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Invasive and non-invasive ventilation strategies for acute respiratory failure in children with COVID-19

Jennifer A. Blumenthal^{1,2}, Melody G. Duvall^{1,*}

¹Division of Critical Care Medicine, Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA.

²Division of Infectious Diseases, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA.

Abstract

Purpose of review—Severe Acute Respiratory Syndrome Coronavirus 2 presents as symptomatic COVID-19 disease in susceptible patients. Severe pediatric COVID-19 disease is rare, limiting potential data accumulation on associated respiratory failure in children. Pediatric intensivists and pulmonologists managing COVID-19 patients look to adult guidelines and pediatric-specific consensus statements to guide management. The purpose of this article is to review the current literature and recommended strategies for escalation of non-invasive and invasive respiratory support for acute respiratory failure associated with COVID-19 disease in children.

Recent Findings—There are no prospective studies comparing COVID-19 treatment strategies in children. Adult and pediatric ventilation management interim guidance is based on evidence-based guidelines in non-COVID acute respiratory distress syndrome, with considerations of 1) non-invasive positive pressure ventilation versus high-flow nasal cannula and 2) high versus lower PEEP strategies related to lung compliance and potential lung recruitability.

Summary—Management of acute respiratory failure from COVID-19 requires individualized titration of non-invasive and invasive ventilation modalities with consideration of preserved or compromised pulmonary compliance. Research regarding best practices in management of pediatric severe COVID-19 with respiratory failure is lacking and is acutely needed as the pandemic surges and vaccination of the pediatric population will be delayed compared to adults.

Keywords

COVID-19; respiratory failure; mechanical ventilation; non-invasive ventilation; pediatric acute respiratory distress syndrome

*Correspondence to Melody Duvall, MD, PhD, Division of Critical Care Medicine, Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA, 02115, USA. Tel: 617-355-7327; melody.duvall@childrens.harvard.edu.

Conflicts of interest
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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection resulting in coronavirus disease 2019 (COVID-19) continues to sweep through the world's vulnerable populations, generally sparing children the worst outcomes [1–3]. Cumulative CDC data on COVID-19 incidence in pediatric patients aged 0–24 years from March to December 2020 reported that 2.5% required hospitalization and 0.8% required admission to an ICU [3]. Early reports on hospitalized COVID-19 pediatric patients indicated that 5.8% required invasive mechanical ventilation, 3.9% were managed with non-invasive positive pressure ventilation (CPAP or BiPAP), 2.4% with HFNC, and 2% met criteria for acute respiratory distress syndrome (ARDS) [2]. Of children with acute COVID-19 disease admitted to pediatric ICUs in North America, 38% required invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO) was required rarely, and mortality was low (4%) [1]. Early in the pandemic, adult COVID-19 management guidelines favored an early intubation strategy given risks of aerosolization with modes of non-invasive ventilation. As more safety data has become available, adult guidelines now allow for a more conservative approach with high flow nasal cannula (HFNC) and self-proning when appropriate [4–6].

Ultimately, there is no definitive pediatric evidence to support one mode of respiratory support over another for severe COVID-19 disease, and it is reasonable to consider that pediatric respiratory illness may be distinct from adult respiratory illness related to differences in the maturation of the alveoli, airways and respiratory musculature [7]. In that setting, pediatric intensivists and pulmonologists should utilize lung protective ventilation strategies, routinely applied in pediatric acute respiratory distress syndrome (PARDS) patients, to titrate support for each child's individual respiratory mechanics [8, 9].

