Respiratory failure in patients infected with SARS-CoV-2

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■ ABSTRACT
The management of patients with COVID-19-induced acute respiratory distress syndrome focuses on identifying the causes for respiratory failure and on following best practices for supportive care with oxygen supplementation and mechanical ventilation. In this patient population, appropriate measures need to be taken to prevent the spread of the coronavirus. Nearly 90% of COVID-19 patients admitted to the ICU need mechanical ventilation and most of these develop severe ARDS, which causes high morbidity and mortality. These patients need to be managed according to guidelines for the low-tidal-volume lung-protective ventilation. Practitioners also need to evaluate for other potential causes of respiratory failure.

■ INTRODUCTION
Treatment for coronavirus disease 2019 (COVID-19)-induced acute respiratory distress syndrome (ARDS) must be based on best practices and guidelines, as for ARDS due to other causes. Other possible reasons for respiratory failure need to be considered in the care of these patients. At present, no specific therapies have been proven to be beneficial, and supportive care based on oxygen supplementation and mechanical ventilation, when needed, is the cornerstone of therapy.

A minority of infected patients. In the current global pandemic of severe acute respiratory syndrome coronavirus (SARS-CoV-2), about 5% to 10% of infected patients need to be admitted to the intensive care unit (ICU), most often because of severe and rapidly evolving hypoxemia. Their most common diagnosis is COVID-19 pneumonia, presenting with fever, fatigue, dry cough, myalgia, and dyspnea. Up to 88% of COVID-19 patients who are admitted to the ICU need mechanical ventilation, and most mechanically ventilated patients go on to develop severe ARDS.

■ MANAGEMENT OF ACUTE RESPIRATORY FAILURE
Oxygen per high-flow nasal cannula. Patients with COVID-19 pneumonia who have rapidly escalating oxygen requirements should be moved to an ICU and should receive supplemental oxygen through a high-flow nasal cannula to maintain oxygen saturation between 92% and 96%.

A high-flow nasal cannula is recommended over noninvasive positive-pressure ventilation (NIPPV), which has a very high failure rate in ARDS patients and is associated with poor outcomes. NIPPV may aggravate lung injury in these patients due to large swings in transpulmonary pressures and tidal volumes. Also of concern is that NPPV generates aerosols that can spread the virus to other patients and to healthcare providers.

Low threshold for intubation. In view of the rapidly fulminant progression of this disease, intubation should not be delayed while trying other, unproven therapies. Delay in intubation is associated with worse outcomes in viral pneumonia, so if adequate oxygenation is not achieved with a high-flow nasal cannula, intubation should not be delayed for a trial of NIPPV.

We do not recommend awake prone positioning. Although cases have been reported in which patients avoided intubation by being placed in the prone position, there is insufficient evidence in support its efficacy or safety. Further, trying awake prone positioning may delay necessary intubation and lead to poor outcomes.

■ MANAGEMENT OF ARDS
Once intubated, patients need to be managed according to the low-tidal-volume lung-protective ventilation strategy tested in the Acute Respiratory Distress Syndrome (ARDS) trials.
Consider neuromuscular blocking agents only for ventilator dyssynchrony despite optimal use of sedation. Consider boluses of neuromuscular blocking agents as the initial treatment of choice instead of continuous infusions to help with synchrony.

We suggest dexamethasone for management of COVID-19 ARDS. This suggestion is based on a preliminary report of a randomized control trial that showed the dexamethasone group had a significantly lower 28-day mortality (21.6% vs 24.6%; \( P \lt 0.001 \)), the effect being more pronounced in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%; \( P \lt 0.001 \)) and supplemental oxygen (21.5% vs. 25.0%; \( P = 0.022 \) (https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1).

Recruitment maneuvers have little or no role, according to current evidence and expert opinion.

Consider extracorporeal membrane oxygenation as a rescue intervention for refractory hypoxemia.

Start appropriate antibiotics if secondary infection is suspected.

Based on early experience, ARDS due to COVID-19 behaves like ARDS due to other viruses, with an average duration of mechanical ventilation of around 2 weeks. This prolonged duration of mechanical ventilation puts patients at risk for developing secondary bacterial pneumonias.

### TWO PHASES OF COVID-19 PNEUMONIA?

Gattinoni et al. hypothesize that COVID-19 pneumonia has two distinct phases of respiratory failure. The initial phase, “type L,” is characterized by low elastance or normal compliance, low ventilation-to-perfusion ratio, low lung weight, and low lung recruitability. With continued inflammation, the alveolar capillary membrane permeability increases, leading to increased interstitial edema, increased lung weight, and dependent atelectasis. They describe this phase as “type H,” or typical ARDS. It is characterized by high elastance, high right-to-left shunt, increased lung weight, and high recruitability.

Some suggest treating the early (type L) phase with low PEEP and a less-restrictive tidal volume strategy. However, in the absence of any evidence, we suggest that mechanically ventilated patients should continue to be managed with low-tidal-volume and high-PEEP strategies.

