Oxygenation and Ventilation for Adults

Last Updated: December 20, 2023

The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations in this section were informed by the Surviving Sepsis Campaign guidelines for managing sepsis and guidelines for managing COVID-19 in adults.

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 measured by pulse oximetry (SpO_2) in adults with COVID-19 who are receiving supplemental oxygen is unknown. However, a target SpO_2 of 92% to 96% seems logical, considering that indirect evidence from patients without COVID-19 suggests that an SpO_2 <92% or >96% may be harmful.[1,2] Special care should be taken when assessing SpO_2 in patients with darker skin pigmentation, as recent reports indicate that occult hypoxemia (defined as arterial oxygen saturation [SaO_2] <88% despite an SpO_2 >92%) is more common in these patients.[3,4] See Clinical Spectrum of SARS-CoV-2 Infection for more information.

The potential harm of maintaining an SpO_2 <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 SpO_2 of 88% to 92%) or a liberal oxygen strategy (target SpO_2 ≥96%).[1] 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 14%; 95% CI, 0.7% to 27%), and a trend toward increased mortality was observed at Day 28 (between-group risk difference 8%; 95% CI, -5% to 21%).

The results of a meta-analysis of 25 randomized trials that involved patients without COVID-19 demonstrated the potential harm of maintaining an SpO_2 >96%.[2] This study found that a liberal oxygen supplementation strategy (a median fraction of inspired oxygen [FiO_2] of 0.52) was associated with an increased risk of in-hospital mortality (relative risk 1.21; 95% CI, 1.03–1.43) when compared with a more conservative SpO_2 supplementation strategy (a median FiO_2 of 0.21).

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 using 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 either continuous positive airway pressure (CPAP) or bilevel positive airway pressure (e.g., BiPAP) 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 starting therapy with HFNC oxygen; if patients fail to respond, NIV or intubation and mechanical ventilation should be initiated **(BIIa)**.

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy 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

Several studies have informed clinical practice on the optimal oxygen delivery system for patients with COVID-19 and acute hypoxemic respiratory failure. A randomized study of 711 patients with COVID-19 in 34 intensive care units (ICUs) in France compared HFNC oxygen delivery to oxygen delivery through a nonrebreather mask.[5] The patients had acute respiratory failure with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ≤200 mm Hg. The mean FiO_2 was 0.58 in both arms. Although the difference between arms for the primary endpoint of 28-day mortality was not statistically significant (10% in the HFNC oxygen arm vs. 11% in the conventional oxygen arm; absolute difference -1.2%; 95% CI, -5.8% to 3.4%; $P = 0.60$), the intubation rate was significantly lower in the HFNC oxygen arm than in the conventional oxygen arm. Unless a contraindication exists, most Panel members would switch to HFNC oxygen delivery for patients with respiratory failure who do not require mechanical ventilation but have worsening hypoxemia or increased work of breathing despite receiving conventional oxygen at flow rates up to 10 L/min.

For patients with COVID-19 and acute hypoxemic respiratory failure who do not respond to conventional oxygen therapy, HFNC oxygen is preferred over NIV. No studies directly compare HFNC oxygen with mask-delivered NIV in patients with COVID-19; therefore, this guidance is based on an unblinded clinical trial in patients without COVID-19 who had acute hypoxemic respiratory failure.[6] 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 24 days) than those in the conventional oxygen therapy arm (mean 22 days) or the NIV arm (mean 19 days; $P = 0.02$). In addition, the conventional oxygen therapy arm (HR 2.01; 95% CI, 1.01–3.99) and the NIV arm (HR 2.50; 95% CI, 1.31–4.78) had higher 90-day mortality than the HFNC oxygen arm. In the subgroup of patients with severe hypoxemia (those with PaO_2/FiO_2 ≤200 mm Hg), the HFNC oxygen arm had a lower intubation rate than the conventional oxygen therapy arm (HR 2.07) and the NIV arm (HR 2.57).

The trial's findings were corroborated by a meta-analysis of 8 trials with 1,084 participants that assessed the effectiveness of oxygenation strategies.[7] Compared to NIV, HFNC oxygen reduced the rate of intubation (OR 0.48; 95% CI, 0.31–0.73) and ICU mortality (OR 0.36; 95% CI, 0.20–0.63).

