Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Clinical Review

EMERGENCY DEPARTMENT MANAGEMENT OF SEVERE HYPOXEMIC RESPIRATORY FAILURE IN ADULTS WITH COVID-19

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☐ **Abstract—Background: While emergency physicians are familiar with the management of hypoxemic respiratory failure, management of mechanical ventilation and advanced therapies for oxygenation in the emergency department have become essential during the coronavirus disease 2019 (COVID-19) pandemic. Objective: We review the current evidence on hypoxemia in COVID-19 and place it in the context of known evidence-based management of hypoxemic respiratory failure in the emergency department. Discussion: COVID-19 causes mortality primarily through the development of acute respiratory distress syndrome (ARDS), with hypoxemia arising from shunt, a mismatch of ventilation and perfusion. Management of patients developing ARDS should focus on mitigating derecruitment and avoiding volutrauma or barotrauma. Conclusions: High flow nasal cannula and noninvasive positive pressure ventilation have a more limited role in COVID-19 because of the risk of aerosolization and minimal benefit in severe cases, but can be considered. Stable patients who can tolerate repositioning should be placed in a prone position while awake. Once intubated, patients should be managed with ventilation strategies appropriate for ARDS, including targeting lung-protective volumes and low pressures. Increasing positive end-expiratory pressure can be beneficial. Inhaled pulmonary vasodilators do not decrease mortality but may be given to improve refractory hypoxemia. Prone positioning of intubated patients is associated with a mortality reduction in ARDS and can be considered for patients with persistent hypoxemia. Neuromuscular blockade should also be administered in patients who remain dyssynchronous with the ventilator despite adequate sedation. Finally, patients with refractory severe hypoxemic respiratory failure in COVID-19 should be considered for venovenous extracorporeal membrane oxygenation.** © **2020 Elsevier Inc. All rights reserved.**

☐ **Keywords—acute respiratory distress syndrome; airway management; COVID-19; critical care medicine; hypoxemic respiratory failure**

CLINICAL SCENARIO

A 68-year-old man with a history of hypertension, obesity, and non–insulin dependent diabetes presents to the emergency department (ED) complaining of a 5-day history of cough with intermittent fevers, and he is now experiencing difficulty breathing since the morning of presentation. He lives with multiple members of his extended family in a 2-bedroom apartment, and 3 of his family members have had similar symptoms for the past week. On examination, he can speak in full sentences but is tachypneic with apparent use of accessory muscles and increased work of breathing. His vitals are as follows: temperature of 100.9°F, heart rate of 107 beats/min, blood pressure 162/98 mm Hg, and oxygen saturation of 78% on room air. After nasal cannula of 6 L oxygen is applied, his oxygen saturation improves to 92% and his work of breathing lessens, but he remains tachypneic. A chest radiograph reveals bilateral patchy infiltrates. Over the

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next few hours, his tachypnea does not improve and his oxygenation worsens until his oxygen saturation is 88% despite 10 L of oxygen on a nonrebreather mask. A nasal swab is positive for severe acute respiratory syndrome coronavirus 2. What are the appropriate next steps in management?

INTRODUCTION

Although management of mechanical ventilation has not been a traditionally significant part of emergency medicine practice, it is gaining increased value in emergency medicine (1–3). With the recent outbreak of coronavirus disease 2019 (COVID-19) and the anticipated need for more frequent and longer mechanical ventilation of patients in the emergency department (ED), appreciating the management of severe hypoxemic respiratory failure has taken on heightened importance for emergency physicians.

We do not yet have detailed studies of ventilator management in COVID-19; however, appropriate management of mechanical ventilation in the ED is associated with improved outcomes (4,5). The most common severe complication of COVID-19 appears to be severe hypoxemic respiratory failure from acute respiratory distress syndrome (ARDS) (6–8). Mortality in ARDS is strongly impacted by lung-protective ventilation (9). Nevertheless, many patients continue to receive suboptimal management. A recent multicentric international observational study of intensive care units (ICUs) from 50 countries found that ARDS is often unrecognized and fewer than two-thirds of patients received appropriate ventilation (10). As such, opportunities remain for emergency physicians to optimize the early management of severe hypoxemia and ARDS, especially in the critical time of an ARDS pandemic.

