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PERSPECTIVE

COVID-19 and Long-Term Outcomes: Lessons from Other Critical Care Illnesses and Potential Mechanisms

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that is currently causing a pandemic and has been termed coronavirus disease (COVID-19). The elderly or those with preexisting conditions like diabetes, hypertension, coronary heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, or kidney dysfunction are more likely to develop severe cases when infected. Patients with COVID-19 admitted to the ICU have higher mortality than non-ICU patients. Critical illness has consistently posed a challenge not only in terms of mortality but also in regard to long-term outcomes of survivors. Patients who survive acute critical illness including, but not limited to, pulmonary and systemic insults associated with acute respiratory distress syndrome, pneumonia, systemic inflammation, and mechanical ventilation, will likely suffer from post-ICU syndrome, a phenomenon of cognitive, psychiatric, and/or physical disability after treatment in the ICU. Post-ICU morbidity and mortality continue to be a cause for concern when considering large-scale studies showing 12-month mortality risks of 11.8–21%. Previous studies have demonstrated that multiple mechanisms, including cytokine release, mitochondrial dysfunction, and even amyloids, may lead to end-organ dysfunction in patients. We hypothesize that COVID-19 infection will lead to post-ICU syndrome via potentially similar mechanisms as other chronic critical illnesses and cause long-term morbidity and mortality in patients. We consider a variety of mechanisms and questions that not only consider the short-term impact of the COVID-19 pandemic but its long-term effects that may not yet be imagined.

Keywords: SARS-CoV-2; chronic critical illness; cytokine storm; mitochondrial dysfunction; amyloids

In December 2019, several patients with unexplained pneumonia emerged in Wuhan City, Hubei Province, Central China. Genome sequencing revealed that this pneumonia was an acute respiratory disease originating from a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has since been termed coronavirus disease (COVID-19) (1). COVID-19 has become a global pandemic, spreading to over 200 countries and territories, infecting more than 400 million people, and causing over 5.7 million deaths as of February 10, 2022 (2).

The clinical spectrum of SARS-CoV-2 infection appears to be wide, ranging from mild and even asymptomatic infection to severe disease, with high morbidity and mortality in patient groups with pre-existing conditions. Clinical and imaging features of COVID-19 are well established; however, the pathophysiology of COVID-19 largely remains unclear (3). Additionally, with hundreds of millions of people globally having "recovered", the long-term morbidity and sequelae caused by COVID-19 are already being observed by clinicians and are

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not well understood. Table 1 offers a general overview of the clinical presentation of COVID-19, potential risk factors, and short- and long-term sequelae in individual organ systems.

The rapid onset of this pandemic triggered a concerted, in some cases heroic, focus on the short-term survival of patients with COVID-19. However, the long-term sequelae in survivors are only starting to be appreciated, and this syndrome has been named post-COVID syndrome (4). Interestingly, this phenomenon is not entirely novel, as postintensive care syndrome (PICS) is well-recognized for survivors of acute illness (5–7). Herein, we consider the long-term outcomes of COVID-19 survivors. Specifically, we examine the potential outcomes of survivors admitted to the ICU. Finally, and most importantly, we consider potential mechanisms, especially compared with what is known about PICS, underlying long-term morbidity in COVID-19 survivors that should lead to novel hypotheses and therapies to better understand and treat the long-term sequelae of COVID-19 survivors. We focus the Perspective on the broader themes of the pro-inflammatory state and mitochondrial dysfunction without significant granular detail, as this could be the focus of many reviews. Finally, we explore amyloid production and/or release as a novel hypothesis for long-term sequelae in COVID-19.

Critical Illness and Known Long-Term Outcomes from Previous Outbreaks

Critical illness secondary to the COVID-19 pandemic has produced an overwhelming surge in ICU admissions, perhaps one of the largest sequential cohorts of critically ill patients that the global community has seen in generations (8, 9). Early reports from China and Lombardy, Italy, indicated a high incidence (23–32% and 16%, respectively) of critical illness among hospitalized patients positive for COVID-19 (10, 11). In the time after this U.S. Centers for Disease Control and Prevention report, more than 28 million new patients have tested positive throughout the United States, and waves of breaking news coverage describing an overburdened healthcare infrastructure have and continue to emerge as hospital capacities and ICU surges continue to cast doubt on our ability to meet demand (2). However, the exact number of critically ill patients is not the focus of this Perspective, but rather, the certainty that a large population of patients will experience critical illness during this pandemic and its long-term sequelae. Lingering symptoms have become an emerging aspect of the clinical presentation related to COVID-19 among postinfectious patients, so much so that a name has been given, "long-haulers", to describe patients that have, in theory, recovered from the worst impacts of COVID-19 and have tested negative, however, still suffer from symptoms (12).