One small study compared the use of NIV delivered by a helmet device to HFNC oxygen in patients with COVID-19. The HENIVOT trial randomized 109 patients with moderate to severe COVID-19 (defined as those who had PaO_2/FiO_2 ≤200 mm Hg) to receive either NIV via a helmet device or HFNC oxygen.[8] The study found no difference between the arms for the primary outcome of respiratory support–free days. However, only 30% of patients in the NIV arm required endotracheal intubation compared to 51% of patients in the HFNC oxygen arm ($P = 0.03$).

Two larger studies compared the use of NIV with conventional oxygen therapy in patients with COVID-19. The RECOVERY-RS trial was an adaptive randomized controlled trial that was essentially conducted as 2 separate trials that compared NIV and HFNC oxygen to the same conventional oxygen therapy control group.[9] The trial was stopped early and enrolled fewer than a third of the planned sample size of 4,002 participants. Between April 2020 and May 2021, 1,273 adults with acute hypoxemic respiratory failure related to COVID-19 were randomized to receive NIV (n = 380), HFNC oxygen (n = 418), or conventional oxygen therapy (n = 475). The primary endpoint was a composite of endotracheal intubation or death within 30 days. The proportion of patients who met the primary endpoint was

significantly lower in the NIV arm than in the conventional oxygen therapy arm (36.3% vs. 44.4%; $P = 0.03$). This difference was not due to mortality but was entirely due to a reduction in the number of patients who required intubation. There was no significant difference between the HFNC oxygen arm and the conventional oxygen therapy arm in the occurrence of the primary endpoint (44.3% vs. 45.1%; $P = 0.83$).

There was substantial crossover between the arms, but an inverse probability weighting analysis that corrected for the bias this may have introduced did not change the results.[9] Adverse events were more common in the NIV arm. Initially, a comparison between NIV and HFNC oxygen was not planned, but a post hoc analysis found that the proportion of patients who required endotracheal intubation or who died was lower in the NIV arm than in the HFNC oxygen arm (34.6% vs. 44.3%; $P = 0.02$).

In contrast to the RECOVERY-RS trial, the HiFlo-COVID trial randomized 220 patients with COVID-19 to receive HFNC oxygen or conventional oxygen therapy and found that a smaller proportion of patients in the HFNC oxygen arm required intubation (34.3% vs. 51.0%; $P = 0.03$).[10] Patients in the HFNC arm also had a shorter median time to recovery (11 vs. 14 days; $P = 0.047$).

The conflicting results of these studies make drawing inferences from the data difficult. Additionally, the RECOVERY-RS trial was stopped long before it reached its planned sample size for reasons not related to futility, efficacy, or harm; inferring benefit in this context is questionable. The Panel recognizes that for patients who need more oxygen support than a conventional nasal cannula can provide, most clinicians will administer oxygen via HFNC and subsequently progress to NIV if needed. Therefore, the pertinent clinical question is whether HFNC oxygen or NIV should be used when a patient does not respond to conventional oxygen therapy. Other than the post hoc analysis in the RECOVERY-RS trial, no study has specifically investigated this question.

NIV is an aerosol-generating procedure, and studies of SARS-CoV show that it may increase the risk of nosocomial transmission.[11,12] For patients with SARS-CoV-2, it remains unclear whether the use of HFNC oxygen results in a lower risk of nosocomial transmission than the use of NIV.

Awake Prone Positioning in Nonmechanically Ventilated Adults

Recommendations

- For adults 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** the use of 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.[13]
- Some patients do not tolerate awake prone positioning. Failure rates as high as 63% have been reported in the literature.[14]
- Awake prone positioning **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 prone positioning 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, delirium, or hemodynamic instability; patients who cannot independently change position; or patients who have had recent abdominal surgery, nausea, or vomiting.

Rationale

Awake prone positioning, or having a nonintubated patient lie on the 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,[15,16] 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 reported that awake prone positioning improved oxygenation,[17-20] and some series have also reported low intubation rates after awake prone positioning.[19,20]

The Awake Prone Positioning Meta-Trial Group has conducted the largest trial on awake prone positioning.[21] This study 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, and the intention-to-treat analysis included 1,121 patients.[21] Of the 564 patients who underwent awake prone positioning, 223 (40%) met the composite primary endpoint 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). The incidence of intubation by Day 28 was lower in the awake prone positioning arm than in the standard care arm (HR 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 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).[21] 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 were associated with treatment success by Day 28. This study evaluated the incidences of certain adverse events, including skin breakdown, vomiting, and central or arterial line dislodgment. These events occurred infrequently during the study, and the incidences were similar in each arm. No cardiac arrests occurred during awake prone positioning.

