Oxygenation and Ventilation for Children

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The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations in this section were informed by recommendations from the Surviving Sepsis Campaign guidelines for managing adult sepsis, pediatric sepsis, and COVID-19, as well as by recommendations from the 2023 Pediatric Acute Lung Injury Consensus Conference (2023 PALICC-2).

Goal of Oxygenation

Recommendations

- A target oxygen saturation measured by pulse oximetry (SpO_2) of 92% to 97% is recommended for most children with COVID-19 who require supplemental oxygen **(AIIb)**.
- For children with severe pediatric acute respiratory distress syndrome (PARDS; i.e., with an oxygenation index ≥16 or an oxygen saturation index ≥12), an SpO_2 <92% can be considered to minimize exposure to a high fraction of inspired oxygen (FiO_2), but prolonged periods of an SpO_2 <88% should be avoided **(CIII)**.

Rationale

The optimal SpO_2 in children with COVID-19 is unknown. However, there is no evidence that the target SpO_2 should differ from the 2023 PALICC-2 recommendation.[1] An SpO_2 of 92% to 97% is recommended for most children with COVID-19 who require supplemental oxygen. The potential harm of hyperoxia in children was demonstrated in a meta-analysis of 11 observational studies of children without COVID-19.[2] The study demonstrated that critically ill children with hyperoxia had greater odds of mortality than those without hyperoxia (OR 1.59; 95% CI, 1.00–2.51). However, across the included studies, there was significant heterogeneity for populations, definitions of hyperoxia, and the timing of assessments for mortality outcomes. For children with severe PARDS, an SpO_2 <92% can be considered to minimize exposure to a high FiO_2.[1] Although no evidence clearly identifies a safe minimum SpO_2 in children, prolonged exposure to an SpO_2 <88% should be avoided. When a patient's SpO_2 is <92%, monitoring oxygen delivery markers, including central venous SpO_2, is suggested.[3]

The limitations of currently available measurement devices should be considered when using pulse oximetry to manage children with COVID-19 or PARDS. Observational studies in children have reported that pulse oximetry may be inaccurate, particularly at lower oxygen saturations (≤90%) and for children who are Black.[4,5] These reports are consistent with several observational studies in adults that identified inaccuracies in pulse oximetry measurements, particularly for patients with darker skin pigmentation.[6-8] See Clinical Spectrum of SARS-CoV-2 Infection for more information.

Although procedures vary across institutions, the treatment of most patients with PARDS is managed without the use of arterial lines or arterial blood gas testing because arterial line placement in children, especially young children, can result in complications.[9-11] Clinicians should monitor for adequate delivery of oxygen or consider lowering the threshold for arterial line placement if a patient's SpO_2 measurements could be unreliable (e.g., for children who have darker skin or low SpO_2 levels). Monitoring methods could include observing the patient for altered mentation, measuring venous oxygen saturation, or using near-infrared spectroscopy.

High-Flow Nasal Cannula Oxygen and Noninvasive Ventilation in Children With COVID-19 and Acute Respiratory Failure

Recommendations

- For infants and children with COVID-19 and persistent respiratory failure despite conventional oxygen therapy who have no indicators for endotracheal intubation, a time-limited trial of noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC) oxygen is recommended **(AIIa)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of HFNC oxygen over NIV or the use of NIV over HFNC oxygen in infants and children with COVID-19.

Rationale

No high-quality studies have evaluated the use of HFNC oxygen or NIV in children with COVID-19. Therefore, when choosing a mode of respiratory support for children with COVID-19, the principles of management used for patients without COVID-19 should be followed. Both the Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children and the 2023 PALICC-2 recommend the use of NIV for children with respiratory failure who have no indication for intubation.[12,13]

Furthermore, the response to NIV, particularly in children with more severe hypoxemia or high work of breathing, should be gauged early (within the first several hours).[13] If the patient does not show improvement, intubation should be considered. To unload respiratory muscles, bilevel modes of NIV (with inspiratory pressure augmentation, such as BiPAP), if tolerated, are preferred over the use of continuous positive airway pressure (CPAP) alone, although CPAP is an alternative for children who cannot achieve an adequate seal with the NIV interface or who have significant patient-ventilator asynchrony.

