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Clinical update on COVID-19 for the emergency clinician: Airway and resuscitation

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ABSTRACT

Introduction: Coronavirus disease of 2019 (COVID-19) has resulted in millions of cases worldwide. As the pandemic has progressed, the understanding of this disease has evolved.

Objective: This narrative review provides emergency clinicians with a focused update of the resuscitation and airway management of COVID-19.

Discussion: Patients with COVID-19 and septic shock should be resuscitated with buffered/balanced crystalloids. If hypotension is present despite intravenous fluids, vasopressors including norepinephrine should be initiated. Stress dose steroids are recommended for patients with severe or refractory septic shock. Airway management is the mainstay of initial resuscitation in patients with COVID-19. Patients with COVID-19 and ARDS should be managed similarly to those ARDS patients without COVID-19. Clinicians should not delay intubation if indicated. In patients who are more clinically stable, physicians can consider a step-wise approach as patients' oxygenation needs escalate. High-flow nasal cannula (HFNC) and non-invasive positive pressure ventilation (NIPPV) are recommended over elective intubation. Prone positioning, even in awake patients, has been shown to lower intubation rates and improve oxygenation. Strategies consistent with ARDSnet can be implemented in this patient population, with a goal tidal volume of 4–8 mL/kg of predicted body weight and targeted plateau pressures <30 cm H₂O. Limited data support the use of neuromuscular blocking agents (NBMA), recruitment maneuvers, inhaled pulmonary vasodilators, and extracorporeal membrane oxygenation (ECMO).

Conclusion: This review presents a concise update of the resuscitation strategies and airway management techniques in patients with COVID-19 for emergency medicine clinicians.

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1. Introduction

Coronavirus disease of 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a global pandemic, with the first outbreak in late 2019 in Wuhan, Hubei Province, China [1,2]. This paper is the final submission of a series that provides focused updates of COVID-19 for emergency clinicians [3,4]. This review will focus specifically on acute resuscitation and airway management in the patient with severe COVID-19 not involving cardiac arrest.

Although our understanding of COVID-19 has evolved, more treatments are available, and the virus itself has changed. Airway management remains a significant contributor to hospital resource utilization and patient outcomes. Early in the pandemic, a strategy of early intubation with mechanical ventilation was used for those with severe hypoxia. However, this strategy was not associated with improved patient outcomes including mortality. As the pandemic progressed, noninvasive techniques including high flow nasal cannula and noninvasive positive pressure ventilation (bilevel positive airway pressure [BPAP] and continuous positive airway pressure [CPAP]) have demonstrated efficacy and safety in improving patient respiratory status. The use of steroids for those with hypoxia has also become a central component of treatment.

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Greater clinician experience and modifications in treatment strategy have resulted in improved patient outcomes during the pandemic. Data from the Centers for Disease Control and Prevention (CDC) and the National Hospital Care Survey (NHCS) submitted by 41 hospitals from March 2020 through September 2021 demonstrated an inpatient mortality rate for COVID-19 patients as high as 23.2% in April 2020, before falling to an all-time low of 2.8% in September 2021. During this same time frame, intubated patients with COVID-19 had a mortality rate ranging from 74.1% in March 2020 to a high of 81.8% in May 2021, before decreasing to under 50% in September 2021. Patients discharged alive following intubation or ventilator use had an average length of stay (LOS) of 30 days at the beginning of the pandemic. The most recent data from August 2021 shows the average length of stay (LOS) for this population is 21.3 days. For those patients requiring ventilation who died in-hospital, LOS was much shorter. In April 2020, average LOS was as short as 14.3 days, increasing to a high of 24.9 days in October 2021, with more recent data in August 2021 showing that the average LOS is approximately 2 weeks. It is important to note these data are not nationally representative of the United States (US) [5].

2. Methods

A literature review of PubMed and Google Scholar databases was performed for articles up to February 23, 2022, using the keywords 'COVID' OR 'COVID-19' OR 'SARS-CoV-2' OR 'coronavirus' AND 'airway' OR 'resuscitation' for this narrative review. The authors included retrospective and prospective studies, systematic reviews and meta-analyses, clinical guidelines, and other narrative reviews. Commentaries and letters were also included. The literature search was restricted to studies published or translated into English. Authors reviewed all relevant articles and decided which studies to include for the review by consensus, with focus on emergency medicine-relevant articles, including guidelines. A total of 131 resources were selected for inclusion in this review.

3. Discussion

3.1. Initial resuscitation in patients with COVID-19 and septic shock

Patients presenting with COVID-19 and septic shock should be treated identically to other medical patients without COVID-19 who present with septic shock [6]. The definition of septic shock is unchanged in patients with COVID-19 (defined as an infectious source present with vasopressors necessary to maintain mean arterial pressure (MAP) > 65 mmHg, and lactate >2 mmol/L, without underlying hypovolemia) [6]. Resuscitation with buffered/balanced crystalloids instead of unbalanced crystalloids or colloids is recommended, and a conservative fluid resuscitation strategy is favored over a liberal approach [6–11]. The World Health Organization (WHO) recommends administering an initial bolus of 250–500 mL of crystalloid (normal saline [NS], Ringer's lactate) rapidly over 15–30 min; additional fluid boluses of similar size should be tailored based on the patient's clinical response (fluid overload, MAP >65 mmHg, urine output (UOP) > 0.5 mL/kg/h, perfusion, capillary refill, hemodynamics, mental status, and lactate) [6]. To assess fluid responsiveness, skin temperature, capillary refill, and lactate measurements may be used in addition to dynamic measurements [6–8]. Limited evidence exists regarding this aspect of resuscitation and is based on historical treatment of patients with acute respiratory distress syndrome (ARDS). Albumin and colloids are not recommended for fluid resuscitation [8]. Hypoalbuminemia has been shown to be a risk factor for poor outcomes, but there is a lack of high-quality data supporting its use as a standard adjunct therapy [12].

