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Patients admitted to the ICU with critical COVID-19 often require prolonged periods of mechanical ventilation. Difficulty weaning, lack of progress, and clinical deterioration are commonly encountered. These conditions should prompt a thorough evaluation for persistent or untreated manifestations of COVID-19, as well as complications from COVID-19 and its various treatments. Inflammation may persist and lead to fibroproliferative changes in the lungs. Infectious complications may arise including bacterial superinfection in the earlier stages of disease. Use of immunosuppressants may lead to the dissemination of latent infections, and to opportunistic infections. Venous thromboembolic disease is common, as are certain neurologic manifestations of COVID-19 including delirium and stroke. High levels of ventilatory support may lead to ventilator-induced injury to the lungs and diaphragm. We present diagnostic and therapeutic considerations for the mechanically ventilated patient with COVID-19 who shows persistent or worsening signs of critical illness, and we offer an approach to treating this complex but common scenario.
Physicians may face uncertainty concerning why a critically ill patient with COVID-19 further deteriorates, and current evidence does not provide actionable guidance as to appropriate diagnostics or interventions under such conditions. Nonetheless, insights can be gleaned by examining the large corpus of observational and interventional studies performed in hospitalized patients with COVID-19, as well as the smaller number of studies with a specific focus on the critically ill. We present an overview of the diagnostic and therapeutic considerations relevant to this common but challenging scenario. Although our focus is on those conditions that are specifically associated with critical COVID-19, it is also important to consider the usual complications encountered during mechanical ventilation in general.

**Critical COVID-19 Disease Trajectory**

Critical COVID-19 can be characterized by different illness phases (Fig 1). Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection is initially met with an interferon-mediated immune response aimed at clearing the virus, which generates the predominant symptoms seen in early disease including fever, myalgias, and fatigue. Impaired interferon signaling is associated with progression to severe or critical disease, suggesting that failure to mount an effective immunologic response to the initial infection may be a risk factor for critical illness.

A second phase of COVID-19 is seen in the subset of patients who, following the initial viral prodrome, show worsening signs and symptoms consequent to an exaggerated inflammatory response affecting the alveolar epithelial cells. Typically classified as severe COVID-19, patients in this second phase develop dyspnea, hypoxemia, and patchy infiltrates on lung imaging, and require respiratory support in the form of supplemental oxygen. Those who go on to develop ARDS, sepsis, or the need for life-sustaining treatment are said to have critical COVID-19. Antiinflammatory treatments including corticosteroids and IL-6 receptor antagonists (IL-6RAs) have shown efficacy at this stage, with salutary effects most notable in those with critical disease.

Among these critically ill patients, there are some whose condition does not improve despite initial ICU management. In this later phase of COVID-19, viral

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**Figure 1** – The course of critical COVID-19 and its potential complications. (1) Initial infection leads to viral replication; impaired viral clearance may hasten the onset of severe and critical COVID-19. (2) Inflammation may recur after completion of antiinflammatory treatments, or may persist despite these, possibly leading to fibroproliferative ARDS (3). (4) Decreases in immune function—whether due to COVID-19 directly or to antiinflammatory treatments—can cause susceptibility to infection including ventilator-associated pneumonia. (5) Antiinflammatories may also precipitate dissemination of latent infections such as Strongyloides. (6) Later in the course of critical COVID-19, prolonged immunosuppression may lead to opportunistic infections including Pneumocystis jiroveci pneumonia and COVID-associated pulmonary aspergillosis. (7) Neurologic sequelae of COVID-19 may also contribute to worsening, including delirium, which is common and may occur at any time during the acute infection. (8) Stroke has been reported as a consequence of COVID-19, and patients requiring prolonged mechanical ventilation may develop ICU-acquired weakness (9). (10) COVID-19 increases the risk of venous thrombosis, including DVT and pulmonary embolism. (11) Prolonged mechanical ventilation, high levels of ventilatory support, and high respiratory drive may contribute to ventilator-induced injury of the lungs and diaphragm. (12) It is hoped that optimal treatment and supportive care lead to an eventual resolution of derangements in inflammation, immunity, and neurologic function; however, it remains uncertain whether in some cases these persist long term.
replication has ceased, and inflammation may be abating, but critical illness persists or even worsens. This is a common but challenging scenario in the ICU. Diagnostic possibilities relate to persistence of inflammation, the development of coinfections, VTE, and neurologic manifestations of COVID-19, including delirium and, less commonly, stroke (Table 1). Given the intensity and duration of mechanical ventilation often used in COVID-19, concerns related to severe ARDS—including ventilator-induced lung and diaphragm injury, as well as ICU-acquired weakness—must also be considered.