Critical illness from COVID-19 should raise an urgent concern, considering the well-established trends seen among survivors of critical illness related to COVID-19 (Table 1). Critical illness has consistently posed a challenge not only in terms of mortality but also in regard to long-term outcomes of survivors (5–7). Originally, the field of critical care held its focus primarily on prolonging the life of the patient in the acute setting with less consideration for the future life of the patient. It has since

Table 1. Acute and Chronic Organ System Sequelae of COVID-19 Infection

Body System	Problem	Reference
Cardiovascular	The binding of SARS-CoV-2 to ACE2 has been shown to cause various forms of heart damage, including myocarditis, acute myocardial injury, increased risk of venous thromboembolism, coagulation, and arrhythmias.	21, 68, 69
Endocrine	Diabetes is a very important comorbidity in patients with COVID-19. Hyperglycemia affects ACE2 expression. Hypothalamic-pituitary involvement by SARS has been reported in a subset of patients.	70
Gastrointestinal	During the early phases of the disease, many patients report nausea, vomiting, diarrhea, or abdominal pain. Loss of intestinal barrier integrity and gut microbiome has been reported as well as the presence of COVID-19 in the stool.	71
Respiratory	Airway, lung parenchymal, pulmonary vascular, and respiratory neuromuscular disorders are all features of COVID-19. The most frequent clinical manifestation of severe COVID-19 has been acute respiratory failure consistent with acute respiratory distress syndrome and severe pneumonia.	19, 72
Brain/central nervous system	A subset of patients experiences delirium and altered mental states, stroke, brain hemorrhage, memory loss, encephalitis, or in some severe cases, acute disseminated encephalomyelitis. Many patients are admitted to the ICU and are subsequently subject to post-intensive care syndrome.	20, 73
Renal	There is little data on kidney histology of patients with COVID-19. Studies have shown the presence of proteinuria, hematuria, raised serum creatine, and blood urea nitrogen. In a study of 51 patients with COVID-19, 100% had kidney abnormalities in computed tomographic scans.	74

Definition of abbreviations: COVID-19 = coronavirus disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

transitioned to consider the challenges of survival not only from a physical but also from an emotional, mental, and social standpoint (5). While examining other experiences with acute critical illness, a large proportion of patients may suffer from PICS, an established phenomenon of cognitive, psychiatric, and/or physical disability after treatment in the ICU (6). Studies have shown that while hospital survival of critically ill patients has improved greatly in the last few decades, the functional and cognitive sequelae that typify PICS have remained largely the same (5–7). Post-ICU morbidity and mortality continue to be a cause for particular concern when considering largescale studies showing 12-month mortality risks of 11.8–21% and increases in mortality risk each additional year for at least the first 3 years after recovery (13).

Critical illness that culminates during the course of COVID-19 infection (acute respiratory distress syndrome, pneumonia, septic shock, multiorgan failure, opportunistic secondary infections, etc.) bears a striking semblance to the conditions that similarly admit non-COVID-19 patients to the ICU (14). Knowing these historical outcomes in critically ill patients, it is important to consider that even when this current pandemic does end, long-term patient sequelae will continue to be seen and need to be treated for years to come.

Long-term evaluation studies on survivors of SARS consistently demonstrate significant impairment of lung diffusing capacity of carbon monoxide, exercise capacity, and mental health status in the months to years after recovery (15). While many such studies were relatively short-lived, evaluating 1 to 3 years after recovery, several studies investigated further, including a 15-year prospective follow-up study on healthcare workers who survived nosocomial SARS infection in 2003 (16). Largely, these studies show that pulmonary injury gradually decreases—most prominently during the first year of recovery; however, for the majority of patients, pulmonary injury does not completely resolve (16). Additionally, among patients whose computed tomographic scans after recovery demonstrated no gross abnormalities earlier on in their recoveries, pulmonary function tests performed at intervals later in the evaluation period would reveal ongoing improvement despite no visual evidence of injury (17). Considering the similarities between SARS and COVID-19, these long-term effects should be anticipated among patients recovering from COVID-19 as recent studies demonstrate the persistence of similar pulmonary and constitutional symptoms in patients recovered from COVID-19, such as fatigue and dyspnea, and radiologic abnormalities such as interstitial thickening and evidence of fibrosis (18).