3.2. Septic shock: Vasopressors and corticosteroids

If patients remain in shock during or after the initial fluid resuscitation, vasopressors should be initiated [6]. Among patients with

COVID-19 treated in the intensive care unit (ICU), studies suggest that 28–94% require vasopressors [13,14]. Norepinephrine is the first-line vasopressor due to its ability to increase MAP with fewer adverse effects such as arrhythmias and lower all-cause mortality in septic shock compared to other pressors, including dopamine [6–8,15]. Vasoactive agents should be titrated to a MAP of 60–65 mmHg, and an arterial catheter should be placed to monitor vascular pressure as soon as reasonably feasible [7,8]. Second line agents include vasopressin and epinephrine [7,8]. Vasopressin and epinephrine may be combined with norepinephrine to reach a MAP goal, while vasopressin can also be used as an adjunct to wean norepinephrine [7,8]. Dobutamine should be considered in patients who have signs of cardiac dysfunction and continuous organ hypoperfusion despite fluids and vasopressors [6,7]. A study of 31 ICU patients on norepinephrine found aerosolized milrinone did not have a positive impact on right ventricular (RV) function or afterload [16]. One retrospective study of 10 patients found adding angiotensin II reduced the norepinephrine equivalent dose by 30.4%; however, 50% of patients died after care was withdrawn and the other 50% of patients remained hospitalized [17]. In patients with severe or refractory septic shock, corticosteroids are recommended with consideration for dexamethasone or hydrocortisone as primary options (e.g., hydrocortisone 200 mg daily) [7]. For patients presenting with septic shock refractory to IV fluids and vasopressors who have previously received steroids for COVID-19, administering stress dose steroids (i.e., hydrocortisone 100 mg IV) should be considered. If they are currently receiving dexamethasone for treatment of COVID-19 but present with refractory septic shock, a steroid with mineralocorticoid effects (e.g., hydrocortisone) can be administered [7,18,19]. Additional discussion of the medical management for patients with COVID-19 has been addressed earlier in this series [4].

3.3. Airway updates and rescue maneuvers

Much of the morbidity and mortality associated with COVID-19 is due to pulmonary complications including hypoxemia and acute respiratory failure [20–22]. These typically occur the second week after the initial onset of symptoms [20,21]. As the disease progresses, patients may require increasing respiratory support, including low flow or high flow oxygen supplementation systems, noninvasive ventilation, and endotracheal intubation with mechanical ventilation. Patients with signs of severe respiratory failure or loss of airway control should be considered for early endotracheal intubation, especially if non-invasive options are unavailable.

3.3.1. Lung pathophysiology

The pathophysiology of lung injury in ventilated patients with COVID-19 and secondary ARDS may differ from those who are spontaneously breathing. Early evidence suggests that patient-self-inflicted lung injury (P-SILI) may be the corollary of ventilator-induced lung injury, which is caused by ventilation at high tidal volumes with increased pressures [23,24]. This can occur in early ARDS due to strong inspiratory effort causing elevated transpulmonary pressures and leakage of fluid. Initially, two subtypes of COVID-19 patients with ARDS (CARDS) were described: type L, which had low lung elastance and thus high compliance with a lower response to PEEP and type H, which were characterized by high lung elastance, low compliance and higher response to PEEP [24]. However, this has fallen out of favor, with more rigorous studies suggesting COVID-19 patients with ARDS should be managed similarly to ARDS patients without COVID-19 [8,25,26].

3.3.2. Oxygen saturation targets

Diagnostic criteria for severe COVID-19 pulmonary infection includes patients with oxygen saturation < 94% on room air, respiratory rate > 30 breaths/min, more than 50% of lung infiltrates, or PaO₂/FiO₂ < 300 mmHg [7]. It is unclear what the ideal oxygen saturation is for those patients with hypoxemia and COVID-19, but the National Institutes of

Health (NIH) suggests 92–96% [7]. The WHO recommends titrating oxygen saturation to $\geq 94\%$ during the initial resuscitation; for those with stable hypoxia without signs of distress a level of $\geq 90\%$ is reasonable. In pregnancy, the WHO recommends a goal oxygen saturation of 92–95% [6]. For patients with a peripheral oxygen saturation $< 90\text{--}92\%$, the Society of Critical Care Medicine (SCCM) recommends initiating supplemental oxygen and titrating to an oxygen saturation no greater than 96% [7]. Supplemental oxygen should be administered by nasal cannula or high-flow nasal cannula (HFNC) for those with severe COVID-19 with pulmonary involvement or hypoxemia as an initial strategy [6,7]. Maintaining oxygenation saturations outside these ranges has been linked to worse clinical outcomes [7,27,28]. Higher oxygen saturation targets and hyperoxia should be avoided. In a multicenter, randomized trial, patients with ARDS assigned to a conservative-oxygen strategy (goal PaO₂ 55–70 mmHg or pulse oximetry 88–92%) compared to a liberal oxygen strategy (goal PaO₂ 90–105 mmHg, pulse oximetry $\geq 96\%$) had higher 28-day (34.3% versus 26.5%) and 90-day mortality rates (44.4% versus 30.4%) [28]. Fig. 1 provides an algorithm for management of hypoxia in COVID-19.

