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RESPONSE TO COVID-19/COMMENTARY

Management Considerations for the COVID-19 Patient with Severe Disease: a Case Scenario and Literature Review

Meghan A. Kirksey, MD, PhD · Elaine I. Yang, MD · Mausam Kuvadia, MD · Andy O. Miller, MD

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Introduction

COVID-19, the disease caused by the novel coronavirus, SARS-CoV-2, has triggered an ongoing global pandemic the likes of which have not been seen in over 100 years. This virus has proven to be remarkable for its ability to spread quickly through the human population with a broad range of manifestations, from asymptomatic infection to flu-like symptoms, multi-organ failure, and death. The mortality rate of COVID-19 is high compared with illnesses such as the seasonal flu in part because of unpredictable effects on nearly every organ system. Physicians and scientists struggle to understand the pathophysiology of SARS-CoV-2 and determine what treatments might improve outcomes while battling the disease in real time.

In this commentary, we use the framework of a fictional patient to explore common concerns related to patients who require hospitalization for COVID-19, particularly the 20% or so who become critically ill and require transfer to an intensive care unit (ICU). We present evidence available as of July 2020.

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M. A. Kirksey, MD, PhD (✉) · E. I. Yang, MD · M. Kuvadia, MD
Department of Anesthesiology, Critical Care, and Pain Management, Hospital for Special Surgery,
535 East 70th Street,
New York, NY 10021, USA
e-mail: kirkseym@hss.edu

M. A. Kirksey, MD, PhD · E. I. Yang, MD
Department of Anesthesiology, Weill Cornell Medicine,
New York, NY 10065, USA

A. O. Miller, MD
Department of Medicine, Infectious Diseases, Hospital for Special Surgery,
535 East 70th Street,
New York, NY 10021, USA

Composite Case

Mr. Z is a 55-year-old man with a past medical history of well-controlled type 2 diabetes, hypertension, and obesity (body mass index [BMI], 34) who presents to the emergency department complaining of 1 week of worsening exhaustion and body aches and several days of low-grade fever. On physical examination, he is found to be tachypneic, flushed, and confused. His vital signs are temperature, 38°C; blood pressure, 120/74 mmHg; heart rate, 115 beats per min; respiratory rate, 20 breaths per min; and oxygen saturation, 90% on room air. He is placed in an isolation room with 2-L oxygen via nasal cannula, and his oxygen saturation improves to 94%. He calls his family when his COVID-19 nasopharyngeal swab rapid test comes back positive, and he is told that he will be hospitalized for treatment.

If antiviral treatments prove useful in managing COVID-19, their utility will most likely be demonstrated in early stages of infection. While many potential antiviral therapies for COVID-19 are being explored in vitro and in vivo, there are not yet any treatments proven to improve clinical outcomes. In the absence of known alternatives early in the pandemic, hydroxychloroquine (HCQ) was prescribed widely due to its availability, perceived safety, and in vitro ability to inhibit entry of coronaviruses into human cells [40, 77]. However, despite early optimism [21], available data from a randomized controlled trial [66] and large cohorts [22] have failed to show benefit and may indicate harm in hospitalized patients [73]. At this time, neither of the two major treatment guidelines for COVID-19 recommend treatment with HCQ outside of clinical trials [7], with specific recommendations to avoid high-dose treatment (600 mg PO every 12 h or higher). Emerging data [42, 66] suggest no benefit on death rates and increased cardiac and gastrointestinal toxicities with the use of HCQ.

Currently, remdesivir is the only agent available in the USA that has shown strong indications of clinical benefit in an adequately powered randomized clinical trial (RCT). A preliminary report on a large RCT recently stated that a 10-day course of the antiviral agent remdesivir in severely (but not critically) ill COVID-19 patients shortened the duration of illness from 15 to 11 days, without a statistical difference in mortality rate [5].