METHODS

The search strategy for narrative review involved a PubMed search using combinations of keywords including “COVID-19,” “COVID,” or “coronavirus” and concepts related to acute hypoxemic respiratory failure, including “acute respiratory distress syndrome,” “ARDS,” “hypoxemia,” “thrombosis,” “thromboembolism,” “noninvasive ventilation,” “high flow oxygen,” “high flow nasal cannula,” “positive end expiratory pressure,” “mechanical ventilation,” “ventilator-induced lung injury,” “neuromuscular blockade,” “cisatracurium,” “recruitment,” “prone position,” “awake prone,” “inhaled epoprostenol,” “inhaled nitric oxide,” “fraction of inspired oxygen,” “hyperoxia,” “steroids,” “dexamethasone,” and “ECMO.” The original search was conducted between April 15 and May 8, 2020, and was updated on November 1, 2020, with no restrictions on publication dates. Titles and abstracts were reviewed by the authors for inclusion. We also reviewed the reference lists of included papers for relevant articles and included articles from searches of the authors’ personal files. We excluded articles that were not published in English.

The data for the management of acute hypoxemic respiratory failure in the setting of COVID-19 have significant limitations because the virus is novel, guidelines and recommendations are rapidly changing, and some incomplete data have been published. As such, many of the COVID-19–specific recommendations are based upon observational studies, case series, and expert opinion. The most evidence-based recommendations drawing heavily upon the existing literature for ARDS and are not specific to patients with COVID-19 (11).

DISCUSSION

Physiology of Hypoxemia in COVID-19

The pathophysiology of COVID-19 is the subject of intense ongoing research, and several key discussions have emerged. An early observation during the pandemic is that patients with COVID-19 who are in severe hypoxemic respiratory failure meet the Berlin criteria for ARDS (12). Patients with COVID-19–associated respiratory failure present with a spectrum of disease, leading to doubts that ARDS is the underlying pathophysiology of the severe form. An early letter to the editor noted that in 16 patients, the shunt fraction was disproportionately low compared with the compliance (13). However, the compliance in that letter, 50.2 $\pm$ 14.3 mL/cm H_2O, is not substantially different than the compliance in earlier works on ARDS (14). The compliance noted in other reports of patients with COVID-19 (15) also aligns with reported values in ARDS (16), and direct comparisons of patients with and without COVID-19 ARDS have found similar pulmonary mechanics (17). While some studies have found the compliance to be slightly higher in COVID-19 ARDS, the differences are not clinically significant (18). Editorials have hypothesized that COVID-19 ARDS is notable for 2 phenotypes (19). However, different subphenotypes of ARDS have long been recognized, indicating that this is not a new or unique finding (11,20–22).

Autopsies of patients with COVID-19 associated hypoxemic respiratory failure reveal diffuse alveolar damage, the underlying pathology in ARDS (23–26). The diffuse alveolar damage seen in COVID-19 is not different from other causes, further supporting the contention that COVID-19 ARDS should be managed similarly to other causes of ARDS (25,27).

Hypoxemia in ARDS arises through a mismatch between ventilation and perfusion, predominantly caused by shunt (13,19,28). A shunt refers to a portion of the blood bypassing gas exchange mechanisms and not receiving oxygen (29). Shunts commonly occur with pathologies rendering lung units ineffective for gas exchange, such as with edema, pneumonia, or atelectasis. Many etiologies of hypoxemic respiratory failure result in substantial heterogeneity of the lungs (30), with areas that are minimally involved and thus effective and others that are severely consolidated, atelectatic, or edematous (30,31). Patients with ARDS have been shown to have heterogeneity of lung parenchyma, correlating with the severity of ARDS, the physiologic dead space, and mortality (32). As noted in the above-referenced research letter, patients with COVID-19 may have a shunt fraction disproportionate to their other pulmonary mechanics (13). Patients often present with diffuse ground glass opacities on chest computed tomography (CT) scans (Figure 1), indicating ineffective lung units, with evidence of disproportionate blood flow, indicating shunt as a major cause of the hypoxemia (33).

The pathophysiology of all ARDS includes microthrombi and macrothrombi formation in the pulmonary vasculature (34). Similarly, COVID-19 critical illness is associated with a hypercoagulable state and clinical and histopathologic data have confirmed microthromboembolic disease and associated decreases in pulmonary perfusion in patients with COVID-19 (23,25,26,35,36). The degree of microthrombi in COVID-19 specimens is greater than patients with ARDS from other etiologies, but the clinical implications are unclear (25,26).