3.3.3. Non-invasive oxygenation treatment modalities

Certain patients with severe COVID-19 require endotracheal intubation with mechanical ventilation early in their treatment course.

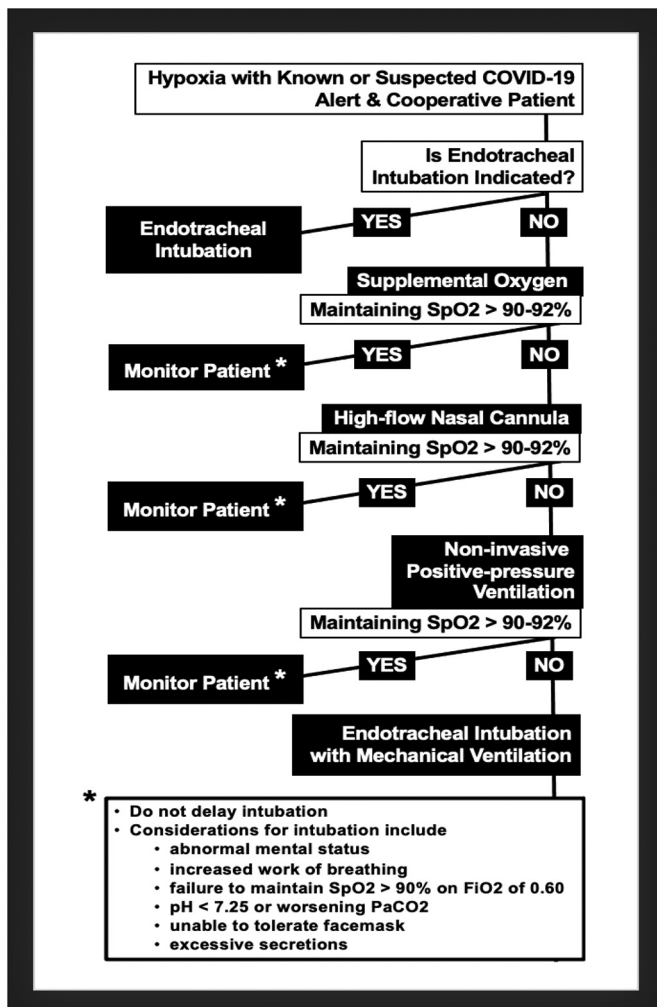


Fig. 1. Algorithm for approaching the hypoxic COVID-19 patient. Physicians should initially assess the need for intubation. If the patient condition does not require immediate intubation, physicians should utilize a step-wise approach escalating oxygen therapy as needed. Patients should be closely monitored to evaluate for potential intubation and response to airway interventions.

However, many patients can be safely and appropriately managed with non-invasive means of oxygenation and ventilation (i.e., interventions other than endotracheal intubation). For patients with hypoxemia, supplemental oxygen via a low-flow system such as nasal cannula can be used initially [7,29]. If oxygen flow rates greater than 6 L/min via nasal cannula are needed to maintain an oxygen saturation $\geq 90\text{--}92\%$, supplementation via a facemask can be utilized for higher flow rates, or a Venturi mask can be utilized [6–8,29]. For patients who remain hypoxic or demonstrate increased work of breathing despite these interventions, HFNC or NIPPV can be utilized [6,7,29]. With respect to terminology in this review, NIPPV refers to either CPAP or BPAP.

The NIH and SCCM recommend HFNC over NIPPV, though contraindications must be considered (Tables 1 and 2) [7,8]. Current data suggest HFNC reduces mortality, increases ventilator-free days, and decreases the risk of intubation [7,23]. HFNC is typically better tolerated compared to NIPPV due to patient comfort and improved ability to eat, drink, and speak. HFNC improves oxygenation by decreasing the anatomical dead space and provides a mechanism for increased PEEP [30,31]. Compared to other oxygen delivery systems, it can also humidify oxygen, allowing for washing out of CO₂ while providing nearly 100% oxygen in certain instances [30,31]. One study of COVID-19 patients with hypoxemic respiratory failure found HFNC was associated with more ventilator-free days than conventional oxygen and NIPPV (24 days vs 22 days vs 19 days, respectively). Subgroup analysis of patients with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO₂/FiO₂] ≤ 200 mmHg found that intubation rates were lower for HFNC versus conventional oxygen or NIPPV (hazard ratio 2.07 and 2.57, respectively) [32]. A later meta-analysis found HFNC reduced intubation rates compared to NIPPV (OR 0.48, 95% CI 0.31–0.73), as well as ICU mortality (OR 0.36, 95% CI 0.20–0.63) [33]. A randomized controlled trial (RCT) of patients with PaO₂/FiO₂ < 200 and COVID-19 found those receiving HFNC were less likely to be intubated (34.3% vs. 51%) and more likely to experience clinical recovery in 28 days (77.8% vs. 71%) compared to those receiving conventional oxygen [34].