HFNC oxygen is a relatively new, but increasingly used, mode of respiratory support for infants and children with acute respiratory failure.[14] Data from studies evaluating the effectiveness of HFNC oxygen relative to NIV or conventional oxygen are limited to studies of children with pneumonia in limited-resource settings and to studies of children with bronchiolitis. Two randomized controlled trials of children with pneumonia were conducted in limited-resource settings. One study demonstrated a slightly lower relative risk of mortality with the use of HFNC oxygen when compared with conventional oxygen therapy (aHR 0.79; 95% CI, 0.54–1.16), although the results were not statistically significant.[15] The other trial randomized patients to receive bubble CPAP, low-flow oxygen, or HFNC oxygen.[16] The children who received bubble CPAP demonstrated a lower risk of mortality than the children who received low-flow oxygen (relative risk 0.25; 95% CI, 0.07–0.89; $P = 0.02$). The results also indicated that for the composite outcome of treatment failure, there was no difference between the use of bubble CPAP and HFNC oxygen (relative risk 0.50; 99.7% CI, 0.11–2.29).

A randomized, noninferiority trial compared HFNC oxygen (2 L/kg/min) and nasal CPAP among 142 infants aged <6 months with bronchiolitis not caused by COVID-19.[17] The primary outcome was treatment failure within 24 hours, defined as an increase of ≥1 point in the modified Wood's Clinical Asthma Score or Échelle Douleur Inconfort Nouveau-Né (EDIN) score (a neonatal pain and discomfort scale), a respiratory rate >60 breaths/min and an increase of >10 breaths/min from baseline, or >2 severe apnea episodes per hour. Treatment failure occurred more often in the HFNC oxygen arm than in the nasal CPAP arm (51% vs. 31%), a result that failed to meet the prespecified noninferiority margin. Notably, in the HFNC oxygen arm, 72% of the patients who had treatment failure were managed successfully with nasal CPAP, and there were no differences between the arms for intubation rates or length of stay in the pediatric intensive care unit (ICU).

A systematic review of the noninferiority trial and 2 smaller trials that compared HFNC oxygen to nasal CPAP summarized the results of 213 infants and children aged ≤2 years with bronchiolitis.[18] Treatment failure in the 2 smaller trials was rare, and no differences were detected between the HFNC oxygen and nasal CPAP arms for any of the clinical outcomes.[19,20]

In a study that assessed whether higher flow rates of HFNC oxygen improved outcomes, 286 infants aged ≤6 months with severe bronchiolitis were randomized to receive HFNC oxygen 2 L/kg/min or HFNC oxygen 3 L/kg/min.[21] The primary outcome of treatment failure (i.e., an increase of ≥1 point in the Wood's Clinical Asthma Score or EDIN score, a respiratory rate >60 breaths/min and an increase of >10 breaths/min from baseline, or >2 severe apnea episodes per hour) occurred in 38.7% of the infants in the 2 L/kg/min arm and in 38.9% of the infants in the 3 L/kg/min arm ($P = 0.98$). Patient discomfort, as measured by EDIN score, occurred more often in the 3 L/kg/min arm than in the 2 L/kg/min arm (43% vs. 16%; $P = 0.002$).

HFNC oxygen is increasingly being used in children. These studies highlight the potential role of an HFNC oxygen trial in the management of children with acute respiratory failure due to COVID-19, particularly infants and young children who may have NIV-related challenges, such as poor mask fit, discomfort, or patient-ventilator asynchrony. For the use of HFNC oxygen in children, consider flow rates of up to 2 L/kg/min, with a maximum of 60 L/min. If patients do not improve within the first few hours of receiving HFNC oxygen, their treatment should be escalated to NIV or intubation.

Awake Prone Positioning in Children Not Receiving Mechanical Ventilation

Recommendations

- There is insufficient evidence for the Panel to recommend either for or against a trial of awake prone positioning in children with persistent hypoxemia who require HFNC oxygen or NIV and do not require endotracheal intubation.
- For patients with refractory hypoxemia who meet the indications for intubation and mechanical ventilation, the Panel **recommends against** the use of awake prone positioning as a rescue therapy to avoid intubation **(AIII)**.