When atelectasis occurs on a large scale, it results in the functional closure of lung units, leading to derecruitment (37). Derecruitment produces a large shunt and is a common cause of hypoxemia. Edematous lungs are at particular high risk of derecruitment, and this appears to be a driving factor for the severe hypoxemia seen in some patients with COVID-19 (18). When a patient presents to the ED in respiratory distress, he or she is often sitting upright, using accessory muscles to maintain adequate negative intrathoracic pressure, and thereby stenting open the distal airways. When the patient is laid down and relaxed for rapid sequence intubation, the pressure from the chest wall, intra-abdominal contents, and even the weight of the lungs themselves can lead to worsening derecruitment (38). Consequently, lying patients flat before intubation can lead to rapid desaturation (39).

Mortality from ARDS is caused by multiorgan system failure rather than from the hypoxemia itself (40). This is because ARDS is a syndrome of diffuse inflammatory response, akin to sepsis, with effects extending far beyond the lungs. The treatments used for ARDS in decades past, including large tidal volume ventilation, led to damage to alveoli from barotrauma and volutrauma with subsequent cytokine release (41). While larger tidal volumes may temporarily improve oxygenation by increasing the mean airway pressure, the increased inflammation leads to increased mortality. A substantial body of literature has shown that lung-protective ventilation with lower tidal volumes and pressures are strongly associated with improved outcomes in patients with and without ARDS (4,9,42).

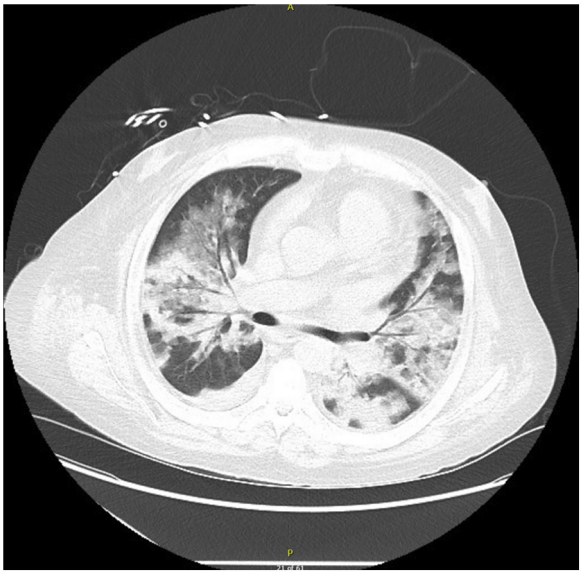

Figure 1. Computed tomography scan showing diffuse ground glass and scattered dense consolidation in a patient with COVID-19 pneumonia.

Noninvasive Management of Hypoxemic Respiratory Failure in COVID-19

Early management of patients with COVID-19 who present with hypoxemia includes proning nonintubated patients, or "awake proning." The posterior surface of the lungs is larger than the anterior surface. Putting the patient in the prone position minimizes the derecruitment on this large surface area and thus improves ventilation and perfusion in the posterior aspect of the lungs (43,44). Proning also changes the mechanics of the rib movement, with more equal distribution of aeration throughout the lungs. Although relatively small in surface area, lifting the heart off the lungs and minimizing the derecruitment in this area can also improve oxygenation. Growing evidence, although limited to single-center reports and retrospective cohorts, suggests significant improvement in hypoxemia in awake prone patients (45–47). However, a recent report in the emergency

medicine literature found no difference in intubation rates when patients were treated with awake proning, with an adjusted hazard ratio of 0.90 (95% confidence interval [CI] 0.55–1.49; p = 0.69) (48). A rapid review of 35 studies of awake proning found that most reported improved oxygenation, but 29% of the total patients ultimately required intubation (49). As such, encouraging prone positioning in stable hypoxemic patients with COVID-19 is a reasonable strategy, but is not well-supported by evidence. The patient's upper body should be supported by pillows or cushions, when possible, to ensure their comfort and improve their ability to tolerate the position. The patient's respiratory status should be closely monitored, and their oxygenation reassessed frequently.