With the onset of the COVID-19 pandemic already over 2 years removed, researchers and clinicians are beginning to uncover the long-term health consequences of COVID-19 survivors, and recently published studies are starting to at least partly uncover the various ill-effects that await post-COVID-19 infection (4, 19). Long-term outcomes are not just isolated to the lungs (19) but are widespread, affecting the brain (20), heart (21), and likely other organ systems. This may not be surprising, as the angiotensin-converting enzyme (ACE) 2 receptor, the functional receptor of SARS-CoV-2, is present in virtually all organs in addition to arterial and venous endothelial cells and smooth muscle (22). Early and long-term follow-up reveals ongoing impairment in both lung mechanics and diffusion capacity in COVID-19 survivors (23).

Growing attention is also being placed on the heart. A cohort study of 100 patients who recently recovered from COVID-19 infection from the University Hospital Frankfurt, Germany, revealed, through cardiac magnetic resonance imaging, cardiac involvement in 78 patients and ongoing myocardial inflammation in 60 patients, both of which were independent of preexisting conditions, severity and overall course of the acute illness, and the time from the original diagnosis (21). Compared with healthy controls and risk factor-matched controls, patients who recently recovered from COVID-19 had lower left ventricular ejection fraction, higher left ventricle volumes, higher left ventricle mass, and raised native T1 and T2 (21).

Potential Mechanisms of Long-Term Morbidity/Mortality from Critical Illness

In the face of this public health emergency, analyzing the causative mechanisms for potential long-term risks associated with COVID-19 remains an important objective. Our Perspective focuses on the hypothesis that poor long-term outcomes from COVID-19 infection involve deteriorating organ function that persists after recovery and analysis of potential mechanisms. It is important to reiterate that even in the wake of a potentially life-threatening physiologic insult, the normal physiologic function of the failing organ systems in patients can be restored in survivors. However, until complete resolution occurs, patients face the burden of end-organ dysfunction (EOD).

Sepsis is most currently defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (24). While the development of EOD is an important clinical event during sepsis, perhaps as significant is the persistence of EOD after the initial recovery (25). Despite the enormous efforts to clarify the mechanisms by which sepsis, pneumonia, and other critical illnesses precipitate EOD in patients in the months after recovery, our understanding remains poor.

EOD is often characterized by significant clinical heterogeneity (a constellation of clinical signs and symptoms), which not only complicates our pathophysiological understanding but limits our approach to improving patient outcomes. Available evidence points to an array of contributing factors (inflammation, adaptive immune responses, hypoxia, metabolic reprogramming, nutrition, availability of resources during recovery, etc.), all individually distinct but, nonetheless, wholly interdependent (25). Two highly regarded models for the aforementioned phenomena, pro-inflammatory cytokines and mitochondrial dysfunction, are the source of intense study. However, a third, novel mechanism describes amyloid species produced during critical illness as a potential new, independent or synergistic etiologic agent of EOD in patients surviving critical illness. All of these mechanisms are discussed hereafter.

Proinflammatory Cytokines in Sepsis and Multiple Organ Failure

Excessive production of cytokines has characterized sepsis and its systematic inflammatory response (*see* Figure 1). The pro-inflammatory cytokines may lead to tissue and organ injury but are also necessary for orchestrating the physiological adjustments required for infection control (26). Antiinflammatory cytokines are important in the regulation of homeostasis and overall immune response; however, when disturbed, they trigger pathogenesis in a similar fashion. Studies by Chaudhry and colleagues indicate that an imbalance of both

cytokine classes produced during sepsis is critical in its pathogenesis (27). Pro-inflammatory and antiinflammatory cytokines have been referred to as a "double-edged sword" in the context of sepsis because while their pathways are critical in limiting infection, their overproduction causes tissue and organ damage.

