The COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations in this section were informed by the recommendations from the Surviving Sepsis Campaign Guidelines for managing adult sepsis, pediatric sepsis, and COVID-19.

Severe illness in people with COVID-19 typically occurs approximately 1 week after the onset of symptoms. The most common symptom is dyspnea, which is often accompanied by hypoxemia. Patients with severe disease typically require supplemental oxygen and should be monitored closely for worsening respiratory status, because some patients may progress to acute respiratory distress syndrome (ARDS).

**Goal of Oxygenation**

The optimal oxygen saturation ($\text{SpO}_2$) in adults with COVID-19 who are receiving supplemental oxygen is unknown. However, a target $\text{SpO}_2$ of 92% to 96% seems logical, considering that indirect evidence from patients without COVID-19 suggests that an $\text{SpO}_2$ of <92% or >96% may be harmful.

The potential harm of maintaining an $\text{SpO}_2$ of <92% was demonstrated during a trial that randomly assigned patients with ARDS who did not have COVID-19 to either a conservative oxygen strategy (target $\text{SpO}_2$ of 88% to 92%) or a liberal oxygen strategy (target $\text{SpO}_2$ of ≥96%). The trial was stopped early due to futility after enrolling 205 patients, but increased mortality was observed at Day 90 in the conservative oxygen strategy arm (between-group risk difference of 14%; 95% CI, 0.7% to 27%) and a trend toward increased mortality was observed at Day 28 (between-group risk difference of 8%; 95% CI, -5% to 21%).

The results of a meta-analysis of 25 randomized trials that involved patients without COVID-19 demonstrate the potential harm of maintaining an $\text{SpO}_2$ of >96%. This study found that a liberal oxygen strategy (median $\text{SpO}_2$ of 96%) was associated with an increased risk of in-hospital mortality when compared to a more conservative $\text{SpO}_2$ strategy (relative risk 1.21; 95% CI, 1.03–1.43).

**Acute Hypoxemic Respiratory Failure**

In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet the oxygen needs of the patient. Options for providing enhanced respiratory support include high-flow nasal canula (HFNC) oxygen, noninvasive ventilation (NIV), intubation and mechanical ventilation, or extracorporeal membrane oxygenation. In this section, mechanical ventilation refers to the delivery of positive pressure ventilation through an endotracheal or tracheostomy tube. NIV refers to the delivery of positive pressure ventilation through a noninvasive interface, such as a face mask or nasal mask.

**Nonmechanically Ventilated Adults With Acute Hypoxemic Respiratory Failure**

**High-Flow Nasal Cannula Oxygen and Noninvasive Ventilation**

**Recommendations**

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends HFNC oxygen over NIV (BIIa).

- For adults with COVID-19 and acute hypoxemic respiratory failure who do not have an indication for endotracheal intubation and for whom HFNC oxygen is not available, the Panel recommends
performing a closely monitored trial of NIV (BIIa).

**Rationale**

HFNC oxygen is preferred over NIV in patients with acute hypoxic respiratory failure; this guidance is based on data from an unblinded clinical trial in patients without COVID-19 who had acute hypoxic respiratory failure. Study participants were randomized to receive HFNC oxygen, conventional oxygen therapy, or NIV. The patients in the HFNC oxygen arm had more ventilator-free days (mean of 24 days) than those in the conventional oxygen therapy arm (mean of 22 days) or NIV arm (mean of 19 days; \( P = 0.02 \)). In addition, 90-day mortality was lower in the HFNC oxygen arm than in either the conventional oxygen therapy arm (HR 2.01; 95% CI, 1.01–3.99) or the NIV arm (HR 2.50; 95% CI, 1.31–4.78). In the subgroup of more severely hypoxic patients (those with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen \([\text{PaO}_2/\text{FiO}_2]\) ≤200 mm Hg), the intubation rate was lower for the HFNC oxygen arm than for the conventional oxygen therapy or NIV arms (HR 2.07 and 2.57, respectively).

The trial’s findings were corroborated by a meta-analysis of 8 trials with 1,084 participants that was conducted to assess the effectiveness of oxygenation strategies prior to intubation. Compared to NIV, HFNC oxygen reduced the rate of intubation (OR 0.48; 95% CI, 0.31–0.73) and intensive care unit (ICU) mortality (OR 0.36; 95% CI, 0.20–0.63).

NIV is an aerosol-generating procedure, and it may increase the risk of nosocomial transmission of SARS-CoV-2. It remains unclear whether the use of HFNC oxygen results in a lower risk of nosocomial SARS-CoV-2 transmission than NIV.

**Awake Prone Positioning in Nonmechanically Ventilated Adults**

**Recommendations**

- For patients with persistent hypoxemia who require HFNC oxygen and for whom endotracheal intubation is not indicated, the Panel recommends a trial of awake prone positioning (BIIa).
- The Panel recommends against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (AIII).