High-flow nasal cannula (HFNC) is an appropriate treatment for many cases of hypoxemic respiratory failure in the ED and is associated with lower rates of intubation compared to conventional oxygen therapy (50–52). However, the role of HFNC is limited in patients with COVID-19. Although the World Health Organization recommends considering a trial of HFNC before endotracheal intubation for patients with moderate to severe hypoxemia, this recommendation has not been universally accepted (53). The advantage of such an intervention is the avoidance of intubation and mechanical ventilation by improving oxygenation and carbon dioxide clearance (54,55). The data regarding the use of HNFC in COVID-19 are limited. However, a small study on patients with influenza A on HFNC showed that 45% avoided intubation, although all of the patients with severe hypoxemia were eventually intubated (56). Some institutions are concerned that HFNC can aerosolize the virus, leading to possible exposure of health care workers, though early evidence suggests appropriate PPE is effective in mitigating this risk (57–59). Manikin studies suggest that the dispersal of liquid from HFNO at 60 L/min is minimal, and significantly less than that caused by coughing and sneezing, providing that nasal cannulae are well fitted (60–62). A recent review of droplet dispersal and aerosol generation in HFNC commissioned by the World Health Organization found mixed evidence regarding risk, with many simulations showing no increase in spread from HFNC. Other studies of healthy adults demonstrated greater aerosol production and leak around the cannulae compared with nasal prongs; no direct evidence in COVID-19 is available (63). As such, HFNC can be considered in stable patients with worsening oxygenation, but should be limited to patients with appropriate isolation precautions (57).

Similarly, noninvasive positive pressure ventilation (NIPPV) is a common means of respiratory support in the ED, but its use in COVID-19 is even more limited. NIPPV failed in 57% to 85% of patients with influenza A H1N1–associated ARDS, and patients who failed had higher ICU mortality than those treated with invasive mechanical ventilation (64,65). Subjects with a Sequential Organ Failure Assessment score ≥5 had a higher risk of NIPPV failure (odds ratio = 3.3 [95% CI 2.4–4.5]) (65). A small study on patients with COVID-19 in Wuhan found that 72% of patients treated with NIPPV died, and the mortality rates were similarly high for those treated with NIPPV and intubation (8). More recent studies have shown patients with moderate-to-severe COVID-19 ARDS may be managed successfully on NIPPV alone, but these remain limited to small retrospective cohorts (58,66). NIPPV also aerosolizes the virus, and given the unclear benefit to patients with hypoxemic respiratory failure, it should not be a first-line treatment in most circumstances (57,67). Institutions should develop their own protocols for the use of the modes of noninvasive respiratory support, as the modality started in the ED will impact the patients and clinicians throughout the hospital.

Timing of Intubation

The decision to intubate patients with COVID-19 has been controversial, with some authors recommending early intubation and others trialing other means of support trying to avoid intubation if possible (68–70). This variation is largely because of early reports of high mortality rates in ventilated patients as well as the previously known risks of intubation and mechanical ventilation (8,71). However, the most concerning report from the United States, indicating an approximately 80% mortality rate for ventilated COVID-19 patients, was published while the majority of patients were still ventilated (71). Later studies providing more complete outcome data had mortality rates from 17% to 36% (72,73). A recent retrospective study of 128 patients with COVID-19 did not find a mortality difference between patients who were intubated early or late in their hospital course (74). With the available respiratory support measures, it is reasonable to try a stepwise approach, monitoring oxygenation, ventilation, and work of breathing, and then intubating as one would in other clinical circumstances (70).

Peri-intubation Hypoxemia

Clinicians are altering their preoxygenation strategy before intubation to limit aerosolizing the virus. Normally, emergency medicine clinicians use flush flow oxygen preoxygenation or positive pressure ventilation with NIPPV for awake patients, or bag-valve masking for others, to help recruit alveoli and maximize preoxygenation, particularly if patients remain hypoxemic before intubation (75–78). With COVID-19, a key goal is to

avoid any procedures that can aerosolize the virus, and therefore NIPPV, bag-valve masking, and even flush flow oxygen should be avoided if possible (57). This makes proper patient positioning all the more important. Preoxygenation with patients sitting up at least 45° is helpful, as it minimizes derecruitment before intubation. If a patient must be bag-ventilated before intubation for hypoxemia, an exhalation high-efficiency particulate air filter should attached between the mask and the bag (57).