Severely ill patients infected with COVID-19 have a high concentration of cytokines, which correlates with a poorer prognosis (28). During postmortem examination of patients with COVID-19, lung tissue samples reveal the presence of excessive infiltration of pro-inflammatory cells. This research indicates that a "cytokine storm" contributes to mortality from COVID-19 infection (29). Cytokine storm has also been referred to as cytokine storm syndrome, which is defined as an activation cascade of auto-amplifying cytokine production due to unregulated host immune response to different pathological triggers, including malignancy, rheumatic disorders, and other autoimmune disorders, etc. In other terms, the cytokine storm syndrome involves a systemic inflammatory response to infections and drugs, leading to excessive activation of immune cells and an abundance of pro-inflammatory cytokines (29).

Patients infected with COVID-19 and admitted to the ICU have significantly higher concentrations of inflammatory indicators including, but not limited to, neutrophils, white blood cells, C-reactive protein, and procalcitonin (30). Severely ill patients have higher concentrations of pro-inflammatory cytokines than moderately ill patients, such as IL-6, IL-8, and TNF-α, strong and independent predictors of disease severity and patient survival (31). The presence of IL-6 specifically has been shown to functionally exhaust lymphocytes, particularly cytotoxic T cells (CD8+) and natural killer cells critical for host defense against viruses (32–34). It is suggested that cytokine storm syndrome may directly mediate the reductions in T-cell populations commonly observed in the peripheral blood of patients with severe COVID-19 infection, a pattern that is concurrently associated with poorer outcomes. Additionally, BAL fluid cells reveal the release of excessive chemokines caused by infection of COVID-19, such as CXCL10 and CCL2, a chemokine which, along with its receptor (CCR2), facilitates monocyte recruitment into tissues, including the central nervous system (28, 35).

The postmortem examination of patients with COVID-19 demonstrates the existence of and the overactivation of T cells as a result of an increase in their number and their high toxicity. The cytokine storm is then hypothesized to have resulted from hyperactivation of both the innate and adaptive immune systems in an uncontrolled inflammatory response (29). This can lead to a slippery slope involving apoptosis of epithelial and endothelial cells and vascular leakage, among worse syndromes, acute respiratory distress syndrome, and death (36). Thus, it is important that we consider the effect of pro-inflammatory cytokines and their multiplication in patients with COVID-19, especially as severity increases.

While an excessive degree of inflammation in response to the infectious insult is a clear trigger for the activation of multiple downstream pathways, the precise pathophysiologic mechanisms underlying the development of EOD remain elusive. EOD, while more commonly described in association with infective insults, is similarly seen in trauma victims and those recovering from major surgery, where pathological processes such as ischemia–reperfusion injury can lead to activation of inflammatory pathways and injury to distant organs. In any case of EOD, implicated in its genesis are widespread activation of inflammatory cascades. Attempts to elucidate the mechanisms by which cytokines released during infection, inflammation, surgery, etc., precipitate long-term dysfunction have been instrumental in our understanding of their pivotal pathogenic role. Xu and colleagues demonstrate that astrocyte-derived CCL2 in the setting of neuroinflammation induced by peripheral trauma plays a key role in the development of postoperative cognitive dysfunction, principally by evoking microglial activation (37). Pre-injection with CCR2 antagonists inhibit microglial activation and reduce neuronal injury and death while improving cognitive function in rodent models. In a similar series of studies focusing on postoperative cognitive decline in aseptic trauma, Feng and colleagues demonstrate the role of increased concentrations of IL-1β in the hippocampus of mice with postoperative cognitive dysfunction, demonstrating that peripheral blockage of TNF-α, a cytokine upstream of IL-1, can prevent neuroinflammation and cognitive decline in mouse models of surgery-induced cognitive decline (38).

