non-COVID19 population, 76% of patients reported dysphonia, 76% pain or odynophagia, and 49% dysphagia (Akst; 2018). Pathophysiology is multifactorial and includes edema of inter-arytenoid space, granulation tissue, vocal fold paresis/immobility, mucosal lesions, airway/glottic/subglottic stenosis, secretion and debris in pharyngeal and laryngeal cavities. Patients with post-extubation dysphagia typically demonstrate pathology in the pharyngeal phase characterized by **delayed pharyngeal swallow response**. In ARDS survivors, of the 32% who self-reported symptoms of dysphagia at hospital discharge, 77% recovered from their dysphagia within 6 months, and 100% recovered within 5 years (Brodsky et al. 2017) and the median time to recovery was 3 months.

#ICU-acquired weakness: Patients admitted to the ICU for COVID19 may present with focal or globalized weakness from a variety of etiologies. At this point, the literature on specific neuromuscular sequelae following SARS-CoV-2 is limited (Guidon and Amato 2020).

Infection with SARS-CoV-2 may be associated with viral myopathies. In recent studies from Wuhan, myalgias have been documented in 33% (Wang et al. 2020a) and 44% (Huang et al. 2020) or patients. In prior studies of coronavirus infections, elevated CK has been documented in about a third of patients (Wang et al. 2004) and rhabdomyolysis has also been observed (Tsai et al. 2004), suggesting the possibility that coronavirus may cause a viral myopathy (Guidon and Amato 2020). For patients who were severely ill, critical illness myopathy and polyneuropathy are likely to manifest following SARS-CoV-2 infections (Guidon and Amato 2020). Another common finding may be type 2 muscle fiber atrophy from disuse which may present after one week for critically ill, bed-ridden patients (Guidon and Amato 2020).

While specific viral infections (eg EBV, H1N1) may precede certain neuromuscular disorders such as GBS, this does not yet appear to be the case with SARS-CoV-2, aside from one case report with unclear causality (Zhao, H, Shen, D, Zhou, H, Liu, J, Chen 2020). Other viruses (polio, West Nile) are known to directly invade peripheral nerves, but no evidence exists for this process with SARS-CoV-2 either (Guidon and Amato 2020).

Elsewhere ICU-associated weakness had been commonly found after acute lung injury, with weakness associated with physical function impairments that may continue after 2 years (Fan et al. 2014). Formal exercise programs may improve SF-36 role physical, self-efficacy to exercise, and shuttle walk test (O'Neill et al. 2014).

#Neurologic sequelae from COVID19: Studies are beginning to document the neurologic sequalae of SARS-CoV-19. Neurological symptoms range considerably across both the central and peripheral nervous system, including headache and dizziness, alterations in consciousness, ataxia, seizures, cerebrovascular complications, smell, taste and vision impairments, and nerve pain (see Table below from an early systematic review) (Asadi-Pooyaa and Simani 2020; Mao et al. 2020).

Table 3
Neurological manifestations of COVID-19.

Author/year	Methods	Neurological manifestations
Mao/ 2020 [9]	Retrospective case series of 214 admitted patients	CNS manifestations: in 25%. Headache (13%), dizziness (17%), impaired consciousness (8%), acute cerebrovascular problems (3%), ataxia (0.5), and seizures (0.5%)
Li/ 2020 [10]	Retrospective case series of 221 admitted patients	5% developed acute ischemic stroke, 0.5% had cerebral venous sinus thrombosis, and 0.5% had cerebral hemorrhage
Huang/ 2020 [11]	Prospective study of 41 admitted patients	Headache in 8%
Yang/ 2020 [12]	Retrospective study of 52 critically ill adult patients	Headache in 6%
Wang/ 2020 [13]	Retrospective case series of the 138 hospitalized patients	Dizziness in 9%; Headache in 7%
Chen/ 2020 [14]	Retrospective case series of the 99 hospitalized patients	Confusion in 9%; Headache in 8%

CNS: central nervous system; CSF: cerebrospinal fluid; EEG: electroencephalography.

The rates of reported neurologic symptoms are fairly high. In a cohort study from Wuhan, 36.4% of hospitalized patients had neurological manifestations (e.g. acute stroke, AMS), which were more common in those with severe disease (Mao et al. 2020).