**Additional Considerations**

- Patients who can adjust their position independently and tolerate lying prone can be considered for awake prone positioning.
- Awake prone positioning is acceptable and feasible for pregnant patients and can be performed in the left lateral decubitus position or the fully prone position.
- Some patients do not tolerate awake prone positioning. Failure rates as high as 63% have been reported in the literature.
- Awake proning should not be used as a substitute for intubation and mechanical ventilation in patients with refractory hypoxemia who otherwise meet the indications for these interventions.
- Awake proning may be infeasible or impractical in patients with:
  - Spinal instability
  - Facial or pelvic fractures
  - An open chest or unstable chest wall
  - Awake prone positioning should be used with caution in patients with confusion or delirium, hemodynamic instability, an inability to independently change position, recent abdominal surgery, or recent nausea or vomiting.
Rationale

Awake proning, or having a nonintubated patient lie on their stomach, may improve oxygenation and prevent the patient from progressing to requiring intubation and mechanical ventilation. Although prone positioning has been shown to improve oxygenation and outcomes in patients with moderate to severe ARDS who are receiving mechanical ventilation, there is less evidence regarding the benefit of prone positioning in awake patients who require supplemental oxygen without mechanical ventilation. Several case series of patients with COVID-19 who required oxygen or NIV have similarly reported that awake prone positioning improves oxygenation, and some series have also reported low intubation rates after proning.

The Awake Prone Positioning Meta-Trial Group conducted the largest trial to date on awake prone positioning. This was a prospective, multinational meta-trial of 6 open-label, randomized controlled superiority trials that compared awake prone positioning to standard care in adults who required HFNC oxygen for acute hypoxemic respiratory failure due to COVID-19.

The study enrolled 1,126 patients between April 2, 2020, and January 26, 2021; the intention-to-treat analysis included 1,121 patients. Two hundred twenty-three of 564 patients (40%) who underwent awake prone positioning met the primary composite outcome of intubation or death within 28 days of enrollment; among the 557 patients who received standard care, 257 (46%) met the primary endpoint (relative risk 0.86; 95% CI, 0.75–0.98). Regarding the individual components of the composite endpoint, the incidence of intubation at Day 28 was lower in the awake prone positioning arm than in the standard care arm (HR for intubation 0.75; 95% CI, 0.62–0.91). There was no difference in 28-day mortality between the awake prone positioning arm and the standard care arm (HR for mortality 0.87; 95% CI, 0.68–1.11). During the first 14 days of the study, the median daily duration of awake prone positioning was 5.0 hours (IQR 1.6–8.8 hours). However, the median daily duration varied from 1.6 hours to 8.6 hours across the individual trials. Longer daily durations for awake prone positioning occurred more frequently in patients who experienced treatment success by Day 28. This study evaluated the incidences of certain adverse events, including skin breakdown, vomiting, and central or arterial line dislodgement. These events occurred infrequently during the study, and the incidences for these events were similar between the arms. No cardiac arrests occurred during awake prone positioning.

Though the optimal daily duration of awake prone positioning is unclear, only 25 of 151 patients (17%) who had an average of ≥8 hours of awake prone positioning per day met the primary endpoint of intubation or death in the Awake Prone Positioning Meta-Trial, compared with 198 of 413 patients (48%) who remained in awake prone positioning for <8 hours per day. This is consistent with past clinical trials of prone positioning in mechanically ventilated patients with ARDS, during which clinical benefits were observed with longer durations of prone positioning.

Intubation for Mechanical Ventilation

Recommendation

- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of exposing health care practitioners to SARS-CoV-2 during intubation (AIII).

Rationale

It is essential to closely monitor hypoxic patients with COVID-19 for signs of respiratory decompensation. To ensure the safety of both patients and health care workers, intubation should be performed in a controlled setting by an experienced practitioner.
Mechanically Ventilated Adults

General Considerations
Recommendations
For mechanically ventilated adults with COVID-19 and ARDS:

• The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (AII).
• The Panel recommends targeting plateau pressures of <30 cm H$_2$O (AIIa).
• The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (BIIa).
• The Panel recommends against the routine use of inhaled nitric oxide (AIIa).

Rationale
There is no evidence that ventilator management of patients with hypoxemic respiratory failure due to COVID-19 should differ from ventilator management of patients with hypoxemic respiratory failure due to other causes.

Positive End-Expiratory Pressure and Prone Positioning in Mechanically Ventilated Adults With Moderate to Severe Acute Respiratory Distress Syndrome
Recommendations
For mechanically ventilated adults with COVID-19 and moderate to severe ARDS:

• The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy (BIIa).
• For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation (BIIa).

Rationale
PEEP is beneficial in patients with ARDS because it prevents alveolar collapse, improves oxygenation, and minimizes atelectotrauma, a source of ventilator-induced lung injury. A meta-analysis of individual patient data from the 3 largest trials that compared lower and higher levels of PEEP in patients without COVID-19 found lower rates of ICU mortality and in-hospital mortality with higher levels of PEEP in those with moderate (PaO$_2$/FiO$_2$ 100–200 mm Hg) and severe ARDS (PaO$_2$/FiO$_2$ <100 mm Hg).