Mitochondrial Dysfunction in Sepsis and Multiple Organ Failure

Organ dysfunction from sepsis has traditionally been attributable to the effects of inflammatory mediators (as described above) and tissue hypoxia, namely reduced oxygen delivery to vital organs, whether by hypoperfusion, vascular hyperpermeability, or loss of vascular control (39). While the presence of impaired circulation leading to tissue hypoperfusion makes a well-recognized contribution to the development of EOD, organ dysfunction can still occur even in the absence of gross macrovascular or microvascular (e.g., shunting) abnormalities. Additionally, studies have revealed that metabolic substrates and oxygen are readily available in sepsis; that is, septic patients in the ICU have adequate tissue oxygen tension, rendering it unlikely that the organ dysfunction of sepsis is a consequence of inadequate substrate supply alone, a paradox that begs the question of whether deranged cellular energetics occurs not just because O_2 delivery is impaired, but because the ability of cells to utilize available O_2 is compromised (40–44). For example, even in scenarios that exhibit derangements in microvascular blood flow, when regional perfusion is held constant, the ability of cells to utilize oxygen remains impaired (45). Since aerobic respiration provides most of the energy supply for metabolically active tissues, it seems likely that altered tissue oxygen utilization, "cytopathic hypoxia", at the mitochondrial level contributes significantly to organ dysfunction during sepsis (46). With a growing body of evidence, the role of bioenergetic dysfunction is becoming increasingly renowned for potentially explaining the paradox of clinical and biochemical organ dysfunction in patients recovering from critical illness (*see* Figure 1).

Mitochondria are an essential part of the cellular infrastructure, serving as the primary site of high energy phosphate production through oxidative phosphorylation and as an important moderator of cellular metabolism—roles that are important in the regulation of tissue repair and remodeling responses to injury (47). A variety of energetic alterations have been noted in sepsis and other inflammatory states, characterized by an initial hypermetabolic state with elevated cellular respiration, ATP production, and hormone release, with an ensuing hypometabolic state with decreased mitochondrial respiration,

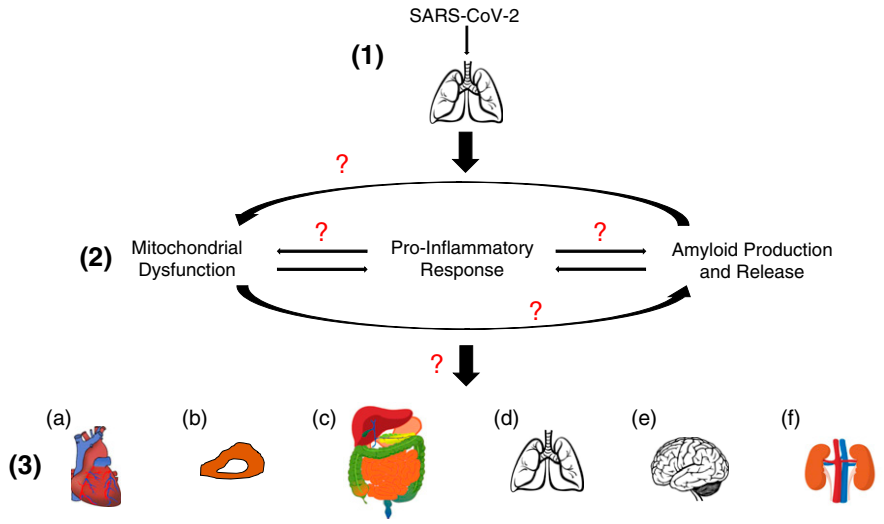

Figure 1. Potential mechanisms of end-organ dysfunction (EOD) after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. (*1*) SARS-CoV-2 infects the lung via airborne transmission and causes symptoms of viral lung infection, including pneumonia. (*2*) SARS-CoV-2 infection of the lung leads to an uncontrolled pro-inflammatory response, mitochondrial dysfunction, and possibly release of cytotoxic amyloids (Aβ). Whether, how much, or in what way these three mechanisms interact to cause EOD is currently unclear but is hypothesized as a source of future investigation. (*3*) Varying end-organs are reported to suffer effects secondary to SARS-CoV-2 infection (outlined in Table 1). Whether any (or multiple) of the mechanisms in (*2*) are involved is unclear but are hypothesized as a source of future investigation. These end-organs include the (*a*) cardiovascular system, (*b*) endocrine system, (*c*) gastrointestinal system, (*d*) respiratory system, (*e*) brain/central nervous system, and (*f*) renal system. Numerous question marks are present as it is currently unclear which of these established mechanisms in critical illness are concurrently present in the long-term sequelae of COVID-19 infection or if their mechanisms overlap and/or act synergistically.