Pathophysiology and Impairment of Gas Exchange

COVID-19 disease is an acute viral illness associated with diffuse alveolar damage and pulmonary endothelial disease that can lead to clinical respiratory failure [10]. SARS-CoV-2 requires angiotensin-converting enzyme 2 (ACE2) receptors for virion entry into susceptible cells [11]. ACE2 receptors are extensively expressed on type II pneumocytes and infection and damage of these surfactant-producing cells can result in significant lung damage with alveolar collapse and widespread atelectasis leading to impaired gas exchange and profound hypoxemia [12, 13]. Pulmonary capillary endothelial cells are also susceptible to SARS-CoV-2 infection and a compromised epithelial-endothelial barrier results in early capillary leak and alveolar influx of inflammatory immune cells [14]. Persistent inflammation leads to increased vascular permeability, pulmonary edema, alveolar interstitial thickening and hyaline membrane formation that, along with microvascular thrombosis, compromises gas exchange [14, 15]. Microvascular thrombi can be caused by direct viral injury to the endovascular tissue and the resultant host immune response and highly active coagulation and inflammatory cascades result in endotheliitis [16]. Pulmonary vasoconstriction driven by hypoxemia likely contributes to increased dead space and is exacerbated by microvascular thrombi which further impairs gas exchange [17]. Together, these insults on both sides of the alveolar-capillary interface results in compromised gas exchange through a mixed disease

process of intrapulmonary shunting, disruption of V/Q matching, and increased pulmonary dead space [18].

Adults with COVID-19 pneumonia and severe hypoxemia generally fulfill the Berlin criteria for acute respiratory distress syndrome (ARDS) [19], yet many patients have preserved ability to exchange CO₂ and near-normal pulmonary compliance [20]. Two subphenotypes of adult COVID-19 ARDS distinguished by pulmonary compliance and lung recruitability have been proposed [20, 21]. Evaluating pulmonary compliance, where compliance equals the change in lung volume over the change in pressure, can help stratify COVID-19 ARDS patients by clinical subphenotype and potentially inform ventilator management strategies. The proposed “H-type” adult COVID-19 ARDS subphenotype is characterized by high elastance and low compliance with extensive pulmonary infiltrates and higher potential lung recruitability where a higher PEEP strategy to recruit lung may be beneficial [20, 21]. The proposed “L-type” adult COVID-19 phenotype is characterized by low elastance and high compliance with less prominent parenchymal disease and low recruitability and a lower PEEP strategy may mitigate risk of overdistention [20, 21]. Given that ARDS is a common endpoint definition for a heterogeneous group of disease processes, these physiologic subphenotypes are not likely to be unique to COVID-19 ARDS. The phenotypic pattern of preserved pulmonary compliance combined with profoundly impaired gas exchange is also evident in a subset of non-COVID-19 ARDS patients [22]. These clinical ARDS subphenotypes are frameworks to consider when determining initial or dynamic PEEP titration to ensure adequate lung expansion for optimal gas exchange while avoiding hemodynamic insult.

Assessing respiratory disease severity in children with COVID-19

Children diagnosed with COVID-19 should be evaluated carefully and serially for evidence of respiratory distress or failure (Figure 1). The international Pediatric Acute Lung Injury Consensus Conference (PALICC) has defined criteria for pediatric ARDS (PARDS) and the PALICC criteria are applicable for diagnosing COVID-19 related ARDS in children and stratifying severity of hypoxemia (Figure 1) [9, 23, 24]. Guidelines for the management of acute respiratory failure with COVID-19 are largely focused on the adult population [4–6]. The European Society of Pediatric and Neonatal Intensive Care (ESPNIC) recently published a consensus statement providing recommendations for the care of critically ill children with COVID-19 [25] and an international collaboration of pediatric intensivists developed ICU guidelines for pediatric COVID-19 patients [26]. The ESPNIC and COVID-19 PICU Guidelines are consistent with PALICC and Pediatric Mechanical Ventilation Consensus Conference (PEMVECC) expert opinion recommendations on ventilation strategies for PARDS [8, 9, 27].

In the following sections, we review and compile recommendations for escalation of respiratory support for critically ill pediatric COVID-19 patients (Figure 1) with reference to available pediatric and adult literature and guidelines.