Rationale

There are no high-quality pediatric data from studies that evaluated the effect of awake prone positioning on clinical outcomes in children with COVID-19 or in children with illness not related to COVID-19. Awake prone positioning may be considered for older children and adolescents. See Oxygenation and Ventilation for Adults for more information on the use of awake prone positioning in adults. In addition, pediatric clinicians should consider a child's developmental stage and ability to comply with the protocols for awake prone positioning.

Intubation for Mechanical Ventilation in Children With Acute COVID-19

Recommendations

- If intubation becomes necessary, the Panel recommends that an experienced practitioner perform the procedure in a controlled setting due to the enhanced risk of exposing health care practitioners to SARS-CoV-2 during intubation **(AIII)**.
- The Panel recommends using cuffed endotracheal tubes over uncuffed endotracheal tubes in children who require endotracheal intubation **(AIIb)**.

Rationale

To optimize the safety of patients and health care workers and maximize first-attempt success, intubation should be performed in a controlled setting by an experienced practitioner. In addition, cuffed endotracheal tubes are preferred for children of all ages to minimize leaks around the endotracheal tube, ensure delivery of ventilator pressure, decrease the risk of aspiration, reduce the need for endotracheal tube exchange, and reduce aerosolization of respiratory secretions during mechanical ventilation.[3,22-24]

General Considerations for Children With COVID-19 and PARDS Who Require Mechanical Ventilation

Recommendations

For children with COVID-19 and PARDS who require mechanical ventilation:

- 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) **(AIIb)**.
- The Panel recommends targeting plateau pressures of ≤28 cm H_2O in children with normal chest wall compliance and ≤32 cm H_2O in those with impaired chest wall compliance **(AIII)**.
- The Panel recommends using positive end-expiratory pressure (PEEP) at or above the level recommended in the Acute Respiratory Distress Syndrome (ARDS) Network's PEEP/FiO_2 table and titration of PEEP based on observed responses in oxygenation, hemodynamics, and respiratory system compliance **(AIIb)**.
- The Panel recommends permissive hypercapnia (i.e., 7.2–7.3 pH) to remain within lung-protective strategies and to minimize ventilator-associated lung injury, provided the patient does not have a coexisting condition that would be worsened by acidosis (e.g., severe pulmonary hypertension, ventricular dysfunction, intracranial hypertension) **(AIII)**.
- The Panel recommends limiting driving pressure as part of a lung-protective ventilation strategy **(BIIb)**.
- The Panel **recommends against** the routine use of inhaled nitric oxide **(AIII)**.

Rationale

There is no evidence that ventilator management in patients with PARDS due to COVID-19 should differ from ventilator management in patients with PARDS due to other causes. The Panel's recommendations are derived from the 2023 PALICC-2 recommendations.[1]

A large observational study conducted in 71 international pediatric ICUs reported that for patients with mild to moderate ARDS, less adherence to the recommended VT of 5 to 8 mL/kg (or 3 to 6 mL/kg for patients with severe ARDS) was associated with higher mortality and with more time on ventilation.[25] In general, supraphysiologic VT ventilation (>8 mL/kg) should not be used in patients with PARDS, and VT should be adjusted within the acceptable range to maintain other lung-protective ventilation targets (e.g., maintaining ≤28 cm H_2O plateau pressure). The use of ultra-low VT ventilation (<4 mL/kg) has not been systematically studied in children, so it should be used with caution.

The ARDS Network established a ventilation protocol that includes suggested low PEEP/high FiO_2 values.[26] Two observational studies reported better clinical outcomes associated with use of the suggested (or higher) PEEP levels when compared with lower PEEP levels.[25,27] The multicenter studies, which included nearly 1,500 pediatric patients with ARDS, demonstrated that PEEP levels lower than those suggested by the ARDS Network were associated with increased mortality.

Driving pressure (i.e., the difference between plateau pressure and PEEP) is a marker for lung strain.