ATP production, and downregulated hormone-release pathways (41). While clinically manifesting as organ dysfunction, such a polarizing shift in cellular metabolism is believed to be an adaptive metabolic response to overwhelming systemic inflammation wherein cells enter a hibernation-like condition to limit the production of reactive oxygen species or to protect from ATP depletion by lowering metabolic demands in cellular environments in which ATP production is impaired (48). An example can be seen with myocardial hibernation, an adaptive response to stress in which hibernating cardiomyocytes are reversibly hypocontractile and demonstrate characteristic metabolic and ultrastructural changes in the septic heart (49). Suppression of metabolic activity can be initiated by mitochondria and is mediated by activation of AMP-dependent protein kinase (AMPK) (50). While a number of studies have evaluated mitochondrial morphology and function in critically ill patients, the relationship between mitochondrial function and organ system dysfunction is still not entirely understood.

Studies have described evidence of mitochondrial damage in experimental models of sepsis, but it is not clear whether this association represents organelle damage as a consequence of inflammation and inflammatory molecules such as nitric oxide or other reactive oxygen species or whether the changes in mitochondria are etiologic in the development of subsequent cellular and organ dysfunction. For example, we know that mitochondria can also activate stress responses in cells through the release of cytochrome C and can activate transcription factors, including hypoxia-inducible factor-1α, NF-κβ, and p53, leading to the dichotomy between "cell-adaptive" and "organ-maladaptive" responses (50). Further questions arise when considering the analysis of histological samples from patients with critical illness, which frequently reveal normal cellular morphology—preservation of cellular architecture with minimal amounts of apoptosis, necrosis, or cell damage—despite organ system dysfunction (41, 50). These findings suggest that tissue changes leading to organ failure are "functional rather than structural", which may help to explain why a decrease in mitochondrial function, which may lead to or coincide with a loss of critical cell-specific functions, may be an adaptive response that prevents cell death to allow for eventual recovery (50).

It appears that the extent, timing, and significance of mitochondrial injury and recovery during critical illness bear considerable weight on the eventual outcome of a patient, perhaps signifying the imperative of maintaining a population of functional mitochondria during times of metabolic or environmental stress. As the primary organelles regulating bioenergetic efficiency and energy expenditure, such adaptation is essential and is often accomplished by mitophagy, mitochondrial biogenesis, and continually undertaking fusion and fission. While there are multiple reviews about each of these processes, such specific depth is beyond the scope of this Perspective. Rather, it is the correlation between mitochondrial dysfunction and the severity and outcome of critical illnesses that are our focus. As eluded to earlier, cellular metabolism regulates tissue repair and remodeling responses to injury. AMPK, which is a critical sensor of cellular bioenergetics, plays a large role in this process by serving as a control switch between anabolic and catabolic metabolisms. With regard to critical illnesses, research studies implicate a deficiency in AMPK activation in nonresolving pathologic conditions such as fibrosis, while in murine models of experimental sepsis, increases in AMPK activation have been shown to protect against organ failure and inflammation (47). Additionally, in *ex vivo* models of myofibroblasts from human lung tissue, pharmacological activation of AMPK in hepatocytes through metformin, a known mediator of AMPK activation, lowers fibrotic activity, accelerates resolution of established fibrosis, and promotes mitochondrial fission and biogenesis (47, 51, 52). In a study investigating metformin's effect on mitochondrial respiration through an AMPK-mediated pathway, scientists observed an increase in mitochondrial density and DNA from mitochondrial fission, which itself is a process mediated by AMPK in response to energy stress and which is associated with increased mitochondrial respiration and nutrient oxidation (53). Several other studies demonstrate that mitochondrial biogenesis through AMPK activation does not only