The optimal daily duration of awake prone positioning is unclear. In the meta-trial of awake prone positioning, 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 when compared with 198 of 413 patients (48%) who remained in awake prone positioning for <8 hours per day.[21] This result is consistent with past clinical trials of prone positioning in mechanically ventilated patients with ARDS, in which clinical benefits were observed after longer durations of prone positioning.[15,16]

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 hypoxemic 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) **(AI)**.
- The Panel recommends targeting plateau pressures of <30 cm H_2O **(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 the ventilator management of patients with hypoxemic respiratory failure due to COVID-19 should differ from the 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 ARDS

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 atelectrauma, 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 that less ICU mortality and in-hospital mortality was associated with higher levels of PEEP in those with moderate (PaO_2/FiO_2 100–200 mm Hg) and severe (PaO_2/FiO_2 <100 mm Hg) ARDS.[22]

Although there is no clear standard for a high level of PEEP, a conventional threshold is >10 cm H_2O.[23] Recent reports have suggested that, in contrast to patients with ARDS not caused by COVID-19, some patients with moderate or severe ARDS due to COVID-19 have normal static lung compliance. In these patients, high levels of PEEP may cause harm by compromising hemodynamics and cardiovascular performance.[24,25] Other studies have 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.[26-29] These seemingly contradictory observations suggest that patients with COVID-19 and ARDS are a heterogeneous population, and assessments for responsiveness to high levels of PEEP should be individualized based on oxygenation and lung compliance. Clinicians should monitor patients for known side effects of high levels of PEEP, such as barotrauma and hypotension.

In the prepandemic PROSEVA study of patients with moderate to 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 throughout the course of mechanical ventilation.[15] 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.[30] A subgroup analysis revealed that mortality was reduced among patients who remained prone for ≥12 hours per day when compared with patients who remained in the supine position (risk ratio 0.74; 95% CI, 0.56–0.99). Prone positioning improved oxygenation in all 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 23.5 mm Hg; 95% CI, 12.4–34.5).

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 between the prone positioning and supine positioning arms in the frequency of these events.[30] The use of prone positioning was associated with an increased risk 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 ARDS

Recommendation

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

- The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBAs) or a continuous NMBA infusion to facilitate protective lung ventilation **(BIIa)**.

Rationale

Although the use of NMBAs in patients with ARDS reduces ventilator dyssynchrony, a large multicenter trial across several ICUs reported no significant difference in mortality between patients who received deep sedation and continuous NMBA infusion and patients who received a usual-care approach of lighter sedation without routine NMBAs.[31]

Rescue Therapies for Mechanically Ventilated Adults With ARDS

Recommendations

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

- The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if rapid improvement in oxygenation is not observed, the treatment should be tapered **(CIII)**.
- The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers **(CIIa)**.
- If recruitment maneuvers are used, the Panel **recommends against** the use of staircase (incremental PEEP) recruitment maneuvers **(AIIa)**.

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 patients with 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.[32] Because recruitment maneuvers can cause barotrauma or hypotension, patients should be closely monitored during the maneuvers. If a patient decompensates during recruitment maneuvers, the maneuvers 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 in-hospital mortality (risk ratio 0.90; 95% CI, 0.78–1.04).[23] However, a subgroup analysis found that traditional recruitment maneuvers significantly reduced in-hospital mortality (risk ratio 0.85; 95% CI, 0.75–0.97). Mortality was higher among patients treated with incremental PEEP titration recruitment maneuvers than among those treated with traditional recruitment maneuvers, but this difference was not statistically significant (risk ratio 1.06; 95% CI, 0.97–1.17).

There are no prospective trials of pulmonary vasodilators in people with COVID-19. However, a meta-analysis of mostly small, retrospective trials did not show improved outcomes.[33] A Cochrane review of 13 trials evaluated the use of inhaled nitric oxide in patients with ARDS who did not have COVID-19 and found no reduction in mortality.[34] 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.

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