One RCT comparing 5-day and 10-day treatment durations showed no difference in outcomes between groups [24]. Remdesivir remains available in limited distribution under emergency-use and expanded-access programs while further trials are underway. A recent press release from Gilead Pharmaceuticals, the producer of remdesivir, reports that there has been no indication of increased risk to pediatric, pregnant, or post-partum patients related to use of this agent [23]. Moreover, in a comparative analysis, their results suggest that study patients receiving remdesivir had better recovery and survival rates relative to non-study patients with similar disease severity who received standard of care. However, this analysis was not randomized or controlled.

Multiple agents that show in vitro activity against SARS-CoV-2 are being evaluated for potential efficacy in human disease [25, 58, 78]. One such drug, the HIV protease inhibitor combination lopinavir/ritonavir (LPV/rtv) [12], has failed to show benefit in RCTs in China and the UK [10, 54]. However, in an open-label RCT of 127 patients comparing LPV/rtv with a three-agent cocktail of LPV/rtv, ribavirin, and interferon beta-1b, the triple combination regimen significantly decreased symptoms and duration of viral shedding [32] in patients with mild to moderate disease. Of note, the drug development company Synairgen has recently issued a press release describing a significant reduction in progression to severe disease and enhanced recovery from COVID-19 for inpatients who received inhaled interferon beta in a phase II trial [64]. Thus, it may be that interferon beta was the sole efficacious component of the triple combination treatment described above.

Treatment of COVID-19 with convalescent plasma from recovered COVID-19 patients is being trialed in several countries, including the USA. Large-scale studies are under way [72], though this approach has historically been of questionable benefit in other viral infections [80]. Monoclonal antibodies are being developed to target COVID-19 and may demonstrate clinical benefit in prevention or treatment in the future [74].

Two days after admission, Mr. Z receives convalescent plasma, but his condition continues to worsen. He is now requiring 100% non-rebreather mask to maintain an oxygen saturation of 88%, is breathing at a rate of 30 breaths per min, and cannot complete a sentence due to shortness of breath. His chest X-ray findings have progressed from patchy opacifications in the lung periphery to bilateral diffuse infiltrates. He receives oxygen through a high-flow nasal cannula but continues to deteriorate and is intubated in a negative-pressure room prior to transfer to the ICU.

The management approach to respiratory failure in COVID-19 patients is based primarily on existing treatment of acute respiratory distress syndrome (ARDS). The European-American Consensus Conference (EACC) denotes the following ARDS criteria: acute in onset, ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) (P/F ratio) of less than 200 mmHg, bilateral infiltrates on chest radiograph, and without evidence of left-sided cardiac failure or overload [6]. Assuming a traditional phenotype of low lung compliance and high recruitability, well-supported strategies for ARDS ventilation favor lung protection using low tidal volumes (4 to 6 mL/kg) with high positive end-expiratory pressure (PEEP) values (more than 12 to 18 cmH_2O) [9]. These metrics, known commonly as the ARDSnet protocol, were developed based on the observation that barotrauma and atelectrauma cause release of inflammatory mediators that adversely affect vascular permeability and lung epithelium [55, 70]. In order to achieve these lung-protective conditions, including minimization of FiO_2 to reduce oxidative stress, patients are permitted to be moderately hypercapnic ($pH > 7.25$) and hypoxemic ($PaO_2 > 55mHg$).

In keeping with ARDSnet guidelines, Mr. Z is placed on assist-control volume-cycled ventilation with tidal volumes of 420 mL (based on an ideal body weight of 70 kg), respiratory rate of 20, FiO_2 of 60%, and PEEP of 14. Despite adequate sedation with propofol and hydromorphone infusions, his tachypnea persists, leading to breath stacking on the ventilator. Ventilator synchrony is achieved with neuromuscular paralysis using a cisatracurium infusion. His respiratory rate and PEEP are adjusted as needed to maintain an end inspiratory pressure (a surrogate for alveolar pressure) below 30 to 35 cmH_2O, as has been previously shown to confer a mortality benefit in ARDS [3].