Although there is no clear standard as to what constitutes a high level of PEEP, a conventional threshold is >10 cm H$_2$O.$^{17}$ Recent reports have suggested that, in contrast to patients with non-COVID-19 causes of ARDS, some patients with moderate or severe ARDS due to COVID-19 have normal static lung compliance. In these patients, higher PEEP levels may cause harm by compromising hemodynamics and cardiovascular performance.$^{18,19}$ Other studies reported that patients with moderate to severe ARDS due to COVID-19 had low lung compliance, similar to the lung compliance seen in patients with conventional ARDS.$^{20,23}$ These seemingly contradictory observations suggest that COVID-19 patients with ARDS are a heterogeneous population, and assessment for responsiveness to higher levels of PEEP should be individualized based on oxygenation and lung compliance. Clinicians should monitor patients for known side effects of higher levels of PEEP, such as barotrauma and hypotension.

In the prepandemic PROSEVA study of patients with moderate or severe early ARDS (PaO$_2$/FiO$_2$ <150 mm Hg) who required mechanical ventilation, the patients who were randomized to undergo prone positioning for ≥16 hours per day had improved survival compared to those who remained in the supine position.
position throughout their course of mechanical ventilation. A meta-analysis evaluated the results of the PROSEVA study and 7 other randomized controlled trials that investigated the use of prone positioning in people with ARDS. The subgroup analysis revealed that patients who remained prone for ≥12 hours per day had a lower mortality rate than those who remained in the supine position (risk ratio 0.74; 95% CI, 0.56–0.99). Prone positioning improved oxygenation in all of the trials; patients in the prone positioning arms had higher PaO$_2$/FiO$_2$ on Day 4 than those in the supine positioning arms (mean difference of 23.5 mm Hg; 95% CI, 12.4–34.5)\textsuperscript{24}.

The use of prone positioning may be associated with serious adverse events, including unplanned extubation or central catheter removal; however, the meta-analysis found no differences in the frequencies of these events between the prone positioning and supine positioning arms. The use of prone positioning was associated with an increase in the frequency of pressure sores (risk ratio 1.22; 95% CI, 1.06–1.41) and endotracheal tube obstruction (risk ratio 1.76; 95% CI, 1.24–2.50) in the 3 studies that evaluated these complications.

**Neuromuscular Blockade in Mechanically Ventilated Adults With Moderate to Severe Acute Respiratory Distress Syndrome**

**Recommendations**

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS:

- The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or a continuous NMBA infusion to facilitate protective lung ventilation (BIIa).
- In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours, as long as the patient’s anxiety and pain can be adequately monitored and controlled (BIII).

**Rationale**

The recommendation for intermittent boluses of NMBA or a continuous infusion of NMBA to facilitate lung protection may require a health care provider to enter the patient’s room frequently for close clinical monitoring. Therefore, in some situations, the risks of SARS-CoV-2 exposure and the need to use personal protective equipment for each entry into a patient’s room may outweigh the benefit of NMBA treatment.

**Rescue Therapies for Mechanically Ventilated Adults With Acute Respiratory Distress Syndrome**

**Recommendations**

For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:

- The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers (CIIa).
- If recruitment maneuvers are used, the Panel recommends against using staircase (incremental PEEP) recruitment maneuvers (AIIa).
- The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off (CIII).
Rationale

A recruitment maneuver refers to a temporary increase in airway pressure during mechanical ventilation to open collapsed alveoli and improve oxygenation. No studies have assessed the effect of recruitment maneuvers on oxygenation in severe ARDS due to COVID-19. However, a systematic review and meta-analysis of 6 trials of recruitment maneuvers in patients with ARDS who did not have COVID-19 found that recruitment maneuvers reduced mortality, improved oxygenation 24 hours after the maneuver, and decreased the need for rescue therapy. Because recruitment maneuvers can cause barotrauma or hypotension, patients should be closely monitored during recruitment maneuvers. If a patient decompensates during recruitment maneuvers, the maneuver should be stopped immediately.

The importance of properly performing recruitment maneuvers was illustrated by an analysis of 8 randomized controlled trials in patients without COVID-19 (n = 2,544) that found that recruitment maneuvers did not reduce hospital mortality (risk ratio 0.90; 95% CI, 0.78–1.04). A subgroup analysis found that traditional recruitment maneuvers significantly reduced hospital mortality (risk ratio 0.85; 95% CI, 0.75–0.97), whereas incremental PEEP titration recruitment maneuvers increased mortality (risk ratio 1.06; 95% CI, 0.97–1.17).

Although there are no published studies of inhaled nitric oxide in patients with COVID-19, a Cochrane review of 13 trials that evaluated inhaled nitric oxide use in patients with ARDS found no mortality benefit. Because the review showed a transient benefit for oxygenation, it is reasonable to attempt using inhaled nitric oxide as a rescue therapy in patients with COVID-19 and severe ARDS after other options have failed. However, if the use of nitric oxide does not improve a patient’s oxygenation, it should be tapered quickly to avoid rebound pulmonary vasoconstriction, which may occur when nitric oxide is discontinued after prolonged use.

References