### TABLE 1 Diagnostic and Therapeutic Considerations for Potential Complications From Critical COVID-19

| Complication                        | Clinical Suspicion                                                                 | Testing                                      | Treatment                                      |
|-------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------|
| Persistent inflammation             | Worsening immediately on stopping corticosteroids; persistently elevated inflammatory markers (eg, C-reactive protein) | None                                         | Increased dose of corticosteroid; increased duration of treatment; additional dosing of IL-6RA |
| Bacterial infection; VAP            | New fever; worsening hypoxemia; hypotension; leukocytosis; radiographic changes    | Sputum culture; chest imaging; blood cultures | Empiric or targeted antibiotics (empiric antibiotics should account for local flora and antibiogram, and should cover gram-negative bacteria, eg, late-generation cephalosporin) |
| Opportunistic infection             | High degree of clinical suspicion                                                 | Chest imaging (ideally cross-sectional); obtaining lower respiratory tract samples (under appropriate infection control precautions) for testing for PJP, direct microscopy, culture, Aspergillus PCR, galactomannan | Pathogen-directed treatment                     |
| Unmasking latent infection          | Risk factors for Strongyloides infection; initiation of corticosteroids or other immunosuppressants | Eosinophil count; Strongyloides serology; stool testing (all low sensitivity) | Ivermectin, 200 µg/kg × 1 dose                 |
| VTE                                 | Limb swelling; tachycardia; worsening hypoxemia                                   | Leg Doppler ultrasound; CT pulmonary angiogram (D-dimer not reliable) | Systemic anticoagulation when VTE is diagnosed; consider monitoring dose with anti-Xa levels |
| Delirium                            | Inattention, confusion, somnolence, agitation, fluctuating course                  | Validated tool (eg, CAM-ICU or ICDSC)        | Avoid benzodiazepines; frequent reorientation; family presence at bedside when possible |
| Stroke                              | Unilateral weakness, obtundation, acute changes on neurologic examination         | CT scan, MRI. Consider venography sequences for possible cerebral venous sinus thrombosis | As per usual stroke treatment                  |
| Neuromuscular weakness              | Difficulty weaning; poor functional status                                        | Diaphragm ultrasound, VC, MIP, MEP; EMG, NCS | Possible benefit from early mobilization or inspiratory muscle training |
| Ventilator-induced lung injury      | High airway pressures, radiographic signs of barotrauma (pneumomediastinum, pneumothorax, subcutaneous emphysema) | Monitoring of airway pressures; imaging; esophageal pressure monitoring | Lung-protective ventilation (lower tidal volume to maintain driving pressure < 15 cm H2O); permissive hypercapnia; ECLS |

CAM-ICU = confusion Assessment Method for the ICU; ECLS = extracorporeal life support; EMG = electromyography; ICDSC = Intensive Care Delirium Screening Checklist; IL-6RA = IL-6 receptor antagonist; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; NCS = nerve conduction studies; PCR = polymerase chain reaction; PJP = Pneumocystis jirovecii pneumonia; VAP = ventilator-associated pneumonia; VC = vital capacity.
Inflammation