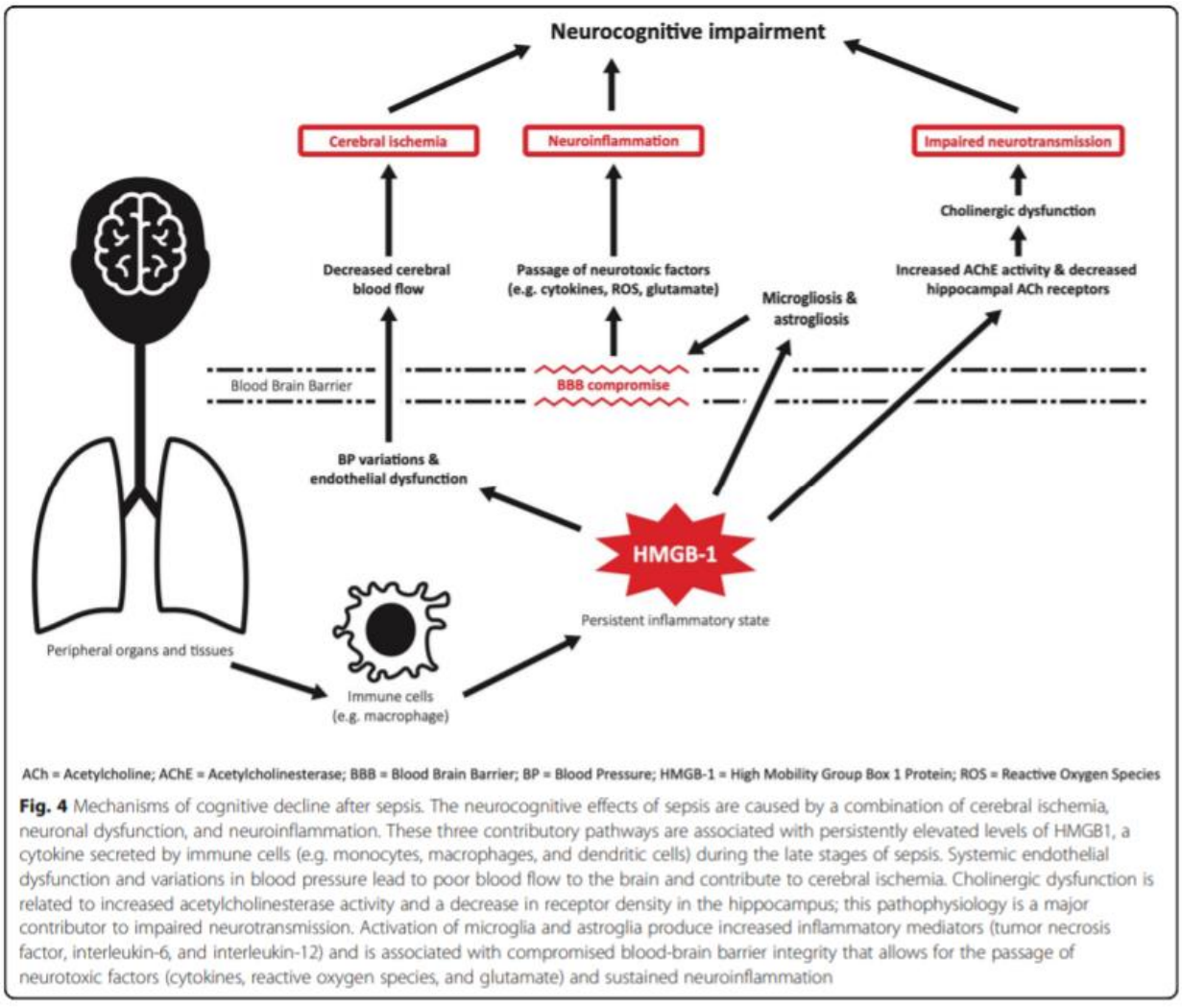
In a study describing the neurologic features of severe SARS-CoV-2 infection and ARDS in France, encephalopathy, prominent agitation and confusion, and acute ischemic stroke were most common (Helms et al. 2020). These symptoms may manifest on admission or later on in the hospitalization. In this cohort, 14% of patients presented to the ICU with neurological findings, and 67% demonstrated neurological findings when sedation and neuromuscular blockade was held (Helms et al. 2020). Among individuals in this study who underwent neuroimaging, in additional to occasional findings of stroke, leptomeningeal enhancement was common (Helms et al. 2020).

