EDITORIAL

Severe COVID-19 Infections—Knowledge Gained and Remaining Questions

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Patients with acute respiratory failure due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have overwhelmed critical care capacity in some cities and countries. The mortality of patients who require critical care is high but varies widely among hospitals.[1] Despite a rapidly increasing understanding of the pathogenesis of coronavirus disease 2019 (COVID-19), uncertainty remains about the reasons that some patients develop respiratory failure and others have no to minimal symptoms, as well as about the optimal management of patients with severe COVID-19 disease.[2] We review the evidence for the management of patients with the acute respiratory distress syndrome (ARDS) that may apply to patients with severe COVID-19, what has been learned about treatment of these patients, and the gaps in knowledge that remain.

Supportive Care

Critically ill patients with severe COVID-19 frequently meet the criteria for ARDS, including bilateral radiographic opacities and a sufficient degree of hypoxemia (partial pressure of arterial oxygen to fraction of inspired oxygen ≤300 mm Hg). Although there are no specific pharmacologic therapies for ARDS, decades of rigorous clinical trials have established that meticulous supportive care with the foundation of lung-protective ventilation improves ARDS outcomes.[3] Lung protective ventilation can be defined as a low-volume, low-pressure ventilation strategy (**Box**). Standardized protocols can help to ensure high-quality care, particularly during a crisis when less experienced physicians may be caring for critically ill patients. In addition to supportive care and lung protective ventilation, treatment of patients with ARDS typically includes symptom-targeted sedation and analgesia, consideration of neuromuscular blockade for ventilator dyssynchrony or severe hypoxemia, prone positioning for moderate to severe ARDS, and consideration of extracorporeal membrane oxygenation for patients with very severe ARDS (Box).[3] At present, most reports suggest that the respiratory physiology of ARDS both associated and not associated with COVID-19 are similar, thus reinforcing the importance of adhering to evidence-based management principles that have proven effective for ARDS management.[3]

Early in the COVID-19 pandemic, there were concerns about emergency endotracheal intubation in patients with a highly infectious respiratory virus. As a result, many intensivists intubated patients before the onset of frank respiratory failure. Although we are unaware of trials that have specifically addressed the timing of intubation for patients with COVID-19, accumulated experience has led most clinicians to approach decisions about the timing of intubation in a similar fashion to decisions for patients without COVID-19 but with incipient respiratory failure. An important caveat is that the optimal timing for intubation in ARDS remains uncertain and was hotly debated, even before COVID-19.

Likewise, an initial reluctance to use various forms of noninvasive ventilation for patients with COVID-19, including high-flow nasal cannula oxygen therapy, owing to concerns about aerosolization of the virus and exposure of essential health care workers, appears to have largely subsided. Moreover, as the pandemic has progressed, new practices around so-called *awake proning* of patients with early, nonintubated respiratory failure have become increasingly widespread. Small studies have provided evidence of improvement in gas exchange when patients who are not intubated are encouraged to maintain themselves in the prone position for prolonged periods of time. Clinical trials to assess the efficacy of this approach for patient-centered outcomes are ongoing.[4]

Treatment of COVID-19

The COVID-19 pandemic has reinforced the fundamental teaching that treatment of the underlying cause of ARDS is essential to improving outcomes. In hospitalized patients, treatment of SARS-CoV-2 with remdesivir shortens the time to

Box. Fundamentals of Acute Respiratory Distress Syndrome Care That Apply to Patients With Severe Coronavirus Disease 2019

- Patients should be ventilated with a lung protective strategy, including targeting low tidal volumes of 4- to 8-cc/kg predicted body weight and limiting plateau pressure to 30 cm H_2O or less.
- Sedation and analgesia should be provided at the minimum level required to promote patient comfort and ventilator synchrony. Neuromuscular blockade (with deeper sedation) can be used if dyssynchronies limit the application of lung protective ventilation or result in life-threatening problems with gas exchange. When possible, the duration of neuromuscular blockade should be brief.
- A conservative strategy for the administration of fluids, including aggressive diuresis, if needed, should be pursued once patients are out of shock (ie, off vasopressors).
- Prone positioning should be strongly considered for patients with a ratio of the partial pressure of arterial oxygen to fraction of inspired oxygen less than 150, unless contraindicated by severe hemodynamic instability, pregnancy, open abdomen, or other reasons.
- Venovenous extracorporeal membrane oxygenation should be considered if severe gas exchange abnormalities (eg, profound hypoxemia, severe respiratory acidosis) persist despite standard interventions, including prone positioning.

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recovery.[5] However, the utility of remdesivir in patients requiring mechanical ventilation remains uncertain, and additional evidence is needed. The RECOVERY trial[6] demonstrated a survival benefit of dexamethasone treatment in patients with COVID-19 who require oxygen or mechanical ventilation. Subsequently, 3 additional randomized clinical trials and a meta-analysis have been published,[7-10] all consistent with a beneficial effect of use of corticosteroids for severe or critical COVID-19. The World Health Organization has issued guidelines recommending use of corticosteroids in such patients.[11] The effect size and clarity of the results for patients with COVID-19 contrasts with the equivocal findings of prior corticosteroid trials in ARDS, in which decades of research have led to conflicting results and no consensus.