Unlike traditional ARDS, patients with COVID-19-associated ARDS (CARDS) may present with an initial period of hypoxemia with high lung compliance that is poorly responsive to attempts at alveolar recruitment with high PEEP [44]. It appears that this "L-phenotype" is characterized by profound hypoxemia in the absence of substantial pulmonary edema [20] and results from pulmonary shunting from hypoxic vasoconstriction and loss of perfusion regulation [46]. Many COVID-19 patients present to the ICU or progress, however, to a more traditional ARDS phenotype involving fluid-filled alveoli resulting in dramatic increases in lung weight and decreased lung compliance [82]. While deviating from the ARDSnet protocol in patients who appear to be manifesting the "L-phenotype" remains controversial, the complex and dynamic nature of CARDS underscores the need for individualized tidal volume and PEEP selection and continued reassessment of plateau, or end inspiratory, pressures.

Despite optimization of his ventilator settings, over the next 2 days, Mr. Z has a gradual reduction in lung compliance, and his P/F ratio drops to 60 on 100% FiO_2.

Patients in this severe ARDS category are sometimes considered for extracorporeal membrane oxygenation (ECMO) therapy [13], which involves the drainage of deoxygenated blood from the patient via a large venous cannula, pumping it through an external oxygenator, and restoring the oxygenated and decarboxylated blood via a second cannula. ECMO is a resource-intensive therapy with limited availability, requiring cannula insertion by a surgical team, a perfusionist to periodically maintain the external oxygenator, and systemic anticoagulation. There is currently a paucity of medical data to support this therapy in CARDS [31, 39], but many institutions will reserve the use of ECMO on a case-by-case basis for severely ill COVID-19 patients who "have the most to gain" and are "most likely to recover" [71]. A more readily available and well-described adjuvant therapy for ARDS, prone position ventilation, allows

recruitment of the dependent portions of the lung and increases chest wall elastane, leading to reduced alveolar shunting and improved ventilation perfusion ratio [28]. Early reports suggest that CARDS is particularly responsive to pronation [82]. Trials are currently under way to determine if inhaled pulmonary vasodilators such as nitric oxide, iloprost, and epoprostenol are beneficial in CARDS. Such agents may better match ventilation-to-perfusion through selective dilation of pulmonary capillaries adjacent to functioning alveoli [1, 60].

Empiric epoprostenol treatment is initiated and prone positioning is trialed with Mr. Z, despite the technical challenges associated with his respiratory instability and his size. He is place prone on a conventional ICU bed for 16 h/day with the assistance of a dedicated proning team, with special attention to avoid corneal abrasions, facial and pressure ulcers, disconnection from the ventilator, and excessive pressure to the abdomen. The prone positioning protocol is discontinued after 4 consecutive days, when it is noted that his supine P/F ratio improved from a nadir of 60 (7.31/65/60 on FiO_2 100%, PEEP of 18) to 158 (7.35/61/95 on FiO_2 60%, PEEP of 12).

Mr. Z's laboratory values at this time are also notable for a creatinine rise from 2.4 (from 1.4 on admission). Mr. Z had been resuscitated with crystalloid fluids in the initial days after intubation, given high insensible fluid losses from fever and prolonged poor oral intake. As his hemodynamics stabilized and his pulmonary status worsened, gentle diuresis was initiated. A combination of bumetanide and acetazolamide was given, with a goal of daily even fluid balance without increasing vasopressor requirements or metabolic alkalosis from elevated bicarbonate levels. On point-of-care ultrasonography, his inferior vena cava and left ventricular size are consistent with adequate intravascular volume [8], *cardiac contractility is normal, and calculated fractional excretion of sodium is consistent with intra-renal azotemia.*

Optimal volume management in CARDS patients remains a challenge. Conventionally, ARDS patients are treated with conservative fluid therapy targeting low central venous pressures in an effort to reduce ventilator days [79]. However, as a large contingency of COVID-19 patients develops both prerenal azotemia and intrinsic acute kidney injury [17], the benefit of permissive hypovolemia and diuresis has to be carefully weighed against the risk of developing fulminant renal failure requiring continuous hemofiltration, a scarce medical resource. This is especially true in patients with "L-phenotype" ARDS, who do not typically have considerable edema and may be vulnerable to aggressive diuresis [18].