Although there has been debate concerning whether critical COVID-19 is a hyperinflammatory syndrome, some degree of inflammation is believed to be an important component of the pathophysiology. Corticosteroids are indicated for patients with moderate to severe disease, defined by the need for supplemental oxygen or more advanced forms of respiratory support. Perhaps the most compelling evidence for the use of corticosteroids in COVID-19 comes from the United Kingdom-based RECOVERY (Randomised Evaluation of COVID-19 Therapy) platform, which randomized more than 6,000 patients with COVID-19 to treatment arms that either did or did not include a regimen of 6 mg of dexamethasone daily, given for up to 10 days. Patients treated with dexamethasone had improved survival compared with those without. This largest study used dexamethasone; however, various other corticosteroid regimens have shown benefit in COVID-19. This includes different formulations of corticosteroid (eg, hydrocortisone), higher doses, or longer term regimens in which treatment is given for more than 7 to 10 days.

In addition, patients may have also received an IL-6RA such as tocilizumab or sarilumab, which have also been shown to be effective in severe or critical COVID-19. Here too the optimal timing of initiation and dosing are unclear, as some patients enrolled in clinical trials received a second dose, and the extent to which real-world dosing mirrors the dosing in clinical trials is unknown.

Taken together, these findings suggest that by the time of admission to ICU, patients with critical COVID-19 will have likely received various antiinflammatory treatments, with variable rates of residual inflammation persisting. Clinical deterioration should therefore prompt the consideration of additional antiinflammatory therapies, once infection is ruled out or treated. Potential measures include adding or giving a second dose of IL-6RAs, or resuming, increasing the dose of, or extending the duration of corticosteroid treatment; however, data from randomized studies evaluating either approach are currently lacking. The extent to which markers of inflammation such as serum C-reactive protein are helpful in guiding antiinflammatory interventions also remains unclear.

In its earliest phases, COVID-associated ARDS is an inflammatory condition. However, as ARDS progresses, inflammation gives way to fibrosis, which in some cases can be severe, resulting in persistent impairments in gas exchange, increased work of breathing, and prolonged mechanical ventilation. Although classified as a "late" complication, there are likely elements of fibroproliferation that start even in the earlier phases of ARDS. In one study, lung biopsy evidence of fibrosis was evident in more than one-half of patients with ARDS a median of 11 days after the initiation of mechanical ventilation. The development of fibrosis or chronic pulmonary parenchymal damage is readily diagnosed on CT imaging, which may reveal interstitial fibrosis, traction bronchiectasis, cystic changes, and hydropneumothoraces.

Therapeutic targets for fibroproliferative ARDS likely overlap to some degree with earlier, predominantly inflammatory, ARDS. Some have suggested a role for prolonged corticosteroid administration, with a slow taper aimed at regulating the host immune response; however, data supporting this approach are limited. There are studies evaluating the role of antifibrotic agents in patients with COVID-19; however, none of these has yet demonstrated efficacy when used in this setting. Lacking specific management options, physicians caring for patients with COVID-19 requiring prolonged mechanical ventilation are most often left hoping time leads to sufficient lung function recovery to facilitate liberation. In patients who develop nonresolving pneumonia with severe permanent destruction of lung tissue, cases of lung transplantation have been reported at expert centers and in select patients; however, this intervention requires further study, and access remains a significant limitation.

The above considerations must also be balanced by the recognition that corticosteroids are not without potential adverse effects, including immunosuppression, metabolic disturbances, and neuromuscular weakness. Although some evidence supports the use of a prolonged course of corticosteroids in ARDS, treatment initiated late in the course of ARDS may worsen outcomes.

Secondary Infection

Ventilator-Associated Pneumonia

Patients admitted to the ICU with COVID-19 may be at increased risk of ventilator-associated pneumonia (VAP), with some reported rates as high as 50%, more than twice that of intubated patients without COVID-19. The onset of VAP usually occurs between 1 and 2 weeks after intubation, and is commonly due to...
organisms such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella* species. High rates of resistant gram-negative species have also been reported, and likely reflect the hospital and community burden of drug-resistant organisms. Physicians caring for critically ill patients with COVID-19 must have a high suspicion for VAP and be prepared to add antibacterial agents in the event of clinical deterioration.