Early in the pandemic, a strategy of early intubation was frequently used, but more recent data and updated guidelines recommend the use of HFNC and NIPPV to avoid intubation, if clinically feasible (Table 1) [6,7,35]. If necessary, endotracheal intubation with mechanical ventilation should be pursued without delay. An RCT of 220 COVID-19 patients with ARDS comparing HFNC to conventional oxygen therapy found lower rates of intubation in the HFNC group (34.3% versus 51.0%, hazard ratio = 0.62, 95% CI 0.39–0.96) and more rapid time to recovery (HFNC: 11 days, IQR 9–14, conventional oxygen therapy: 14 days, IQR 11–19; hazard ratio = 1.39; 95% CI 1.00–1.92) [34]. When comparing HFNC and NIPPV, other studies have found no significant difference in intubation rate, mortality, or nosocomial infection of staff [36].

Table 1
HFNC and NIPPV Indications and Contraindications in COVID-19

Indications for HFNC

- Oxygen saturation $< 90\%$ on supplemental oxygen
- RR > 25
- Increased work of breathing despite supplemental oxygen
- Mild ARDS (PaO₂/FiO₂ 200–300)

Indications for NIPPV

- Patient history of obstructive lung disease, congestive heart failure, pulmonary edema
- Hypercapnic respiratory failure
- Severe dyspnea/increased work of breathing on HFNC

Contraindications to HFNC and NIPPV

- Cardiac/respiratory arrest
- Significantly altered mental status
- Unable to tolerate NIPPV facial equipment
- Poorly controlled respiratory secretions
- Recurrent emesis, upper gastrointestinal bleeding, aspiration
- Facial trauma or facial surgery

Table 2

Considerations in non-invasive oxygenation and ventilation for the known or suspected COVID-19 patient with acute hypoxic respiratory failure – the pros and cons of high-flow nasal cannula and non-invasive positive-pressure ventilation

High-flow Nasal Cannula (HFNC)	Non-invasive Positive-pressure Ventilation (NIPPV)
<p>Pros</p> <ul style="list-style-type: none"> Ability to deliver FiO₂ approaching 1.0 Modest increase in PEEP with limited adjustment ability Tolerated in patients with borderline hemodynamic status Patient comfort / tolerance <ul style="list-style-type: none"> lack of facemask warmed and humidified gas delivery ability to speak and take PO Reduced need for endotracheal intubation-more “ventilator-free” days Decreased rate of re-intubation Uncommon infectious complications Mortality reduction Less aerosol generation (clinician contagion) <p>Cons</p> <ul style="list-style-type: none"> Minimal positive pressure delivery-limited impact on work of breathing reduction Not appropriate for patients with <ul style="list-style-type: none"> diminished respiratory drive abnormal mental status May result in aerosol generation (potential risk for clinician contagion) 	<p>Pros</p> <ul style="list-style-type: none"> Beneficial for patients with co-existing obstructive pulmonary disease and congestive heart failure (CHF) (cardiogenic pulmonary edema) exacerbations Increased ability to provide PEEP with adjustment Reduced need for endotracheal intubation-more “ventilator-free” days Decreased rate of re-intubation Mortality reduction <p>Cons</p> <ul style="list-style-type: none"> Occurrence of pressure-related lung injury Patient discomfort / intolerance due to facemask and positive pressure Not appropriate for patients with <ul style="list-style-type: none"> diminished respiratory drive abnormal mental status hemodynamic instability excessive respiratory secretions and emesis May result in aerosol generation (potential risk for clinician contagion)

NIPPV can be utilized in patients who fail HFNC or in those with diseases which may benefit significantly from NIPPV, including chronic obstructive pulmonary disease (COPD) or left-sided heart failure with pulmonary edema. It may also be used in settings where there is no clear indication for endotracheal intubation, but HFNC is unavailable [7]. CPAP may be used initially to improve oxygenation in the setting of COVID-19 hypoxia and respiratory distress. If the patient has hypercarbia or obstructive lung disease, BPAP may be preferable [30,37]. Both BPAP and CPAP may be less effective in patients unable to tolerate the mask or with productive cough or secretions [30]. One study of 79 patients with respiratory failure due to COVID-19 found NIPPV was successful in 48.1% ($n = 38$) in providing appropriate oxygenation and thus avoided intubation, while NIPPV failed in 51.9% ($n = 41$) of patients. Of these patients failing NIPPV, 20 (25.3%) died, while 21 were intubated (26.6%) [38]. Another study of 286 patients found NIPPV was successfully used without the need for intubation in 63.6% ($n = 182$; 118 had moderate to severe ARDS) [39]. NIPPV failed in 82 patients (28.7%), and for patients in whom NIPPV failed and required mechanical ventilation, mortality was 78%. Failure of NIPPV was more common in those with higher disease severity, lower admission PaO₂/FiO₂ ratio, higher respiratory rates, and need for organ support [39].

A retrospective study of 318 patients with COVID-19 found that 41% of patients with acute respiratory failure failed HFNC and were managed with NIPPV [40]. This study found that those with PaO₂/FiO₂ ratios <200 were more likely to fail HFNC, and of those who failed and required NIPPV, their PaO₂/FiO₂ ratio improved significantly 1–2 h after starting NIPPV [40]. An RCT published in January 2022 including 1273 patients with COVID-19 respiratory failure found CPAP reduced the need for

intubation and mortality within 30 days compared to conventional oxygen (33.3% vs. 44.4%) [41]. Other studies have found intubation may be avoided in 37–80% of patients with COVID-19 undergoing NIPPV [42–45]. A retrospective analysis of 88 patients receiving CPAP in the United Kingdom found a 56% survival rate, and a prospective observational study demonstrated 55% of cases successfully avoided intubation using helmet CPAP and were transferred to the general ward [46,47]. The SCCM and NIH guidelines do not include recommendations concerning the use of helmet NIPPV.