Supplemental oxygen and high flow nasal cannula (HFNC)

For children with COVID-19 and hypoxemia ($SpO_2 < 90\%$), supplemental oxygen should be initiated via nasal cannula and titrated to target SpO_2 92–96% [25, 26]. If hypoxemia persists, oxygen via simple facemask may be initiated [26]. There are not clear recommendations on escalation to non-rebreather facemasks in pediatric patients. In adult COVID-19 patients in whom conventional oxygen therapy is insufficient to achieve oxygenation goals, guidelines recommend humidified HFNC over non-invasive positive pressure ventilation (NIPPV) for escalation of support [4–6]. HFNC has been shown to be more effective than standard oxygen supplementation or NIPPV in adults with non-COVID-19 acute hypoxemic respiratory failure in achieving lower rates of intubation and lower mortality [28–30]. In adults with COVID-19, HFNC may reduce the need for intubation and invasive mechanical ventilation [31] and can be utilized in lower resource settings [32]. Awake self-prone positioning combined with HFNC may be an effective non-invasive strategy for hypoxemia in adults with COVID-19 [33–35]. Physiologic mechanisms by which HFNC provides benefit are likely multifactorial with contributions of anatomic dead space washout with reduced minute ventilation and decreased work of breathing, increased alveolar PaO_2 via reduced entrainment of ambient air, and possibly improved dynamic compliance and V/Q matching [36, 37].

Children with COVID-19 with persistent hypoxemia or labored work of breathing despite supplemental oxygen can be escalated to humidified HFNC, particularly if SpO_2/FiO_2 ratio is maintained > 264 [25, 26]. For children with $SpO_2/FiO_2 < 264$ but > 221 , ESPNIC guidelines recommend NIPPV rather than HFNC [25]. Pediatric practitioners are versed in the use of HFNC for children with viral bronchiolitis [38, 39] and HFNC reduces work of breathing in pediatric acute respiratory failure [40]. Vigilant monitoring for clinical deterioration is imperative when escalating respiratory support in infants and children and the clinical response to a trial of non-invasive respiratory support should be determined within ~60 minutes [25].

Non-invasive positive pressure ventilation: CPAP and BiPAP

Current adult guidelines generally recommend the use of HFNC over NIPPV for worsening COVID-19 associated hypoxemia unless HFNC is unavailable or if intubation is not within the patient's goals of care [4–6]. Contraindications to the safe use of NIPPV in children and adults include altered mental status, risk of aspiration, vomiting, significant secretions, or severe respiratory distress and high work of breathing. Pediatric COVID-19 patients with progressive or persistently increased work of breathing and hypoxemia can be escalated to NIPPV (CPAP or BiPAP) [25, 26]. Recommendations differ as to whether NIPPV or HFNC should be the first line approach, but for the pediatric patient whose SpO_2/FiO_2 is < 264 but > 221 (or PaO_2 / FiO_2 200–300) or where HFNC is unavailable, use of NIPPV can be considered [25, 26]. The use of NIPPV remains appropriate per standard of care treatment algorithms for status asthmaticus in pediatric asthma patients with SARS-CoV-2 [41, 42]. Helmet type non-invasive interfaces are preferable if available given reduced risk of aerosolized droplet dispersion [25]. Care must be taken to observe the spontaneously breathing patient for signs of significant work of breathing and large tidal volumes that could result in patient self-inflicted lung injury and may contribute to non-invasive

ventilation failure [43, 44]. Pediatric data on self-inflicted lung injury is insufficient to determine the relevance of this pathophysiology in children.

Signs of success with non-invasive ventilation strategies include improvement in oxygenation, reduction in respiratory rate, and diminished work of breathing. Evaluating for clinical improvement after initiation of NIPPV in a child should occur rapidly (~60 minutes), and intubation should be pursued if non-invasive support fails to achieve target SpO₂ 92–96% and FiO₂ < 60% [25]. Failure of non-invasive ventilation in non-COVID-19 PARDS is strongly correlated with degree of hypoxemia with 50% of patients with PaO₂ / FiO₂ ratio < 100 on NIPPV requiring intubation within 24 hours [45].

Indications for intubation of pediatric COVID-19 patients

In the event of progressive respiratory distress or inadequate gas exchange despite HFNC or NIPPV support, intubation and mechanical ventilation should be initiated. Guidelines are clear that intubation should not be delayed in pediatric COVID-19 patients with clinical deterioration and evidence of severe respiratory distress, high work of breathing and compromised respiratory mechanics, moderate to severe hypoxemia (PaO₂/FiO₂ < 200 or SpO₂/FiO₂ < 221), inadequate ventilation (pH < 7.2) or lethargy and evidence of progressive fatigue (Figure 1) [25, 26]. A higher threshold for intubation is noted to be a reasonable approach in patients with isolated hypoxemia with non-labored work of breathing and non-injurious respiratory mechanics [25].