Despite the high rates of VAP seen in intubated patients with COVID-19, there is currently no evidence to support a strategy of prophylactic antibiotics. VAP prevention should focus on measures previously shown to be effective, including elevating the head of the bed, and using a closed suctioning system. VAP should be suspected in the setting of worsening respiratory status, fever, increased sputum purulence, leukocytosis, and new or evolving infiltrates on radiographic imaging, and may be identified using structured tools such as the Clinical Pulmonary Infection Score. Empiric management should be tailored to local flora, but should cover gram-negative bacteria, and possibly resistant gram-negative bacteria, until respiratory cultures are available to guide targeted prescribing. VAP may also progress to sepsis and septic shock, which may necessitate a revisiting of adjunctive therapies including corticosteroids and vasopressors.

**Reactivation of Latent Infection**

The potent antiinflammatories used to treat severe COVID-19 may exert a strong immunosuppressive effect, with the potential to cause reactivation of latent or dormant infections. A recently highlighted concern is that of *Strongyloides* hyperinfection syndrome among patients with severe COVID-19 receiving corticosteroids and/or IL-6RAs. *Strongyloides stercoralis* is a parasitic nematode estimated to infect between 30 and 100 million people worldwide, mostly in tropical and subtropical regions. It is often asymptomatic in adults and can persist for decades but can become disseminated in the setting of immunocompromise, including from the administration of corticosteroids. *Strongyloides* hyperinfection and dissemination are associated with high mortality rates, frequently greater than 70%.

Patients at highest risk of latent *Strongyloides* infection include those from West Africa, South and Southeast Asia, South America, and the Caribbean, in particular migrants, refugees, and those with a history of rural travel in endemic regions. Hyperinfection manifests as fever, respiratory symptoms, and GI symptoms, and can be associated with gram-negative sepsis. *Strongyloides* infection may be suspected on the basis of peripheral eosinophilia, and can be demonstrated by positive stool testing or serology; however, these methods lack sensitivity, and eosinophilia is frequently absent in *Strongyloides* hyperinfection or disseminated disease. Treatment algorithms have recently been proposed for severely ill patients with COVID-19 that mostly favor empiric therapy for high-risk patients with a single dose of ivermectin (200 μg/kg), a medication that is inexpensive, widely available, and generally well tolerated. Ivermectin has been proposed as a possible treatment for COVID-19 itself; however, current data are insufficient to support its use outside of clinical trials. Although published reports are currently lacking, the reactivation of latent TB poses a similar concern for patients from endemic regions who are receiving corticosteroids for severe COVID-19.

**Opportunistic Infection**

Although only a small minority of patients with COVID-19 admitted to the ICU may have an underlying immunodeficiency, some elements of immune dysfunction are likely universal in the later stages of this condition. COVID-19 itself causes a relative lymphopenia, and therapies such as corticosteroids and IL-6RAs further impair immune function. Invasive support devices such as endotracheal tubes and central venous catheters further predispose patients to new infections. Patients may therefore be at increased risk of opportunistic infections, especially in the weeks after initial ICU admission.