Clinically, patients who do not require immediate intubation are often trialed through several oxygenation/ventilation strategies prior to endotracheal intubation, with escalation if one modality fails [6]. One such general strategy is depicted in Fig. 1. In a trial of COVID-19 patients with acute hypoxic respiratory failure, 65 patients in the HFNC group had escalation to CPAP, with only 15% ultimately requiring intubation, while a second group of 48 patients utilizing an initial combined therapy of both HFNC and CPAP failed non-invasive methods with 42% requiring intubation [48]. Another study examined a non-invasive trial (delivered in this study using facemask and ventilator with positive pressure support and defined as NIV by the study authors) as rescue therapy if CPAP failed to avoid intubation, finding slightly lower mortality rates in patients who used a stepwise approach of CPAP, BPAP, and then endotracheal intubation (20%) versus CPAP followed by endotracheal intubation (22%) (Kaplan Meier overall survival probability $P < 0.01$) [49]. A suggested ladder to approaching oxygen therapy may include: 1) NC up to 6 L/min 2) Venturi mask up to 50% or NRB 3) NC + NRB 4) HFNC +/- NRB 5) NIPPV 6) endotracheal intubation (Table 2) [29,30,40,50–55].

3.3.4. Aerosolization and clinician infection risk for HFNC and NIPPV

Both HFNC and NIPPV are aerosol-generating procedures. Higher flows with HFNC may increase the risk of aerosolization, with one study finding a flow of 10 L/min had a dispersion distance of 6.5 cm and a flow of 60 L/min had a dispersion of 17.2 cm, though this is less than a facemask at 10 L/min (9.5 cm) and non-rebreather at 10 L/min (24.6 cm) [56,57]. Cough droplets may spread to 2.91 m with HFNC at 60 L/min [58]. However, there is currently a lack of evidence regarding the risk of aerosolization and risk of infection for COVID-19 specifically, and HFNC has not demonstrated increased aerosolization compared to conventional oxygen [59–61]. In fact, some authors suggest HFNC has a similar risk as conventional oxygen therapy [62]. Limited data suggest an increase in aerosolization of virus particles near the patient but no definitive relationship with nosocomial infection of hospital staff, and the risk is low if appropriate PPE is used [63]. If possible, an airborne infection isolation room (negative pressure room) should be utilized, but if unavailable, a room with a closed door can be used. Both HFNC and NIPPV should be utilized at the lowest effective flow rate/pressure to improve patient oxygenation and work of breathing while reducing unnecessary aerosolization of infectious particles [23]. A surgical mask can be placed over the HFNC device on the patient's face [62,64]. If NIPPV is utilized, a full face mask or oronasal mask should be used with a good seal and not an anti-asphyxiation valve or port. A dual limb circuit with an expiratory limb viral filter may reduce dispersion [23]. A viral filter should otherwise be applied directly to the NIPPV mask to reduce dispersion of viral particles [23].

3.3.5. Predictors of endotracheal intubation

In all patients receiving oxygen supplementation (conventional oxygen, HFNC, and NIPPV), close monitoring of the patient's respiratory status is necessary, including respiratory rate, work of breathing, oxygen saturation (absolute and relative to the fraction of inspired oxygen), and mental status (Table 3). Of note, the ROX index which integrates the oxygen saturation, FiO₂, and respiratory rate, can be utilized to predict failure of HFNC and need for endotracheal intubation [65–68]. Prior to the COVID-19 pandemic, evidence suggested a ROX index ≥ 4.88 at 2, 6, and 12 h after initiation of HFNC is associated with lower

risk of intubation, but the risk of failure is high with levels <3.85 [65,68]. Among COVID-19 patients, a ROX index >3 at 2, 6, and 12 h is associated with HFNC success (85.3% sensitivity), though a separate study found the most sensitive value was 5.37 at 4 h [66,67]. The most important consideration regarding the ROX index is to incorporate patient appearance with the trend of the ROX index, rather than using ROX as an isolated value [69]. Patients who improve with HFNC or NIPPV after 3 h may be continued on the therapy or weaned. If the patient does not improve but is stable, awake repositioning/proning can be attempted.

3.3.6. Rescue strategies: Awake proning

Prone positioning can be used for those on conventional oxygen, HFNC, NIPPV, and mechanical ventilation [6–8]. Several studies conducted in patients with COVID-19 requiring oxygen supplementation found that prone positioning improved oxygenation and lowered intubation rates [70–74]. Guidelines recommend that for patients with an increasing oxygen requirement, but no other indication for intubation, awake prone positioning can be used [7]. While the prone position is the most common position utilized, patients may also lie on their sides [75–77]. Another variation has been described in which the patient sits on a chair and rests in a semi-prone position with their chest on an elevated/flat surface [78].