As such at present it is not clear whether neurologic symptoms should be attributed to critical illness–related factors, medication effects versus directly related to SARS-CoV-2 infection (Helms et al. 2020). That being said, numerous mechanisms are already accumulating to account for spread to the CNS, including retrograde axonal transport from peripheral nerves such as the olfactory nerve to the brain, possible spread via synapses from mechano and chemoreceptors in the lungs and lower airways to medullary cardiorespiratory centers, hematogenous spread, consequences of CNS inflammation, peripheral immune cell transmigration, or post-infectious autoimmunity (Li, Bai, and Hashikawa 2020; Troyer, Kohn, and Hong 2020).

#Loss of taste and smell: Loss of smell and taste has been identified as a common symptom associated with COVID-19, reported in more than two-thirds of patients. Possible mechanisms

may include disruption of nasal epithelium versus infiltration of higher-order structures in the CNS, such as cranial nerves or the vagus nerve (Troyer et al. 2020). Within weeks of symptom recovery, most of these individuals report resolution of anosmia (Yan et al. 2020). Only a single case study on SARS-CoV-1 reports on anosmia lasting permanently (Hwang 2006).

#Cognitive symptoms: Short and long-term cognitive impairment has been documented in ICU survivors and are likely to appear following severe cases of COVID-19 as well. Limited data on this topic exists at this time. In one study of individuals hospitalized in France for SARS-CoV-2 following ARDS, at the time of discharge, 33% demonstrated a dysexecutive syndrome, including inattention, disorientation, and poorly organized movements to command (Helms et al. 2020). Implicated mechanisms for cognitive decline after critical illness include neurological injury due to cerebrovascular injury, metabolic derangements, and neuroinflammation (see Figure below) (Mostel et al. 2019).

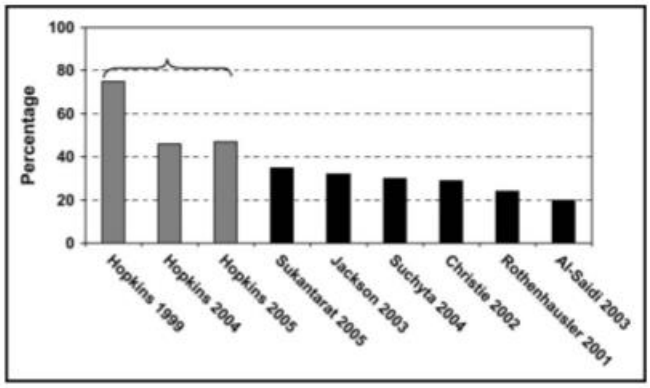


ACh = Acetylcholine; AChE = Acetylcholinesterase; BBB = Blood Brain Barrier; BP = Blood Pressure; HMGB-1 = High Mobility Group Box 1 Protein; ROS = Reactive Oxygen Species

Fig. 4 Mechanisms of cognitive decline after sepsis. The neurocognitive effects of sepsis are caused by a combination of cerebral ischemia, neuronal dysfunction, and neuroinflammation. These three contributory pathways are associated with persistently elevated levels of HMGB1, a cytokine secreted by immune cells (e.g. monocytes, macrophages, and dendritic cells) during the late stages of sepsis. Systemic endothelial dysfunction and variations in blood pressure lead to poor blood flow to the brain and contribute to cerebral ischemia. Cholinergic dysfunction is related to increased acetylcholinesterase activity and a decrease in receptor density in the hippocampus; this pathophysiology is a major contributor to impaired neurotransmission. Activation of microglia and astroglia produce increased inflammatory mediators (tumor necrosis factor, interleukin-6, and interleukin-12) and is associated with compromised blood-brain barrier integrity that allows for the passage of neurotoxic factors (cytokines, reactive oxygen species, and glutamate) and sustained neuroinflammation

Extrapolating further from the literature on post-ICU critical illness, studies vary in the range of reported cognitive impairment from about 20% to more than 70% (see Figure) (Hopkins and Brett 2005). The level of cognitive impairment can be functionally significant in these cases. For example, the BRAIN-ICU clinical trial showed that at 12 months post-discharge, 34% and 24%

Figure 1. Percentage of critically ill patients with cognitive impairments by study