Conventional Mechanical Ventilation

A lung protective ventilation strategy targeting expiratory tidal volume 5–7 ml/kg ideal body weight, inspiratory plateau pressure < 28–32 cm H₂O, driving pressure < 15 cm H₂O, and permissive hypercapnia (pH > 7.2) is recommended (Figure 1) [25]. Lower tidal volumes (3–6 ml/kg) may be necessary for patients with impaired compliance [9, 25, 27]. Measurements of static respiratory system compliance may facilitate distinguishing patients with preserved versus impaired compliance [46] and can inform PEEP management. Considering the proposed clinical subphenotypes of adult COVID-19 ARDS patients with preserved compliance (“L type”, low elastance) versus those with low compliance (“H type”, high elastance) [20, 21] may also guide ventilator management in pediatric patients [25]. It should be noted, however, that there is no data from prospective clinical trials to support that subphenotype classification predicts treatment response or improves outcomes. Many experts conclude that tailored ventilation strategies based on subphenotypes is premature and advocate for applying evidence-based lung protective ventilation protocols developed in the pre-COVID-19 era to COVID-19 ARDS patients as standard of care [47–49].

ESPNEC recommend initiating PEEP at 8–10cm H₂O and titrating PEEP and FiO₂ according to the ARDSNet “low PEEP/FiO₂ grid” [50, 51] to maintain SpO₂ 92–96% for moderate or 88–92% for severe PARDS [25]. Patients with preserved lung compliance may require lower PEEP (and higher PEEP may be injurious given risk of overdistension and volutrauma) whereas patients with impaired compliance may benefit from higher PEEP to improve lung recruitment [20, 21, 52]. Optimal application of PEEP for recruitment of the injured lung must balance prevention of both atelectrauma and volutrauma while weighing

improvements in oxygenation and lung recruitment against deleterious effects on hemodynamics [53]. Individualized titration of PEEP with stepwise trials of increasing and decreasing PEEP to optimize oxygenation and lung recruitment while closely monitoring for and avoiding hemodynamic compromise is warranted [8, 9, 20, 21, 25–27].

Ancillary supportive measures and advanced modes of ventilation

Neuromuscular blockade is advised for ~48 hours in patients with profound hypoxemia ($\text{PaO}_2 / \text{FiO}_2 < 150$, Oxygenation index (OI) ≤ 16 or Oxygenation Saturation Index (OSI) ≤ 10) to mitigate patient/ventilator dyssynchrony and to avoid high plateau pressures [25]. Prone positioning can be considered for refractory hypoxemia despite PEEP titration [25] – see also “TITLE” by Dr. Peter Mourani in this edition. A trial of inhaled nitric oxide (iNO) could be considered if refractory hypoxemia is presumed related to hypoxic pulmonary vasoconstriction, increased dead space fraction, and V/Q mismatch [25], but improved oxygenation with iNO in PARDS has not been shown to reduce mortality [54]. High frequency oscillatory ventilation (HFOV) could be considered for the patient requiring high ventilator pressures or when hypoxemia is refractory to PEEP, but mitigating aerosol generation by HFOV by adding a filter to the expiratory limb would be required [25]. Alternate ventilation modes (e.g. APRV) should be considered with caution unless pediatric providers are experienced with the mode. Support with extracorporeal membrane oxygenation (ECMO) may be considered in available centers for pediatric COVID-19 patients without contraindications with refractory hypoxemia despite maximal medical management [25, 26, 55].