### TO AVOID SPREADING THE VIRUS WHEN CARING FOR VENTILATED PATIENTS

Mechanical ventilation and other care for patients with acute respiratory failure is associated with a

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**TABLE 1**

<table>
<thead>
<tr>
<th>Fio2</th>
<th>PEEP</th>
</tr>
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<tbody>
<tr>
<td>0.3</td>
<td>5</td>
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<tr>
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<tr>
<td>0.4</td>
<td>16</td>
</tr>
<tr>
<td>0.5</td>
<td>18</td>
</tr>
<tr>
<td>0.5</td>
<td>18</td>
</tr>
<tr>
<td>0.5–0.8</td>
<td>20</td>
</tr>
<tr>
<td>0.8</td>
<td>22</td>
</tr>
<tr>
<td>0.9</td>
<td>22</td>
</tr>
<tr>
<td>1.0</td>
<td>22</td>
</tr>
<tr>
<td>1.0</td>
<td>24</td>
</tr>
</tbody>
</table>

Use a minimum positive end-expiratory pressure (PEEP) of 5 cm H2O. Consider using incremental combinations of fraction of inspired oxygen Fio2 and PEEP as shown to achieve PaO2 of 5–80 mm Hg or SpO2 88%–95%.

From the Acute Respiratory Distress Syndrome Network, reference 6.

Syndrome Network study and recommended by the Surviving Sepsis Campaign COVID-19 panel.

**Low tidal volumes:** 4 to 8 mL per kg of predicted body weight.

**Plateau pressures:** lower than 30 cm H2O.

**High PEEP:** COVID-19-associated ARDS responds dramatically to a high positive end-expiratory pressure (PEEP) strategy, with recruitment of the lung parenchyma. A modified high-PEEP strategy (Table 1) should be considered. These patients should be placed on high PEEP, and the fraction of inspired oxygen (Fio2) should be reduced quickly once they are clinically stable. PEEP down-titration needs to be very slow, as there is a high risk of recruitment in these patients.

**Conservative fluid management.** Other ARDS trials have clearly demonstrated better outcomes with conservative fluid management. Therefore, for patients who are not in shock, a net negative fluid balance using the Fluid and Catheter Treatment Trial Lite protocol should be attempted (Table 2).

Consider early prone position ventilation for patients with moderate to severe ARDS (PaO2/Fio2 ratio less than 150, on FiO2 0.6 or greater), in view of the recruitability of the lung parenchyma.
higher risk of nosocomial transmission. Therefore, caregivers should keep the following in mind.

Minimize unnecessary disconnection of the endotracheal tube to avoid derecruitment and unnecessary release of the virus into the environment.

Adhere to personal protective equipment protocols.

Keep fittings tight. Ventilator circuits need to have tight seals to prevent aerosolization.

Place ventilator and intravenous line monitors outside the room to allow frequent ventilator adjustments while simultaneously decreasing the risk of exposure to staff.

Provide other general supportive care such as sedation, delirium prevention, and infection surveillance based on standard ICU practice and protocols.

CONSIDER OTHER CAUSES OF RESPIRATORY FAILURE

Asthma, COPD exacerbations. Like most other viral infections, COVID-19 pneumonia can lead to exacerbations of both chronic obstructive pulmonary disease (COPD) and asthma. SARS-CoV-2 infections can trigger an inflammatory reaction leading to these exacerbations, which need to be managed with corticosteroids and bronchodilators based on best practice guidelines for the underlying disease processes.

Pulmonary embolism. Initial observational data have suggested abnormal coagulation patterns in COVID-19 patents. One study found that up to 31% of patients with COVID-19 infection who required ICU care had thrombotic complications, with pulmonary embolism being the prominent diagnosis.

We suggest checking D-dimer at admission and every other day.

- If the initial D-dimer value is less than 3,000 ng/mL we suggest standard thromboprophylaxis.
- If the initial D-dimer value is higher than 3,000 ng/mL, we suggest point-of-care ultrasonography to assess for thrombotic events. If no thrombosis is detected, consider thromboprophylaxis in a higher dose.

Heart failure. COVID-19 patients who otherwise have minimal lung involvement could potentially present with dyspnea and hypoxemia that may be triggered by pulmonary embolism and right heart failure.

Myocarditis. SARS-CoV-2 infections have also been linked to myocarditis as a result of direct myocardial injury leading to severe heart failure exacerbations and cardiogenic shock. These patients can present with signs and symptoms ranging from mild dyspnea to acute pulmonary edema or even sudden cardiac death. Cardiac involvement can be seen in up to 25% of cases; therefore, we suggest following serial troponin measurements on presentation.

REFERENCES


TABLE 2
Simplified conservative fluid management protocol (Fluid and Catheter Treatment Trial Lite)

<table>
<thead>
<tr>
<th>Central venous pressure, mm Hg (recommended)</th>
<th>Pulmonary artery occlusion pressure, mm Hg (optional)</th>
<th>Mean arterial pressure ≥40 mm Hg and off vasopressors ≥12 hour</th>
<th>Urine output ≤0.5 mL/kg/hr</th>
<th>Urine output ≥0.5 mL/kg/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 8</td>
<td>&gt; 12</td>
<td>Furosemide⁸; reassess in 1 hour</td>
<td>Furosemide⁸; reassess in 4 hours</td>
<td></td>
</tr>
<tr>
<td>4–8</td>
<td>8–12</td>
<td>Give fluid bolus; reassess in 1 hour</td>
<td>Furosemide⁸; reassess in 4 hours</td>
<td></td>
</tr>
<tr>
<td>&lt; 4</td>
<td>&lt; 8</td>
<td>Give fluid bolus; reassess in 1 hour</td>
<td>No intervention; reassess in 4 hours</td>
<td></td>
</tr>
</tbody>
</table>

⁸Recommended furosemide dosing: begin with 20-mg bolus or 3-mg/hour infusion or last known effective dose. Double each subsequent dose until goal achieved (oliguria reversal or intravascular pressure target) or a maximum infusion rate of 24 mg/hour or a 160-mg bolus is reached. Do not exceed 620 mg/day. Also, if patient has heart failure, consider treatment with dobutamine.

From reference 8.

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