Along with his acute kidney injury, Mr. Z is experiencing high continuous fevers refractory to acetaminophen, with increased metabolic demand (ventilation > 16 L per minute) rendering ventilator weaning difficult [2]. *His vasopressor requirements rise, and his laboratory values reveal rising levels of ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), and D-dimer, consistent with cytokine storm* [68].

COVID-19-specific hyperinflammatory syndrome, caused by the uncontrolled release of cytokines and chemokines by immune effector cells, is implicated in the development of CARDS and multi-organ dysfunction and has a high associated mortality [47]. There are currently no Food and Drug Administration (FDA)–approved therapeutics for the treatment of COVID-19 cytokine storm. However, drug options such as interleukin inhibitors [15], antivirals, interferons (IFN), and cytokine filters [63] are under investigation, many with considerable promise [36, 51] Despite this, widespread treatment of COVID-19 patients with immunologic agents and/or corticosteroids [59] without consideration of the clinical picture may also lead to undue immunosuppression and reduce the patients' ability to combat bacterial and/or fungal superinfections. Preliminary non-peer-reviewed evidence suggested that increased risks of secondary infections may be of particular concern among COVID-19 patients receiving tocilizumab [35] and steroids. In addition, while a recent study of COVID-19 patients requiring mechanical ventilation showed decreased mortality rates in those receiving tocilizumab, rates of bacterial superinfection in this group were also significantly higher. Similarly, preliminary results suggest that dexamethasone administration is associated with decreased mortality in patients requiring supplemental oxygen or mechanical ventilation; however, there was no benefit and possible harm among those not requiring oxygen [57]. Thus, immunomodulatory agents should be carefully chosen on a case-by-case basis by the treating intensivist and infectious disease consultant.

Mr. Z receives tocilizumab, an interleukin-6 blocker, and rapidly defervesces, with resolution of hypotension and improvement of inflammatory markers. His renal function slowly improves. However, now, 2 weeks after admission, fever returns and laboratory values are notable for an increase in procalcitonin (0.2 to 1.5 ng/mL) and leukocytosis (white cell count, 4.7 to 14.2 K/μL) suggestive of bacterial superinfection. Tracheal aspirate cultures grow pansensitive Klebsiella pneumoniae, and he is treated for ventilator-associated pneumonia.

Patients presenting to hospitals with lower-respiratory infection are often treated with empiric antibiotics, with unclear benefit in COVID-19; they can often be stopped once the COVID-19 diagnosis is made as bacterial coinfection on presentation and the absence of leukocytosis is uncommon [34]. However, secondary infections remain an important source of morbidity in hospitalized COVID-19 patients, particularly the critically ill. Standard of care practices to avoid nosocomial infection in COVID-19 patients in the ICU are made more difficult by the infectious risks posed to healthcare workers and the atypically long ICU stays required for these patients. Bacteremia was present in 12% of intubated patients in a recent large series of cases from New York City [26], the US epicenter in the weeks of the COVID-19 pandemic. An important component of hospital care of patients with COVID-19 is management of bacterial and fungal complications such as central venous catheter infections, ventilator-associated pneumonias, and infected pressure ulcers. Prompt recognition of and response to incipient sepsis and judicious use of antibiotics in consultation with infectious disease specialists are essential.

Mr. Z has now had his central venous catheter (CVC) in place for several weeks and will continue to need a CVC for medication infusions and laboratory blood draws. In order to prevent a central line–associated blood stream infection (CLABSI), the decision is made to replace the CVC. While doing so, his clinicians discover a deep venous thrombosis (DVT) on ultrasound.