Aerosol generation with different modes of ventilatory support

A challenging aspect of caring for patients with severe COVID-19 disease has been mitigating the risk of transmission of SARS-CoV-2 to providers during aerosol generating procedures (AGPs). Which procedures and supports are considered AGPs varies amongst hospitals, but commonly include HFNC, CPAP, BiPAP, bag-valve-mask ventilation, intubation, extubation, bronchoscopy, open tracheal suctioning, and chest compressions. Transmission of SARS-CoV-2 occurs primarily through spread of respiratory droplets (particles $> 5\text{--}10\ \mu\text{m}$ in diameter) but AGPs can generate smaller aerosol particles ($< 5\text{--}10\ \mu\text{m}$ in diameter) that may remain suspended in air and more easily dispersed [56]. Quantifying the risk of aerosol transmission should include considerations of both the amount of aerosol particles generated and the distance of dispersion. Respiratory droplet dispersion distance is determined by both the force of expiration (e.g. coughing) and the mechanical support device and filtration system utilized [57]. In healthy adults, the amount of aerosol particles generated from the respiratory tract may be equivalent between low flow oxygen, HFNC, and BiPAP [58]. CPAP and BiPAP, however, disperse particles over a further distance than low flow oxygen or HFNC, but utilization of oronasal interfaces or helmet devices can significantly mitigate droplet dispersion during NIPPV (reviewed in [57]). Notably, HFNC may not increase aerosol dispersion more than low flow oxygen as initially feared [57, 59] and a surgical mask placed over HFNC could be an effective strategy to mitigate droplet dispersion in COVID-19 [57, 60]. Comparative data are lacking in children who are generally managed on lower flow rates of HFNC and lower CPAP/BiPAP pressures, which could influence both aerosol generation and dispersion.

Intubation of COVID-19 patients is ideally performed in a negative pressure room by an expert in airway management utilizing maximal PPE, video laryngoscopy, cuffed endotracheal tube, and avoidance of positive pressure to minimize respiratory droplet dispersion [61]. Best patient care practices should be followed at individual hospitals to keep both healthcare providers and patients safe from exposure to infectious particles during AGPs [62] and frameworks to safely address airway complications in mechanically ventilated COVID-19 patients can be helpful tools [63].

Conclusion

Management of COVID-19 associated respiratory failure in pediatric patients requires a multidisciplinary team of pediatric intensivists, pulmonologists, respiratory therapists and expert nurses to monitor and escalate respiratory support rapidly. The phenotypes of COVID-19 associated lung disease in children appear to be on the well-described spectrum of classic PARDS [9]. Utilizing evidence-based PARDS criteria and management guidelines, including adjusting ventilation strategy for dynamic respiratory mechanics, should guide escalation of respiratory support for severe pediatric COVID-19 disease. As data and experience in managing children with COVID-19 is expected to accumulate over time as the pandemic persists, pediatric clinicians would be prudent to continue proactive and ongoing updates to their hospital's approach to the care of the child with COVID-19 disease as the collective knowledge advances.

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Key Points

- Severe pediatric COVID-19 disease is relatively uncommon, but some children develop respiratory failure requiring escalation of respiratory support.
- Severe COVID-19 compromises gas exchange through V/Q mismatch, increased pulmonary dead space, and intrapulmonary shunting.
- High flow nasal cannula or non-invasive support with CPAP or BiPAP can be trialed with close monitoring for clinical deterioration and need for rapid escalation.
- Mechanical ventilation strategies for children with COVID-19 should follow lung protective ventilation guidelines for pediatric acute respiratory distress syndrome.
- Aerosol generation should be minimized while providing adequate respiratory support.