A multinational randomized controlled open-label study of 1126 patients on HFNC receiving either awake prone positioning or standard care concluded the number needed to treat (NNT) to avoid treatment failure (intubation or death) within 28 days of enrollment was 15 (95% CI 8–156) [73]. The relative risk of treatment failure at day 28 was 0.86 (95% CI 0.75–0.98) [73]. Although there was no significant difference in 28-day mortality (RR 0.87, 95% CI 0.71–1.07), patients in the awake prone positioning study group had higher odds of weaning from HFNC compared to the usual care group (HR 1.19, 95% CI 1.01–1.39) [73]. Importantly, the rate of adverse effects associated with position changes (e.g., line dislodgement, skin breakdown, cardiac arrest) was similar between the awake proning group and standard care [73]. In the PROFLO multicenter RCT, 75 patients were randomized to the prone group or control to determine its impact on rates of intubation [79]. The authors found no significant difference between the two groups, and the study was terminated prematurely due to futility [79]. One study of 27 patients with COVID-19 requiring oxygen supplementation randomized to self-proning versus control found no statistically significant decrease in oxygen requirements, though authors found self-proning was easy to implement and that it was well tolerated [80]. A prospective study of non-intubated patients with hypoxemic respiratory failure with COVID-19 found those tolerating prone positioning experienced improvement with prone positioning [71]. A prospective cohort including 56 non-intubated patients found oxygenation improved the $\text{PaO}_2/\text{FiO}_2$ ratio from 181 mmHg (supine) to 286 mmHg (prone). This improvement was maintained in 23% of patients [81]. For awake patients, the WHO recommends a total proning duration of 8–12 h each day, divided into shorter periods [6].

Pregnant patients with COVID-19 are an especially vulnerable population, and limited data exist evaluating optimal practices, with most peer-reviewed literature in the form of case reports or case series [82–86]. Appropriate care of the critically ill pregnant COVID-19 patient requires early collaboration between multiple care teams including

obstetrics, intensivists, pulmonologists, infectious diseases, and neonatology to ensure the best outcomes for mother and child [82,87–89]. According to the Society for Maternal-Fetal Medicine and guidance published by the American Journal of Obstetrics and Gynecology Maternal Fetal Medicine, prone positioning can be considered in pregnant patients, especially if complicated by ARDS, in either the left lateral decubitus position, fully prone, or a modified prone position combined with left lateral tilt and has been done successfully in women with gestational age as late as 24 weeks [7,87–93]. In order to successfully support patients with optimal prone or lateral decubitus positioning, clinicians should be cognizant of the potential need for additional resources including padding, mechanical rotating beds, fetal observation, invasive hemodynamic monitoring, and definitive airway management. Prone positioning may be especially challenging once the patient reaches 34 weeks of pregnancy due to physical constraints; delivery as an alternative to proning should be critically examined [87,88].

Awake prone positioning is not recommended as a rescue therapy in patients who clinically should be intubated, are in respiratory distress, or hemodynamically unstable [7]. Patients who have undergone recent abdominal surgery, with facial and/or pelvic fractures or open/unstable chest, or have an unstable spine are not candidates for awake prone positioning either [7].

3.3.7. Endotracheal intubation

The decision to intubate can be challenging but should be individualized based on the patient. HFNC and NIPPV should be trialed with frequent evaluations. If these measures fail or if contraindications to HFNC and NIPPV are present, endotracheal intubation is recommended [6–8]. Early intubation compared to delayed or no intubation has not been associated with improved ICU mortality (21% versus 33%) or fewer ventilator-free days (3 days versus 2 days) [94]. A meta-analysis of 8944 patients with COVID-19 found no difference in mortality in patients receiving HFNC or NIPPV prior to intubation compared to those intubated without HFNC or NIPPV [95].

Patients who demonstrate rapid progression of respiratory compromise, persistent need for high flows of FiO_2 , worsening hypercapnia, increasing work of breathing, worsening mental status, decreasing tidal volume, worsening desaturations, and hemodynamic instability will likely require endotracheal intubation [96]. Other patients requiring endotracheal intubation include those with poorly controlled secretions, mask intolerance, and multiorgan dysfunction [96–98].

3.3.8. Aerosolization and clinician infection risk for endotracheal intubation

Intubation can be a high-risk procedure for infection if clinicians are not wearing appropriate personal protective equipment [3]. In the beginning of the COVID-19 pandemic, the rate of infection for clinicians performing the intubation was 3.6% at 7 days, 6.1% at 14 days, and 8.5% at 21 days, but more current data suggest far lower numbers [99–102]. A study of 72 intubations found that although PPE was used in 97% of cases, the clinician performing the intubation did not report being sick or require time off work at 5, 10, or 14 days [103].

If intubation is required, full contact and airborne personal protective equipment (PPE) should be utilized including a powered air-purifying respirator or fit-tested disposable N95 respiratory mask with eye protection [6,8]. If possible, intubation should be performed in an airborne infection isolation room, but if this is not available, a room with a closed door should be utilized [6]. The most experienced clinician should perform the intubation [6]. The patient should be preoxygenated prior to the event, ideally with a tight-fitting bag-valve-mask (BVM) with a high-efficiency hydrophobic viral filter to minimize aerosolization [3,96,104,105]. Video laryngoscopy is recommended for the intubation attempt [7,8]. BVM ventilation should be minimally used before and after intubation if possible, with the viral filter placed between the breathing circuit or resuscitation bag and the facemask [1,3]. If the patient does require BVM, a two-person technique with two-hand