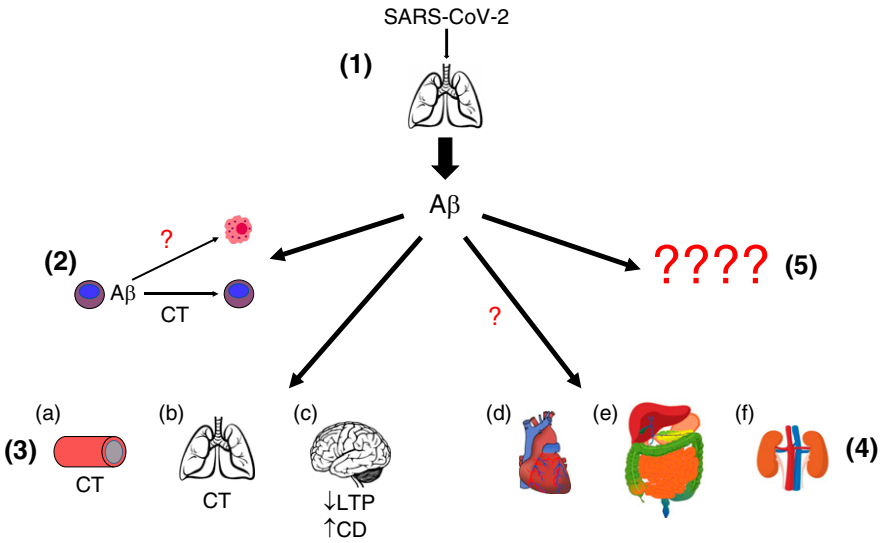

Figure 2. Potential mechanisms of amyloid-mediated cytotoxicity after SARS-CoV-2 infection. (*1*) SARS-CoV-2 infects the lung via airborne transmission and causes symptoms of viral lung infection, including pneumonia. Based on studies on bacterial pneumonia, we suggest that one mechanism of EOD is the release of cytotoxic Aβ. (*2*) Aβ generated after bacterial infection is transmissible and can propagate between cells of the same type. Whether it is transmissible between different cell types is unclear but is hypothesized as a source of future investigation. (*3*) Prior studies have established that Aβ generated after a bacterial infection has damaging effects on the (*a*) endothelium, (*b*) lungs, and (*c*) brain via direct cytotoxicity (*a* and *b*) or decreases in long-term potentiation and increased cognitive dysfunction (*c*). (*4*) Whether Aβ generated after bacterial infection (or SARS-CoV-2 infection) has damaging effects on the (*d*) heart, (*e*) gastrointestinal system, and (*f*) kidneys is unclear but is hypothesized as a source of future investigation. (*5*) Other potential effects of Aβ generated after bacterial infection (or SARS-CoV-2 infection) are outside the scope of this review and are unclear but are hypothesized as a source of future investigation. CD = cognitive dysfunction; CT = cytotoxicity; LTP = long-term potentiation.

modulate the severity of sepsis-induced lung injury but, in fact, can reverse lung fibrosis in already fibrotic tissues (52, 53). Research in this field continues to strengthen the associations between the degree of mitochondrial dysfunction and outcomes in the critically ill, and while this does not confirm cause-and-effect, these well-recognized associations nevertheless suggest that mitochondrial integrity presumably plays a larger role in biology than already believed and is another mechanism by which poor long-term outcomes after critical illness may occur.

Amyloids in Critical Illness

Thus far, we have reviewed two of the more prominent theories about the etiology of sepsis, EOD, and long-term morbidity in patients that become critically ill—pro-inflammatory cytokines and mitochondrial dysfunction. Here, we will discuss a third potential mechanism that can lead to mediate EOD and long-term morbidity and mortality in sepsis: amyloids (*see* Figures 1 and 2). Amyloids are traditionally considered pathological protein aggregates that play causative roles in a range of various diseases, from neurodegenerative diseases to diabetes and other prionopathies (54). Such disorders are characterized by the formation and deposition of insoluble amyloid fibrils with a highly ordered cross-β sheet structure, mainly in the extracellular spaces of affected organs and tissues. The oligomers and, probably, the misfolded protein may exert toxic effects, impairing cell function and reducing cell viability in target organs.

The idea that infection can generate cytotoxic molecules with prion-like activity, or more specifically amyloids, is not entirely new. Alois Alzheimer, the man credited with identifying the disease that is most popularly connected to β-amyloids (Aβ), also considered a role for infection when considering its pathogenesis (55). This construct for amyloid pathology has evolved into what is known as the "infection hypothesis", a construct that has traditionally received little attention. After decades of investigation, heightened interest has evolved toward this age-old theory (55, 56). Empirical backing for the infection hypothesis of amyloidosis was recently raised when a preclinical study demonstrated that neurological impairment and EOD in survivors of critical illnesses might be related to Aβ and tau oligomer formation, particularly in patients with nosocomial, bacterial pneumonia (57). It is well established that patients who recover from pneumonia subsequently have elevated rates of mortality after hospital discharge, often attributed to secondary EOD (57–59). Neurological dysfunction and declines in cognitive function are also frequently observed in survivors of such critical illnesses as sepsis and pneumonia (60).