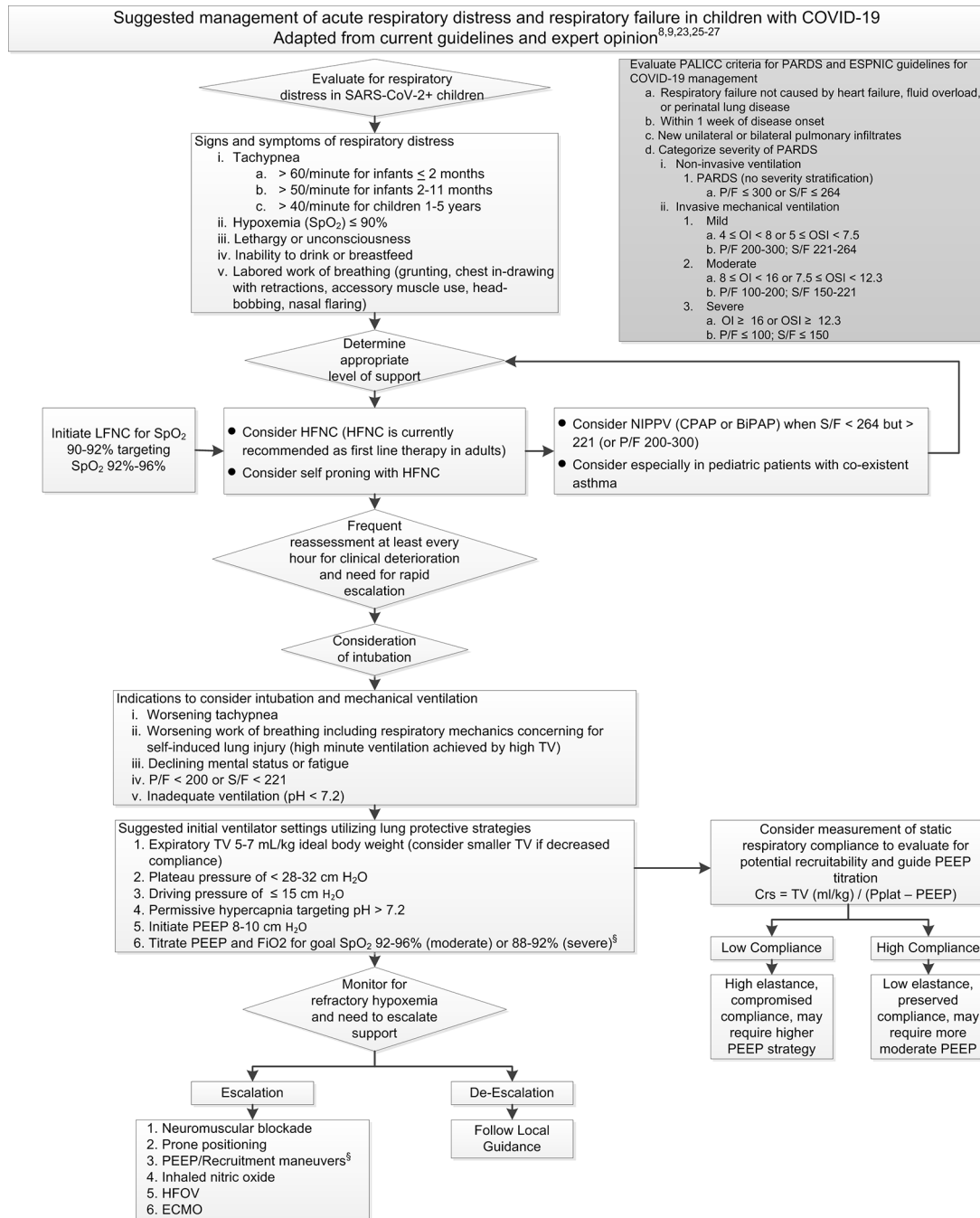


Figure 1. Suggested management of acute respiratory distress and respiratory failure in children with COVID-19.

Abbreviations: PARDS – pediatric acute respiratory distress syndrome, SpO₂ – oxygen saturation, LFNC – low flow nasal cannula, HFNC – high flow nasal cannula, NIPPV – non-invasive positive pressure ventilation, CPAP – continuous positive airway pressure, BiPAP – bilevel positive airway pressure, S/F – SpO₂/FiO₂ ratio, P/F – PaO₂/FiO₂ ratio, TV – tidal volume, HFOV – high frequency oscillatory ventilation, ECMO – extracorporeal membrane oxygenation, Cr_s – respiratory system compliance, VT – tidal volume, P_{plat} – plateau pressure. OI – oxygenation index = [(FiO₂ × mean airway pressure)/PaO₂]. OSI –

oxygenation saturation index = $[(\text{FiO}_2 \times \text{mean airway pressure})/\text{SpO}_2]$. [§] Evaluate closely for deleterious changes in hemodynamics with all ventilator pressure titrations.

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