It represents the ratio of delivered VT to respiratory system compliance. An observational study demonstrated that adults with ARDS who were mechanically ventilated and had a driving pressure >15 cm H_2O had increased mortality.[28] An observational study in children reported that higher driving pressure was associated with a longer duration of ventilation and fewer ventilator-free days.[29] The Panel's recommendation aligns with the 2023 PALICC-2 recommendation to limit driving pressure in patients with PARDS.

Inhaled nitric oxide can be considered as a rescue therapy for children with severe PARDS and COVID-19. In a small, randomized trial, the use of inhaled nitric oxide resulted in reduced use of extracorporeal membrane oxygenation (ECMO).[30] However, inhaled nitric oxide has a heterogeneous treatment effect, and many patients do not show improved gas exchange. Although adverse effects are rare, use of inhaled nitric oxide can have a substantial effect on health care costs. Therefore, inhaled nitric oxide should not be considered routine therapy for children with PARDS or COVID-19 who are receiving mechanical ventilation.

Fluid Management in Children With PARDS

Recommendation

- Following an initial resuscitation in children with PARDS due to COVID-19, clinicians should monitor and titrate fluid balance to maintain adequate intravascular volume while aiming to prevent positive fluid balance **(BIIb)**.

Rationale

There is no evidence that fluid management in patients with PARDS due to COVID-19 should differ from fluid management in patients with PARDS due to other causes. Therefore, the Panel's recommendation aligns with the 2023 PALICC-2 recommendations.[1] No pediatric randomized trials have directly compared a liberal fluid strategy to a conservative fluid strategy in patients with PARDS of any etiology. Several observational studies have demonstrated an association between greater fluid overload and worse clinical outcomes, including fewer ventilator-free days and increased mortality.[31-33]

In a multicenter study of 168 children with acute lung injury, daily and cumulative fluid balance were measured over the first 7 days after participants met the inclusion criteria.[31] After adjusting for demographic characteristics, pediatric risk of mortality III (PRISM III) scores, vasopressor use, and the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2), the study found that an increasing cumulative fluid balance on Day 3 was associated with fewer ventilator-free days, but no association with mortality was detected.

A more recent single-center study that included 732 children with acute lung injury demonstrated an association between higher cumulative fluid balance on Days 5 to 7 and increased mortality (OR 1.34 for 100 mL/kg on Day 5; 95% CI, 1.11–1.61) after adjusting for oxygenation index, the number of nonpulmonary organ failures, immunocompromised status, and vasopressor scores.[33] Also, greater cumulative fluid balance on Days 4 to 7 was associated with a lower probability of successful extubation by Day 28.

Collectively, the findings from these pediatric observational studies demonstrate the potential harm of fluid overload in patients with PARDS, particularly after 3 to 4 days of illness. These results are consistent with the findings from FACTT, a trial of conservative versus liberal fluid management strategies in adults.[34] In adults, FACTT found no difference between the arms for 60-day mortality, but the conservative strategy arm demonstrated improved oxygenation and less time on mechanical ventilation and in the ICU when compared with the liberal strategy arm. However, no analysis of data from prospective pediatric

trials delineates a causal relationship between a specific, protocolized fluid management strategy, or the timing of such a strategy, and clinical outcomes. Therefore, an individualized fluid management approach that is titrated to maintain intravascular volume while preventing excessive positive fluid balance, as suggested by the 2023 PALICC-2 recommendations, is appropriate.[1]

Neuromuscular Blockade in Mechanically Ventilated Children With Severe PARDS

Recommendation

- For mechanically ventilated children with severe PARDS and COVID-19, the Panel recommends minimal yet effective use of neuromuscular blocking agents in conjunction with sedation if sedation alone is inadequate to achieve lung-protective ventilation **(BIII)**.