Coagulation abnormalities and thromboses are known sequelae of COVID-19. Reports have shown that pulmonary embolism and DVT are the most frequent thrombotic complications; however, myocardial infarction, ischemic stroke, and mesenteric ischemia have been seen as well [30, 37]. Of note, most patients have not demonstrated bleeding tendencies, even in the setting of disseminated intravascular coagulation (DIC), but rather remain in a hypercoagulable and prothrombotic state. ICU patients are already at a high risk of DVT due to prolonged immobilization, mechanical ventilation, and the use of CVCs, but COVID-19 may pose even higher risk. Studies have shown that profound inflammation and release of cytokines, such as interleukin-6, are correlated with a procoagulant state. In addition, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors on endothelial cells causing cell dysfunction, which can lead to a prothrombotic environment [14, 56]. One French hospital found thrombotic complications in 42.6% of ICU patients, 25% of whom had pulmonary embolism [30]. The same hospital found that out of their 29 patients receiving continuous renal replacement therapy (CRRT), 28 (96.6%) experienced circuit clotting [30]. A study in the Netherlands found that 31% of COVID-19 ICU patients had thromboembolic events despite having standard doses of thromboprophylaxis, with a similar study from the USA reporting an incidence of 28% [37, 41]. Finally, an Austrian study reported that 100% of COVID-19 patients examined on autopsy had evidence of pulmonary artery thrombosis, despite 91% having received anticoagulation [38].

Patients with COVID-19 should have coagulation testing, including D-dimer, fibrinogen, partial thromboplastin time (PTT), prothrombin time, and platelet count, performed on admission. Several studies from Wuhan have shown a correlation between D-dimer and ICU admission and mortality risk [65, 75]. Though coagulation markers may be increased initially due to inflammation, trending these values may help diagnose venous thromboembolism (VTE) as well as DIC. Unfortunately, imaging may not always be feasible due to patient positioning, clinical status, and potential staff exposure. Diagnosis and treatment of VTE may require appropriate clinical suspicion especially in the context of worsening oxygenation, right heart strain, and/or increasing vasopressor requirements; empiric treatment may be warranted.

Currently, the National Institutes of Health, the International Society of Thrombosis and Hemostasis (ISTH), and many institutional guidelines recommend VTE prophylaxis for all COVID-19 patients including non-critically ill patients [16]. Pharmacologic prophylaxis with standard dosing of low molecular weight heparin (LMWH) is preferred due to its infrequent dosing and minimal blood draws. In the event of a contraindication, such as renal failure or heparin-induced thrombocytopenia, patients can be placed on unfractionated heparin or non-heparin alternatives. If the patient is not a candidate for systemic anticoagulation, mechanical prophylaxis may be used instead [16, 44, 67]. Of note, given the accumulating evidence that COVID-19 patients are prone to thrombosis even with standard prophylaxis, many clinicians are opting for pre-emptive intermediate- or therapeutic-dose anticoagulation. In patients with confirmed or suspected VTE, recommended treatment includes therapeutic-dose LMWH or an unfractionated heparin drip. As PTT may be unreliable in this population, anticoagulation may need to be monitored by anti–factor Xa levels [45]. There have been case reports of suspected VTE being treated with fibrinolytics, such as tissue plasminogen activator (tPA), although this therapy is still under investigation [76]. Some hospital protocols have incorporated the use of the factor Xa inhibitor apixaban into treatment protocols with anecdotal reports of success in patients when ECMO and CRRT circuits become clotted even with standard anticoagulation regimens.

Treatment was initiated with therapeutic-dose LMWH for Mr. Z's confirmed DVT. His clinical status is much improved. With renal function normalized, he is hemodynamically stable, spontaneously breathing with minimal ventilatory support, and requiring minimal sedation for comfort. However, on wakeup tests, while he spontaneously moves his extremities and responds weakly to noxious stimuli, he does not track with his eyes, attempt purposeful movement, or follow commands.