Data regarding opportunistic infection in COVID-19 are sparse, but hint at the presence of clinically important immunosuppression. One French study of 108 critically ill patients with COVID-19 found that *Pneumocystis jirovecii* was detected in 9% of respiratory tract specimens, 74% of which were BAL samples. All but three patients were intubated at the time of ICU admission, and only 10% had underlying immunocompromise. Whether the presence of *P. jirovecii* was indicative of infection in these cases is less clear. Of the patients positive for *P. jirovecii*, more than two-thirds had not received corticosteroids before sample collection, suggesting that the incidence may in fact be higher still, now that corticosteroids and IL-6RAs have become a mainstay of therapy for severe COVID-19. Some case reports describe patients with SARS-CoV-2 and *P. jirovecii* coinfection who responded favorably to treatment with trimethoprim-sulfamethoxazole.
SARS-CoV-2, like other respiratory viruses, causes direct damage to airway epithelium, leaving patients vulnerable to invasive fungal pneumonia. COVID-associated pulmonary aspergillosis (CAPA) has been characterized in a number of cohorts, with estimates of the incidence ranging from 10% to 35%, and an overall mortality rate approaching 50%. A consensus statement on CAPA from medical mycology groups has defined criteria for possible, probable, and proven CAPA, based on the presence of clinical signs including refractory fever and hemoptysis, infiltrates or cavitating lesions on lung imaging, and microbiology or histology suggesting the presence of fungal elements. The mainstay of therapy is voriconazole.

The diagnosis of both P. jirovecii and CAPA benefits from the testing of respiratory samples obtained by bronchoscopy. Because this is considered an aerosol-generating medical procedure, many centers may exercise caution with its use in critically ill patients with active COVID-19, given concerns of potential spread, particularly to health care workers. Opportunistic infections tend to occur beyond the first week of ICU admission, which itself tends to occur beyond the first week of COVID-19 symptoms. The extent to which patients at this late stage of disease remain infectious is not entirely known, and likely varies among patients and according to the presence of underlying immunosuppression. Time- and testing-based criteria have been proposed to inform infection control decisions concerning discontinuing droplet isolation.

Rhino-orbital-cerebral mucormycosis and pulmonary mucormycosis in the setting of COVID-19 have been described in a number of case reports, particularly from India. COVID-19 patients with diabetes—a known risk factor for mucormycosis—may be particularly vulnerable, with the risks further increased by the use of immunosuppressive treatments for COVID-19. Further observational and epidemiologic studies are needed to better characterize these risks.

Thrombosis

COVID-19 is associated with disorders of coagulation, evidenced by elevated plasma D-dimer levels, as well as autopsy studies showing fibrin thrombi within small vessels and capillaries. Venous thrombosis is common in patients with COVID-19 admitted to the ICU, with reported incidence rates as high as 15% to 28% from recent systematic reviews. In hospitalized COVID-19 patients with VTE, DVT appears to be more common than pulmonary embolism (PE), whereas isolated subsegmental PE is uncommon.

Most patients with PE have some degree of hypoxia due to ventilation-perfusion mismatch and intrapulmonary shunting, and thus a new or previously undiagnosed PE could be a contributing factor in the clinical deterioration of a critically ill patient with COVID-19. Patients diagnosed with DVT who have not undergone imaging tests for PE may well have pulmonary embolic involvement; either DVT or PE is an indication for systemic anticoagulation. There is no direct randomized trial evidence comparing anticoagulants in this population. In observational studies, low-molecular-weight heparins such as enoxaparin have been associated with decreased mortality in COVID-19 compared with unfractionated heparin, as well as compared with no anticoagulation. Heparin may have other beneficial effects in COVID-19 beyond its anticoagulant properties through antiinflammatory effects and reduction of viral cellular entry.

Despite increased risk of VTE in COVID-19 there is currently no randomized controlled trial-derived evidence to support the use of intermediate or therapeutic anticoagulation in patients with severe COVID-19 without confirmed VTE, and in critically ill patients prophylactic dose anticoagulation is recommended. The INSPIRATION (Intermediate-Dose vs Standard Prophylactic Anticoagulation and Statin vs Placebo in ICU Patients With COVID-19) randomized controlled trial compared the effects of intermediate dose vs standard dose thromboprophylaxis with enoxaparin on the composite outcome of thrombosis, need for extracorporeal membrane oxygenation, and mortality and found no differences between groups, even with stratification by disease severity. The observational study STOP-COVID (Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19) found that therapeutic anticoagulation was not associated with improved survival among critically ill patients with COVID-19.