A positive end-expiratory pressure (PEEP) valve is a device attached to the exhalation port of the bag. The valve can be adjusted to provide varying levels of PEEP, from 5 to 20 cm H_2O. After intubation, a PEEP valve set to 10 to 15 cm H_2O can mitigate the profound hypoxemia seen in patients with COVID-19. Note that a high-efficiency particulate air filter should also be attached to the bag, between the endotracheal tube and the bag (Figure 2). The patient should be placed on the ventilator as soon as possible after intubation, while trying to minimize aerosolizing spray when doing so.

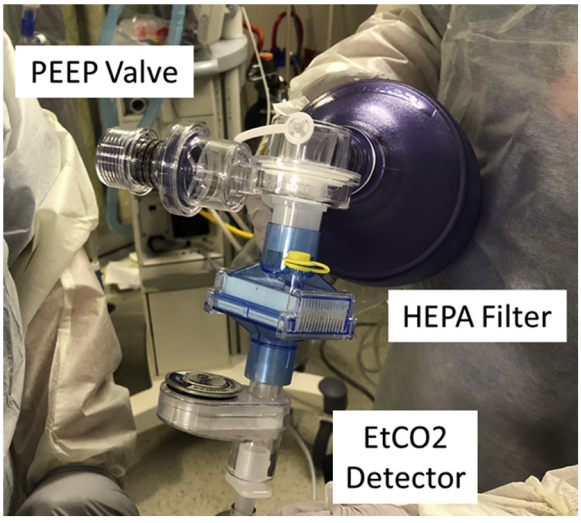

Figure 2. Demonstration of high-efficiency particulate air filter use with positive end-expiratory pressure valve and bag ventilation.

Mechanical Ventilation in the ED

Optimizing mechanical ventilation is the most important step in the evidence-based care of patients with severe hypoxemia. The principles of ventilating patients with COVID-19 are similar to all patients with ARDS (7). A recent study on 66 mechanically ventilated patients with COVID-19 treated with lung-protective ventilation found a 62% extubation rate and only 16.7% ICU mortality rate, supporting these established approaches in this patient population (72). The first maneuver is to ensure that the patient is receiving a low tidal volume and low pressure ventilation. Tidal volumes should be started at 6 mL/kg of predicted body weight, determined by the patient's height and biologic sex (79).

The plateau pressure should then be checked by performing an inspiratory hold on the ventilator, with a goal pressure of <30 cm H_2O (Figure 3) (55). If the plateau pressure is >30 cm H_2O, the tidal volume can be decreased to as low as 4 mL/kg of predicted body weight. If the plateau pressure is <25 cmH_2O, and the patient continues to have significant respiratory acidosis, the tidal volume can be increased up to a total of 8 mL/kg.

The driving pressure, or the pressure to distend alveoli, has also been strongly correlated with outcomes in ARDS, even in patients receiving otherwise lung-protective ventilation (80). The driving pressure is the difference between the plateau pressure and PEEP (79). Driving pressure should be targeted to <15 cm H_2O (55,81).

Permissive hypercapnia, or tolerance of a pH down to 7.15 to 7.20, has traditionally been proscribed to allow lower tidal volume ventilation. While still an acceptable approach, there are concerns that severe hypercapnia can have deleterious effects, especially for patients with underlying pulmonary hypertension or right ventricular failure (82). To manage ventilation and acidosis, the respiratory rate can be increased up to 35 breaths/min, monitoring for air-trapping with faster rates.

Despite evidence that careful ventilator management improves outcomes, few patients in the ED have ventilator settings changed, even with prolonged lengths of stay in the ED (3,83–86). Clinicians should prioritize management of the ventilation to prevent secondary lung injury and worsening cytokine release in patients with COVID-19.

PEEP

PEEP increases the mean airway pressure, reduces atelectasis, and at higher levels, can recruit heterogeneous lung parenchyma (14,32). PEEP can be increased by 2 to 3 cm H_2O every 15 to 30 minutes while monitoring the plateau pressure (55). A study of ventilated patients found that higher PEEP values, ventilated with otherwise low tidal volumes, improved oxygenation, decreased refractory hypoxemia (4.6% vs. 10.2%; relative risk [RR] = 0.54 [95% CI 0.34–0.86]; $p = 0.01$) and lowered death rates with refractory hypoxemia (4.2% vs. 8.9%; RR = 0.56 [95% CI 0.34–0.93]; $p = 0.03$), although there was no significant difference in all-cause hospital mortality or barotrauma compared with more traditional low tidal volume–protocolized ventilation strategy (87).