Table 3
Indicators of HFNC/NIPPV failure

- No improvement/worsening dyspnea or work of breathing after 1 h of NIPPV
- No improvement/worsening oxygen saturation or $\text{PaO}_2/\text{FiO}_2$ after 1 h of NIPPV
- Failure to maintain oxygen saturation $>90\%$ or $\text{PaO}_2 > 60$ using FiO_2 of 0.60
- Tidal volume > 9 mL/kg predicted tidal volume while using NIPPV
- ROX value <2.85 at 2 h, < 3.47 at 6 h, or < 3.85 at 12 h
- pH < 7.25 or worsening PaCO_2 after 1 h NIPPV
- Unable to tolerate mask
- Worsening respiratory secretions

mask seal is recommended [1,3]. The ventilator, including the circuit, should be prepared to immediately connect to the endotracheal tube (ETT) as soon as placement is confirmed without using BVM to reduce exposure. In-line suction devices and adapters should also be attached in advance [106]. A high-efficiency particulate air (HEPA) filter should be present on the ventilator expiratory limb to reduce the risk of contamination [106]. Point-of-care ultrasound can be used to rapidly confirm correct endotracheal tube position after placement [107–109].

3.3.9. Ventilation strategies in COVID-19 complicated by ARDS

In patients with ARDS who are mechanically ventilated, the COVID-19 Treatment Guidelines Panel recommends using a tidal volume of 4–8 mL/kg of predicted body weight and targeting plateau pressures <30 cm H₂O in conjunction with a conservative fluid strategy [6–8]. A tidal volume of 6 mL/kg predicted body weight (PBW) is the recommended starting point by WHO; escalation up to 8 mL/kg PBW can be considered based on the patient scenario such as acidosis or dyssynchrony. Additionally, permissive hypercapnia is allowed and is thought to minimize ventilator-induced lung injury (VILI) [6,24]. Oxygen should be titrated to an oxygen saturation of 88–96%. These recommendations persist given that there is no evidence that significantly differentiates ARDS associated with COVID-19 from ARDS due to other causes [7]. As such, patients with COVID-19 who are mechanically ventilated should be treated similarly to patients with ARDS according to ARDSnet protocols [7]. Higher positive end-expiratory pressure (PEEP) is preferred over lower PEEP [6–8]. An early study of 7 intubated patients undergoing decremental PEEP trials, with optimal PEEP calculated to give maximum values of PaO₂/FiO₂ of 17.9 (SD +/- 3.6) millibars, concluded higher PEEP is preferred to lower PEEP [110]. A study of mechanically ventilated patients with COVID-19 found low tidal volumes, high PEEP, and low driving pressures were widely used [111]. If the PEEP is >10 mmHg, clinicians should closely monitor for effects of potential barotrauma [8]. The patient's response to ventilation should be assessed frequently. For those with an FiO₂ less than 0.6 and a PaO₂/FiO₂ > 150 mmHg, this ventilator strategy may be continued.

3.3.10. Rescue strategies in intubated patients with COVID-19 and ARDS

In patients who are mechanically ventilated with refractory hypoxemia despite maximized ventilation strategies, proning should be implemented for 12–16 h per day [7]. Patients should be monitored for barotrauma and other complications related to higher PEEP protocols [7]. As proning of the intubated patient requires significant coordination and monitoring, this should be performed at the times of greatest staff availability to ensure safety. Low quality evidence suggests patients with COVID-19 and ARDS respond well to proning with one small study suggesting a reduction in mortality (NNT = 8) [112–114]. It is unclear the ideal duration of proning, although some authors suggest a minimum of 12 h [115]. Current guidelines recommend proning ventilated patients with either moderate or severe ARDS for 12–16 h [7,8]. A retrospective study of 38 patients compared standard proning duration (more than 75% of proning cycles were approximately 16 h) versus prolonged proning duration (more than 75% of the proning cycles were approximately 40 h) and found no difference in ICU LOS or mortality, but there was a non-significant increase in bed sores in the prolonged prone group (67% versus 44%, $P = 0.167$) [116].

In intubated, mechanically ventilated patients with moderate-to-severe ARDS, either intermittent boluses of neuromuscular blocking agents (NMBA) or continuous infusions may be used to improve ventilation [7]. A continuous NMBA infusion can be used for up to 48 h, assuming the patient's anxiety and pain can be monitored and treated. NMBA infusions may also be used in instances of persistent high plateau pressures, patient-ventilator dyssynchrony, ongoing deep sedation, or prone ventilation [6–8]. In a multicenter observational trial of 407 patients with COVID-19 and severe ARDS, researchers found no significant difference in unassisted respiratory support or time to extubation by 28 days between patients who received NMBA for shorter (<2 days) or

longer (>2 days) duration [117]. However, additional studies of NMBAs in COVID-19 are necessary.

Recruitment maneuvers to improve oxygenation in severe COVID-19 are recommended, apart from staircase or incremental PEEP method [6–8]. A small study of 20 patients found after a recruitability assessment with a PEEP of 15 cm H₂O, PaO₂ slightly improved (68.0 ± 10.3 vs. 69.7 ± 7.9 mmHg, $p = 0.31$) but PaCO₂ (72.5 ± 7.1 vs. 75.1 ± 9.0 mmHg; $p < 0.01$) and static respiratory system compliance (17.5 ± 3.5 vs. 16.6 ± 3.9 mL/cm H₂O; $p = 0.05$) worsened [118]. Other studies of PEEP recruitment maneuvers found ventilation strategies utilizing ARDSnet low PEEP-FiO₂ table (PEEP 11 ± 6 cm H₂O) and best-oxygenation (highest PaO₂/FiO₂) (PEEP 11 ± 3 cm H₂O) led to higher PEEP, compared to the best-compliance strategy (6 ± 2 cm H₂O, $p = 0.001$) [119]. This elevation in PEEP with use of the ARDSnet low PEEP-FiO₂ table and best-oxygenation strategy led to higher plateau and driving pressures and mechanical power, potentially increasing the risk of ventilator-induced lung injury, compared to the best-compliance strategy. However, gas exchange was not significantly affected regardless of PEEP strategy [119].