In terms of interventional studies, a multiplatform trial (REMAP-CAP [Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia], ATTACC [Antithrombotic Therapy to Ameliorate Complications of COVID-19], and ACTIV-4 [Accelerating COVID-19 Therapeutic Interventions and Vaccines 4]) compared routine therapeutic anticoagulation with prophylaxis in critically ill patients with COVID-19. Therapeutic anticoagulation did not result in improved survival or number of days without organ support, as compared to usual-care prophylaxis.

There have been reports of heparin resistance in patients with COVID-19, which may be explained by several
prothrombotic mechanisms induced by SARS-CoV-2. These include high factor VIII and fibrinogen levels, low antithrombin levels, and thrombotic microangiopathy due to von Willebrand factor multimers and ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type-1 repeats) deficiency.\textsuperscript{46-48} The partial prothrombin time can be affected by an increased factor VIII level, making the patient appear to be therapeutically anticoagulated while failing to achieve inhibition of activated factor X.\textsuperscript{49} Anti-Xa monitoring improves heparin effectiveness when used in critically ill patients and should be considered in the COVID-19 population in particular.\textsuperscript{50}

The CHEST guideline and expert panel report recommends anticoagulation therapy for a minimum duration of 3 months for patients with COVID-19 diagnosed with a proximal DVT or PE, although there are no randomized studies to support this.\textsuperscript{51}

Neurologic Sequelae

\textbf{Delirium and Coma}

Impaired consciousness may be an additional barrier to weaning from mechanical ventilation in critically ill patients with COVID-19. Delirium is an acute change in level of consciousness, characterized by an impairment in attention and fluctuating course. The rate of delirium in critically ill COVID-19 has been difficult to summarize, but by most estimates is higher than in the general ICU population. One of the largest multicenter studies assessed more than 2,000 critically ill patients with COVID-19 from 14 countries\textsuperscript{52} and found that 55\% of them experienced delirium, with a median duration of 3 days. Importantly, coma (defined as a Richmond Agitation-Sedation Scale score of $-4/-5$, or Glasgow Coma Scale score $<8$) was also common, with a median duration of 10 days. Higher severity of illness, benzodiazepine and opioid infusions, and older age were risk factors for impaired consciousness. Family presence (either in person or virtual) was associated with a reduced risk of delirium.

\textbf{Stroke}

Whereas delirium is a common complication of critical COVID-19, acute ischemic stroke is a rare but serious neurologic event that may underlie a patient’s depressed level of consciousness and inability to wean from mechanical ventilation. Rates of ischemic stroke in critically ill patients with COVID-19 range from 2.1\% to 7\%.\textsuperscript{53,54} When assessing patients for whom a complete neurologic examination is challenging due to the severity of illness, it may be reasonable to perform cerebral imaging (eg, a CT scan) for patients when depressed consciousness is a barrier to liberation from mechanical ventilation.

\textbf{ICU-Acquired Weakness}

Mechanically ventilated patients with COVID-19 are at risk of critical illness neuropathy and critical illness myopathy, conditions that are often combined into the single syndrome of ICU-acquired weakness (ICUAW). Risk factors for ICUAW include high-dose steroids, high severity of illness, and possibly the use of neuromuscular blockers, all of which are seen in patients with critical COVID-19.\textsuperscript{55} Few data exist on the prevalence of ICUAW in patients with COVID-19. A recent single-center prospective observational study compared electrophysiologic evidence of both critical illness neuropathy and myopathy, although there seemed to be a slightly higher prevalence of critical illness neuropathy in patients with COVID-19.\textsuperscript{56} To determine whether ICUAW is contributing to difficulties in weaning from mechanical ventilation, bedside assessments of parameters such as vital capacity, maximum inspiratory pressure, and maximum expiratory pressure may be helpful. A 20/30/40 rule of thumb (reflecting a vital capacity $>20$ cm$^3$/kg, maximum inspiratory pressure $\geq30$ cm H$_2$O, and maximum expiratory pressure $>40$ cm H$_2$O) has been suggested when considering intubation for a patient with respiratory failure due to neuromuscular weakness (eg, Guillain-Barré syndrome).\textsuperscript{57} It would be reasonable to consider values at or below these criteria as indicative of neuromuscular weakness contributing to the difficult weaning of a critically ill patient with COVID-19. Although early mobilization makes intuitive sense as a treatment for ICUAW, a beneficial effect was not seen in a recent systematic review and meta-analysis.\textsuperscript{58}