Rationale

There is no evidence that the use of neuromuscular blockade in children with COVID-19 should differ from practices used for severe PARDS from other causes. Therefore, the Panel's recommendation aligns directly with the 2023 PALICC-2 recommendation.[1]

Therapies for Mechanically Ventilated Children With Severe PARDS and Refractory Hypoxemia

Recommendations

For children with severe PARDS and refractory hypoxemia after other oxygenation strategies have been optimized:

- The Panel recommends the use of inhaled nitric oxide as a rescue therapy; if a patient's oxygenation does not improve rapidly, the inhaled nitric oxide should be discontinued **(BIIb)**.
- The Panel recommends prone positioning for 12 to 16 hours per day over no prone positioning **(BIII)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of recruitment maneuvers, but if they are used in children, slow incremental and decremental adjustments in PEEP are preferred over sustained inflation maneuvers.
- There is insufficient evidence for the Panel to recommend either for or against the use of high-frequency oscillatory ventilation (HFOV) in patients with PARDS.

Rationale

There is no evidence that the use of inhaled nitric oxide, prone positioning, or HFOV in children with COVID-19 should differ from practices used for severe PARDS from other causes. Therefore, the Panel's recommendations are based on the 2023 PALICC-2 recommendations.[1]

One randomized controlled trial and 2 propensity-matched, observational studies in the past 10 years evaluated the use of inhaled nitric oxide in patients with PARDS.[30,35,36] The randomized controlled trial included 55 patients and found that the use of inhaled nitric oxide resulted in no statistical difference between the arms for 28-day mortality (8% mortality in the inhaled nitric oxide arm vs. 28% in the placebo arm), although the trial was underpowered for this outcome.[30] However, the inhaled nitric oxide arm had approximately 5 more ventilator-free days than the placebo arm, a result that was primarily mediated by avoiding the use of ECMO.

Results from observational studies have shown that patients who received inhaled nitric oxide did not improve or have fewer ventilator-free days.[35,36] A meta-analysis of randomized controlled trials

in patients with PARDS reported that treatment with inhaled nitric oxide did not decrease mortality, ventilator-free days, or duration of ventilation.[37] Although the evidence is insufficient to recommend the use of inhaled nitric oxide for all patients with ARDS, in cases of severe hypoxemia, it can be considered as a rescue therapy to potentially avoid the use of ECMO.

No recent studies have evaluated the role of prone positioning in patients with PARDS, although a large, multicenter trial is ongoing. Therefore, the Panel's recommendation to consider prone positioning in cases of severe PARDS aligns with the 2023 PALICC-2 recommendation and is supported by data from studies in adults, primarily from PROSEVA, a trial on prone positioning in patients with ARDS.[38]

The 2023 PALICC-2 does not recommend for or against recruitment maneuvers.[1] However, the Panel suggests using careful incremental and decremental adjustments in PEEP if these maneuvers are applied in children with refractory hypoxemia. In children, this approach to recruitment maneuvers is preferred over sustained inflation maneuvers due to the increased risk of harm from barotrauma and hemodynamic compromise in patients with sustained inflation. Clinical trials in adults have highlighted the potential harm of applying these maneuvers to patients who may not have the potential for lung recruitment.[39,40]

Three small randomized controlled trials examined the use of HFOV for PARDS.[41-43] None of these studies found a significant difference for mortality. Several observational studies that used propensity matching reported no difference in outcomes between the HFOV and conventional ventilation arms or reported a potential for higher mortality or longer ventilation time with the use of HFOV when compared with conventional ventilation.[44-48] In some of these analyses, residual confounding has been a concern. Therefore, the Panel determined that there is insufficient evidence to recommend either for or against the use of HFOV in patients with PARDS due to COVID-19. Some concerns have been raised about the use of HFOV and the aerosolization of COVID-19; however, adding a filter to the expiratory limb of the HFOV circuit may alleviate these concerns.

Multisystem Inflammatory Syndrome in Children

More than half of the patients with multisystem inflammatory syndrome in children (MIS-C) require mechanical ventilation or NIV.[49-51] For patients with MIS-C, the indications for mechanical ventilation vary and include shock or cardiac dysfunction, pulmonary edema, procedural preparation (e.g., to facilitate sedation for central venous catheter placement), respiratory failure, or neurologic failure. The management of oxygenation and ventilation in patients with MIS-C should follow the usual principles of shock management outlined in the Surviving Sepsis Campaign guidelines for children, as well as the principles for clinical management of heart failure and general critical care, as appropriate.[12]

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