Unproven Therapies

The need to exercise caution when using unproven therapies for COVID-19 on the basis of theoretical understandings of disease pathogenesis is another important lesson. Despite the hype around use of hydroxychloroquine and lopinavir/ritonavir early in the pandemic, these agents have proven ineffective for treatment of COVID-19. Similarly, on the basis of media reports and some scientific articles describing a *cytokine storm* that was thought to characterize COVID-19, many patients have been treated with agents that block interleukin-6 (IL-6), an adaptation of the treatment of patients with cytokine release syndrome following chimeric antigen receptor T-cell therapy. However, the limited data that are available indicate that plasma IL-6 levels in patients with COVID-19 are orders of magnitude lower than in patients with cytokine release syndrome and, in some cases, lower than in patients with ARDS not associated with COVID-19.[12,13] At present, there is no evidence from randomized clinical trials that IL-6 blockade has beneficial effects for patients with severe COVID-19. Moreover, there are increasing reports of opportunistic infections associated with these therapies.[14] The lessons are that unproven therapies for COVID-19 may provide more harm than benefit and that there are no substitutes or shortcuts for well-conducted randomized clinical trials.

Outcomes of Critical Care

Evidence is increasing that clinical outcomes for patients with ARDS associated with COVID-19 may be quite similar to those for patients with ARDS not associated with COVID-19, and much better than was initially feared. Whereas studies published early in the pandemic, largely from hospitals overwhelmed by critically ill patients, reported hospital mortality rates approaching 90%, more recent studies have reported outcomes more typical for patients with ARDS, with hospital mortality of 30% to 40% and in some cases remarkably lower.[1] This hopeful development may be seen as a testament to the value of meticulous critical care that can be provided in hospitals with adequate resources and that are not operating under severe strain. At the same time, the disproportionate effects of COVID-19 on vulnerable populations, including minority communities, those with low socioeconomic status, and the elderly, demonstrate the imperative to bridge the gaps in health care systems, address systemic biases, and lessen these disparities.

Remaining Questions

Despite rapid progress, much remains to be learned about severe COVID-19. For example, the pathophysiological pathways in COVID-19 that result in ARDS and how these relate to the classical understanding of ARDS are uncertain. Over the past decades, it has become increasingly evident that the clinical definition of ARDS captures a heterogenous syndrome without a uniform pathologic process. In a given patient, there is wide variance in the degree to which the key pathways of injury (ie, epithelial, endothelial, inflammatory, coagulation) are operative. With a single causal etiology (ie, SARS-CoV-2), COVID-19 likely results in a more specific and more uniform clinical and biological phenotype of ARDS. An important goal of elucidating the distinct pathways of injury that are shared between patients with severe COVID-19 is to determine which are specifically treatable. Although autopsy findings have been variable, some evidence suggests that endothelial injury and coagulopathy may be central mediators of lung injury in COVID-19.[15] If confirmed, therapies that target endothelial activation or coagulopathy may hold promise and should be evaluated for ARDS associated with COVID-19.

The importance of a single causal phenotype is exemplified by the effect of dexamethasone in treatment of COVID-19 pneumonia, in contrast with the conflicting prior studies in treatment of ARDS. The survival benefit of dexamethasone suggests that the host response in severe COVID-19 is, at least partly, injurious. Yet inflammatory cytokine levels in plasma are similar to or, in some cases, lower in patients with ARDS associated with COVID-19 than in patients with ARDS due to other causes.[12,16] One explanation for this finding may be that the injurious host response is more compartmentalized to the lung, rather than a systemic cytokine storm. Moreover, in patients with COVID-19 not requiring oxygen, dexamethasone may be harmful.[6] Deeper biological phenotyping of lung-specific vs systemic inflammatory responses, as well as studies identifying which specific aspects of the immune response are associated with poor clinical outcomes in COVID-19,[17] should increase our understanding of how to best modulate the deleterious aspects of the host response while preserving its beneficial effects.

The RECOVERY trial[6] has demonstrated that pragmatic trials are possible during a pandemic and can rapidly provide answers to important clinical problems. Ongoing trials are testing a variety of therapies, including aggressive anticoagulation, convalescent plasma, monoclonal antibodies, and additional immunomodulatory agents. Access to randomized clinical trials should be expanded to as many patients as possible, including the elderly and those in minority communities hardest hit by the pandemic who have not traditionally had equal access to research protocols, to ensure that these potentially lifesaving therapies can be systematically evaluated.

Finally, many patients, gratefully, recover from severe COVID-19. The long-term sequelae of the disease need to be further studied, including how recovery from COVID-19 does or does not differ from recovery of other forms of severe critical illness. Critical care has been revolutionized by the realization that many patients survive their acute illness only to suffer serious long-term functional and psychological conse-

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quences of their stay in intensive care units.[18] A better understanding of the most common postrecovery sequelae of severe COVID-19 can help clinicians best care for the increasing number of patients who do survive.

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