Inhaled pulmonary vasodilators can be used as rescue therapy, but if no significant improvement is seen quickly, then they should be weaned and discontinued [7,8,120]. A study of 38 patients receiving either inhaled epoprostenol or nitric oxide with COVID-19 found no significant difference in outcomes (PaO₂, SpO₂, and less than 10% increase in PaO₂/FiO₂) between non-responders and responders (>10% increase PaO₂/FiO₂) [120]. Clinicians should be cautioned about the development of hemodynamic instability and methemoglobinemia [120]. The Society of Critical Care Medicine (SCCM) recommends against the routine use of nitric oxide [8].

3.3.11. Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is an invasive treatment modality that may be required if mechanical ventilation is ineffective despite other rescue therapies [7,8]. WHO recommends considering ECMO for patients with refractory hypoxemia Pa:FiO₂ < 50 mmHg for 3 h or Pa:FiO₂ < 80 mmHg for 6 h in spite of lung protective strategies [6]. Pre-pandemic data from the Extracorporeal Life Support Organization (ELSO) registry found venous-venous (V-V) ECMO mortality to be approximately 40% with a mean duration of 12 days; of those patients with COVID-19 on ECMO therapy, more than 90% used V-V ECMO with a mean duration of 18 days [121]. According to the ELSO COVID-19 Dashboard, in-hospital mortality is 47% [122]. This is slightly higher than a systematic review and meta-analysis of 4044 COVID-19 patients receiving ECMO, which found in-hospital mortality was 39% [123]. Early in the pandemic, it appeared that the duration of ECMO was longer for patients with COVID-19 and mortality rates were similar, but this trend appears to be changing as studies continue to be published [121]. Centers that initiated ECMO in COVID-19 patients after May 1, 2020, had a higher adjusted relative risk of in-hospital mortality 90 days after ECMO initiation compared to centers who initiated ECMO in COVID-19 patients prior to that date (1.42, 95% CI 1.17–1.73) [124]. Over time, emerging evidence demonstrates varying mortality rates among patients with COVID-19 receiving ECMO compared to non-COVID-19 ECMO patients [121]. Much of this variation may be due to patient selection and timing in their clinical course rather than ECMO itself [121,125]. An early single-site study of 27 COVID-19 patients on V-V ECMO found the survival rate to be 96.3% [126]. As the pandemic has progressed, other studies have not been as promising, with a multi-institutional analysis of 100 ECMO patients to have a survival rate from 25% (V-A ECMO) to 51% (V-V ECMO) [127]. A meta-analysis of 22 studies of 1896 COVID-19 patients on ECMO (98.6% V-V ECMO) found the pooled in-hospital mortality to be 37.1% (95% CI 32.3%–42.0%) [128]. This mortality rate is comparable to two RCTs (Extracorporeal Membrane Oxygenation for Severe ARDS [EOLIA] and Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure [CESAR]) and a meta-analysis studying mortality rates of ARDS patients without

COVID-19 receiving ECMO [128–131]. In the EOLIA trial, the mortality rate was 35% in the ECMO group compared to 57% in the control group, (RR = 0.76, 95% CI 0.55–1.04) [131]. In the CESAR trial, 63% of those designated for ECMO survived to 6 months without disability compared to 47% in the conventional management group (95% CI 0.05–0.97) [130]. In the meta-analysis of these two studies, the 90-day mortality in the ECMO group was 36% compared to 48% in the control group (RR = 0.75, 95% CI 0.6–0.94) [129]. Additional data are necessary for further decisions regarding the use of ECMO in patients with COVID-19.

4. Conclusions

COVID-19 can result in respiratory failure, septic shock, and multi-organ failure. Hypotension should be managed with balanced crystalloids, and if they demonstrate refractory hypotension, vasopressors should be initiated. Stress dose steroids such as hydrocortisone are recommended for patients with severe or refractory septic shock. Airway management is a key component of initial resuscitation. Patients with COVID-19 and ARDS should be managed similarly to ARDS patients without COVID-19. Clinicians should not delay intubation if needed. For patients with hypoxia, a step-wise approach can be utilized as oxygenation needs escalate. HFNC and NIPPV are recommended over elective intubation. Prone positioning is associated with lower intubation rates and improved oxygenation. Ventilation strategies based on ARDSnet can be implemented in this patient population, using a tidal volume of 4–8 mL/kg of predicted body weight and targeted plateau pressures <30 cm H₂O. Other treatments include NBMA, recruitment maneuvers, inhaled pulmonary vasodilators, and ECMO.

CRedit authorship contribution statement

Summer Chavez: Writing – review & editing, Writing – original draft, Conceptualization. **William J. Brady:** Conceptualization, Writing – original draft, Writing – review & editing. **Michael Gottlieb:** Writing – review & editing, Conceptualization. **Brandon M. Carius:** Writing – review & editing, Conceptualization. **Stephen Y. Liang:** Conceptualization, Writing – review & editing. **Alex Koyfman:** Conceptualization, Writing – review & editing. **Brit Long:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of Competing Interest

None.

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