\textbf{Ventilator-Induced Injury to Lungs and Diaphragm}

Given the severity and duration of respiratory failure commonly encountered in critical COVID-19, it is not surprising that injury to the lungs is common, with an incidence of overt barotrauma in excess of 10\%.\textsuperscript{59} Many
patients with COVID-19 undergoing mechanical ventilation have been shown to have relatively low lung compliance and high airway pressures, which can lead to regional lung overdistention, and a cascade of pathophysiologic factors associated with ventilator-induced lung injury (VILI). Although pneumomediastinum and pneumothorax may be obvious manifestations, the clinical and radiographic findings of VILI may simply mimic those of the underlying ARDS and present as worsening or nonresolving disease. Mechanical ventilation can also induce diaphragm dysfunction, which is also associated with difficulty weaning and prolonged ICU stay.61

The mainstay of preventing and treating VILI is lung-protective ventilation. Although there has been some discussion that ARDS due to COVID-19 is a pathophysiologically distinct entity,62,63 the general principles of ARDS management remain the mainstay of treatment in COVID-19 as well.64 Tidal volumes should be kept low enough to maintain driving pressure below 15 cm H2O,65 with a target plateau pressure of < 30 cm H2O. High driving pressures (tidal volume/respiratory system compliance) have been associated with an increased risk of mortality in ARDS.66 Permissive hypercapnia may be useful in limiting airway pressures and reducing injurious forces. A recent metatrical suggests that awake prone positioning of patients with COVID-19 requiring high-flow nasal cannula oxygen reduced the incidence of treatment failure, defined as intubation or death within 28 days.67 In intubated patients with severe ARDS, prone positioning has been shown to reduce mortality.68 Optimal lung protection can be achieved through the use of venovenous extracorporeal membrane oxygenation, with one recent meta-analysis of 1,896 patients suggesting that better outcomes were associated with younger age.69

Because many patients with COVID-19 exhibit extraordinarily high respiratory drive,70 it is important to monitor respiratory effort to avoid excessive lung-distending pressures, even when airway pressure is low.71 This can be accomplished by means of minimally invasive and noninvasive maneuvers including esophageal manometry, diaphragm ultrasound, and monitoring of airway occlusion pressures.71-73

Diaphragm muscle atrophy is associated with poor outcomes in mechanically ventilated patients, and preliminary data suggest a possible association with COVID-19 pneumonia in particular.74-76 Diaphragmatic weakness is readily diagnosed in mechanically ventilated patients, using diaphragm ultrasound and other techniques.77 Inspiratory muscle training can be used to specifically target the diaphragm and respiratory muscles for rehabilitation. Inspiratory muscle training increases respiratory muscle strength and may accelerate liberation from mechanical ventilation, with some preliminary observations suggesting it may improve dyspnea and quality of life for patients with COVID-19 pneumonia when applied in the recovery phase.78

Conclusions
Patients with severe COVID-19 admitted to the ICU are at high risk for prolonged periods of mechanical ventilation. This translates to a long period at risk for complications. Clinical management can be fraught with challenges and frustration, as setbacks are common, and mortality remains high. Patients with COVID-19 may be at enhanced risk of the usual complications associated with prolonged critical illness but face additional risks specific to COVID-19 itself. Many of the potential complications—including VILI, VTE, and secondary or latent infection—may be difficult to disentangle from the underlying condition. Physicians must therefore maintain a high degree of suspicion, and pursue timely investigation and treatment as indicated in patients who either fail to improve or worsen despite optimal management.

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