The gray bars indicate studies in the same group of patients with acute respiratory distress syndrome (ARDS). The Hopkins *et al.* [21] 1999 study reports neurocognitive outcome in 55 ARDS patients at hospital discharge and 1 year. The Hopkins *et al.* [29] 2004 study reports neurocognitive outcome in 74 ARDS patients at hospital discharge and 1 year, and the Hopkins *et al.* [23] 2005 reports 2-year neurocognitive outcome in the same patients.

of patients demonstrated cognitive impairment in line with those with a history of moderate traumatic brain injury and mild Alzheimer's disease, respectively, regardless of age (Pandharipande et al. 2013). In many of these studies rates of cognitive impairment following critical illness decrease over time. Accordingly, following ARDS in one study, 74% of individuals experienced neurocognitive sequelae at hospital discharge, 46% at one year, and 47% at two years (Hopkins et al. 2005). For some however, cognitive impairments can be long-lasting. Worsened cognitive function lasted at least 8 years in a longitudinal survey of post-sepsis survivors (Iwashyna et al. 2010).

Various domains of cognitive function may be impaired. In a large systematic review, post-sepsis cognitive impairment was observed in domains of attention, cognitive flexibility, processing speed, associative learning, visual perception, work memory, verbal memory, and semantic memory (Calsavara et al. 2018).

#Sleep: Sleep patterns are frequently disrupted during admission to the ICU and for some, also afterward. In one study, following discharge from the ICU for ARDS, 67% reported sleep disruption <1 month post-discharge and 39% reported disrupted sleep >1 month post-discharge (Dhooria et al. 2016). In another systematic review of individuals previously hospitalized for critical illness in the ICU, 10-61% of patients continued to report sleep disturbances >6 months after discharge. Risk factors for sleep disruption after discharge from the ICU include prehospital factors (comorbidities, pre-existing sleep abnormalities) and in-hospital factors (severity of illness, in-hospital sleep disturbances, pain, medication use, ICU acute stress symptoms); sleep disturbances were also associated with post-discharged psychological comorbidities (Altman, Knauert, and Pisani 2017).

#Mental Health: Patients who have been critically ill report high rates of depression, PTSD, and anxiety (Hatch et al. 2018). Survivors of ARDS reported moderate to severe depression (16% and 23%) and anxiety (24% and 23%) at 1 and 2 years respectively (Hopkins et al. 2005). Health Related Quality of Life was found to be lower in patients and their family members after a critical illness, particularly those with ARDS, prolonged mechanical ventilation, and severe sepsis. However, this reduction tended to gradually improve and after a few years HRQL was comparable to age-matched population values over several years (Oeyen et al. 2010).

#Pain:
What are possible etiologies that might be overlooked?
-Hypercoagulable states are common in acute COVID19 raising suspicion of DVT or PE.
-Avascular necrosis of the femoral head can be seen in patients who receive systemic glucocorticoids such as those with ARDS.

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-Joint contractures can develop as a complication of prolonged immobility; elbow and ankle are the most common, followed by hip and knee.
-Heterotopic ossification can develop due to prolonged immobility. Common signs include pain, swelling, fever, and decreased joint mobility.

#Effectiveness of rehab:
In one RCT of intensive care unit survivors, participants with cognitive or functional impairments at discharge were randomized to receive either sporadic rehab or a combination of in-home cognitive (six in-person visits), physical and functional rehab (six televisits) over a 3 month period. At three months, those in the intervention group demonstrated greater cognitive executive function on the Tower test and reported greater performance (Jackson et al. 2012).

Borg Scale

How you might describe your exertion	Borg rating of your exertion	Examples (for most adults <65 years old)
None	6	Reading a book, watching television
Very, very light	7 to 8	Tying shoes
Very light	9 to 10	Chores like folding clothes that seem to take little effort
Fairly light	11 to 12	Walking through the grocery store or other activities that require some effort but not enough to speed up your breathing
Somewhat hard	13 to 14	Brisk walking or other activities that require moderate effort and speed your heart rate and breathing but don't make you out of breath
Hard	15 to 16	Bicycling, swimming, or other activities that take vigorous effort and get the heart pounding and make breathing very fast
Very hard	17 to 18	The highest level of activity you can sustain
Very, very hard	19 to 20	A finishing kick in a race or other burst of activity that you can't maintain for long

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