In an attempt to elucidate this phenomenon and partially explain the long-term effects that have been reported to occur in various organs after pneumonia, Balczon and colleagues utilized *Pseudomonas aeruginosa*, a gram-negative opportunistic pathogen and common culprit of nosocomial and ventilator-associated pneumonia, as a model system of infection in isolated rat pulmonary microvascular endothelial cells (PMVEC) (57, 61). Their work reveals that a common infectious bacterium is a trigger for the formation of a long-acting host-derived transmissible toxin—namely, that acute *P. aeruginosa* infection elicits the production of cytotoxic tau and oligomeric Aβ species from pulmonary endothelium (57). Furthermore, they demonstrated that supernatant from PMVECs infected by *P. aeruginosa* could initiate cytotoxicity and cell death in naive PMVECs and neurons and that amyloids were present in these supernatants (57). This may, in part, explain how patients who recover from infection subsequently succumb to secondary organ failure, even after rigorous antibiotic treatment (57). Additionally, these cytotoxic products are detectable in the BAL fluid, plasma, and cerebrospinal fluid (CSF) of patients with bacterial pneumonia, revealing how both peripheral structures and the brain can be affected (57, 62, 63). Furthermore, in *ex vivo* electrophysiology assays, rodent hippocampal slices bathed in CSF of patients with nosocomial pneumonia demonstrated severely impaired or abolished long-term potentiation compared with CSF from uninfected patients (63, 64).

The infection hypothesis is also supported by reports suggesting a viral link to amyloid-related pathologies. Alzheimer's disease offers an interesting and relevant perspective as we consider the theory that viral infections, such as COVID-19, could lead to long-term sequelae through the production of cytotoxic amyloid species because Alzheimer's disease, which is characteristically an amyloid syndrome, has long been suspected of having a viral etiology (55). Whether SARS-CoV-2 can induce the production of amyloids or whether it may induce EOD via other aforementioned mechanisms remain unclear.

Conclusions

We have highlighted potential mechanisms of EOD and long-term morbidity and mortality due to sepsis from COVID-19 infection based, in part, on currently understood models of PICS. These include the pro-inflammatory response, mitochondrial dysfunction, and amyloids as a novel hypothesis. We believe that all of these mechanisms are important and that patients should be followed long-term with samples collected to determine what happens with these cellular mechanisms long-term and how they relate to clinical findings, clinical tests, and imaging. Most work that has been done regarding COVID-19 has focused on acute infection and therapies to maximize patient survival, and rightly so. However, as patients recover from the infection, whether they have been hospitalized, in the ICU or outpatient, they may experience long-term morbidity. Clearly, then, this is an opportunity for us as physicians and scientists to establish long-term observation of the disease via testing (e.g., pulmonary function tests, transthoracic echocardiography, blood tests) and understand the mechanisms of long-term morbidity in survivors.

A multitude of important questions and critical gaps in knowledge exist that relate to our aforementioned mechanisms. For example, is there a survivorship bias? In other words, do we see these mechanisms in patients with PICS because they survive the acute insult? How are the molecular mechanisms described affected by sedation, COVID-19 therapies (e.g., dexamethasone), or other ICU maladies (or vice-versa)? Additionally, a published paper indicates that the inflammatory cytokine storm is decreased compared with other critical illnesses (65). Does this mean that the cytokine storm is more pronounced in patients that die? Or that patients survive but have a chronic critical illness from an increased, albeit lower concentration, of cytokine release? Finally, it is known that patients with community-acquired pneumonia can have cognitive dysfunction (66). Is there a smaller, more insidious cytokine/metabolic/biomarker effect in patients that were never hospitalized that may never be appreciated until multiple years have passed?

A complimentary example of short- and long-term morbidity was observed in survivors and first-responders of the 9/11 incidents (67). Victims and workers exposed to the dust and airborne toxicants from the initial incident and the subsequent clean-up have significant long-term health consequences that we continue to deal with as a nation to this day. It is possible that we will be fighting the long-term effects of COVID-19 for multiple years to come, and we currently have more questions than answers. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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