Discerning the etiology of neurological derangements in ICU patients can be challenging, as prolonged mechanical ventilation and sedation with benzodiazepines and opioids often lead to delirium, which masks underlying neuropathology [50, 52]. Likewise, though the respiratory system is most commonly affected, neurologic manifestations can range from headaches and loss of smell or taste to generalized myopathy, altered mental status (AMS), and stroke [48]. One study from Wuhan, China, showed that neurologic symptoms, which developed more readily in those with severe infection, were seen in 36.4% of patients [43].

The mechanism of AMS in the COVID-19 population may be multifaceted, with effects both on the cerebral vasculature and neuronal cells. At the vascular level, hemorrhagic and ischemic strokes have been reported, potentially related to hypercoagulability as well as direct effect of SARS-CoV-2 on vascular ACE2 receptors, which can lead to extreme hypertension [11, 81]. Furthermore, COVID-19 patients with severe disease are more likely to have comorbidities that are independent risk factors for cerebral vascular accidents, putting them at even greater threat. At the neuronal level, SARS-CoV-2 can cause neuronal damage and cell apoptosis [4, 62], resulting in encephalopathy or viral encephalitis [19, 29, 49, 53]. Other potential mechanisms of injury include retrograde neuronal transport and an exaggerated immune response, which could also indicate that the virus is neurotropic [81].

Though central nervous system manifestations seem to be more common, patients may also develop peripheral

neuropathies such as Guillain-Barré syndrome (GBS), an immune-mediated, demyelinating disorder of the peripheral nerves that can progress to tetraparesis or tetraplegia [61, 69]. Though the exact mechanism by which GBS occurs is unknown, the cytokine storm induced by COVID-19 likely plays a role [61]. Cytokine storm may also precipitate skeletal muscle injury, demonstrated by commonly reported symptoms of myalgias and arthralgias [27] as well as elevated creatine kinase (CK) and LDH [43]. This should be distinguished from rhabdomyolysis, which can also present as myalgia and fatigue but requires a different treatment [33]. In such cases, a workup including CK and LDH levels, renal and hepatic function, and urinalysis may be warranted. Peripheral neuropathy and skeletal muscle injury should be suspected if patients have new onset weakness or neuropathic pain.

After two consecutively negative viral swabs, Mr. Z undergoes a brain MRI that shows no notable abnormalities. Given his prolonged intubation, persistent weakness, and poor neurologic exam, a tracheostomy is performed, a percutaneous endoscopic gastrostomy tube is placed for continued nutrition, and he is transferred to the step-down unit for further management. After several weeks of rehabilitation, his strength improves, and he gradually becomes more interactive. With great fanfare from his care team, he is discharged from the hospital to a sub-acute rehabilitation facility to continue his recovery.

COVID-19 is a devastating disease that over the course of 6 months progressed from the first described case to causing more than 175,000 deaths in the USA by August 2020 and more than800,000 deaths worldwide, with no signs of abating. The clinical narrative described above is a composite assembled from common experiences with COVID-19 patients who develop disease severe enough to require ICU care. The trajectory of each patient is unique, with some undergoing acute catastrophic collapse leading to death in the first several days and others going on to apparent full recovery after resolution of single-organ respiratory failure. Unfortunately, the array of challenges presented here is not uncommonly confronted in a single COVID-19 patient, resulting in ICU stays extending from weeks to months. We are hopeful that further study of the natural history and pathogenesis of this novel virus and development of curative and preventative strategies will allow us to curtail this pandemic, prevent further death, and allow this grave new disease to be relegated, along with the 1918 influenza pandemic, to history.

Compliance with Ethical Standards

Conflict of Interest: Meghan A. Kirksey, MD, PhD; Elaine I. Yang, MD; Mausam Kuvadia, MD; and Andy O. Miller, MD, declare that they have no conflicts of interest.

Human/Animal Rights: N/A.

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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