In patients with severe hypoxemic respiratory failure, though, more PEEP is not always a better option. Using too much PEEP may also overexpand the good portions

Figure 3. An inspiratory hold maneuver on a ventilator, showing a peak inspiratory pressure of 35 cm H_2O and a plateau pressure of 32 cm H_2O, on a tidal volume of 330 mL and 18 cm H_2O of positive end-expiratory pressure.

of the lung and decrease blood flow to these areas, which then shunts blood flow to the ineffective lung units (88). The PEEP should be optimized for the patient, focusing on improved compliance, with frequent reassessment of the patient's oxygenation and hemodynamic status.

Conversely, because derecruitment is a major driver of severe hypoxemia in COVID-19, clinicians should minimize further derecruitment by maintaining PEEP (37). By expert consensus, if a patient requires changing from one ventilator to another, such as when being placed on a travel ventilator, the end of the endotracheal tube should be clamped with a Kelly clamp to prevent release of pressure and minimize aerosolization. Similarly, unless the clinicians have strong reason to believe mucus plugs are an etiology of the hypoxemia, suctioning should be minimized to prevent worsening of derecruitment.

Decreasing Fraction of Inspired Oxygen

Decreasing the fraction of inspired oxygen (FiO_2) is not commonly considered part of the treatment for severe refractory hypoxemic respiratory failure in the ED. Prospective observational evidence shows that emergency physicians rarely decrease the FiO_2, even when the patient has hyperoxia, defined as a PaO_2 a >300 (85). However, evidence continues to grow for the risks of hyperoxygenation (89). An observational cohort study conducted in the ED and ICUs of an academic center categorized patients into 3 oxygen exposure groups based on PaO_2 values: hypoxia, normoxia, and hyperoxia (defined as PaO_2 <60 mm Hg, PaO_2 60–120 mm Hg, and PaO_2 >120 mm Hg). Hyperoxia in the ED was an independent predictor of hospital mortality, with an adjusted OR of 1.95 (95% CI 1.34–2.85) in a multivariate logistic regression analysis (90). It is therefore appropriate for emergency physicians to actively attempt to decrease the FiO_2 while monitoring the patient's oxygen saturation and checking ≥1 arterial blood gas in the ED in patients with COVID-19.

Neuromuscular Blockade

The role of neuromuscular blockade (NMB) in ARDS has evolved over the last few years. Early administration of NMB with cisatracurium has been shown to improve respiratory system compliance and oxygenation (91,92). In fact, a randomized, placebo-controlled trial of early cisatracurium in patients with ARDS showed a reduction in adjusted 90-day mortality and a decrease in the number of ventilator days in those treated (93).

However, a much larger randomized controlled trial of NMB in 1006 patients found no difference in 90-day mortality (42.5% in the intervention group vs. 42.8% in the control group) (94). As such, NMB has no evidence of benefit or of harm. NMB has been shown to prevent ventilator dyssynchrony from breath stacking, thereby reducing the risk of additional ventilator-associated lung injury and allowing lung-protective ventilation

(95). In the subset of patients who are well-sedated yet remain dyssynchronous with the ventilator, NMB should be given.

Recruitment Maneuvers

Given that derecruitment is a major driver of hypoxemia, attempts to recruit compressed lung segments may be appropriate in refractory hypoxemia (37,96). With the heterogeneity of ARDS, patients vary in their recruitability, and a similar variation is seen with patients with COVID-19 (19,20,22,31). A recruitment maneuver indicates a gradual, sustained inflation with a moderate pressure to reopen atelectatic lung units, thereby increasing the surface area for gas exchange and improving compliance. There are multiple methods for performing a recruitment maneuver.

The risks of performing a recruitment maneuver are threefold. Should a patient have severely stiff lungs, even gentle and sustained pressures can lead to pneumothorax, pneumomediastinum, or other barotraumas (37,97,98). Increased intrathoracic pressure from a recruitment maneuver can lead to decrease preload in a patient who is hypovolemic or an increase in afterload for the right ventricle, either of which may result in hypotension. While the hypotension is not usually sustained, in patients with borderline hemodynamics, even a transient drop in preload can be destabilizing (97,98). Lastly, with a recruitment maneuver, the heterogeneously aerated units may become overdistended, as they will preferentially distend with the increased pressure. This overdistension, as noted above, can lead to decreased blood flow through the capillaries and shunting of blood to the ineffective lung units. Therefore, a temporary decrement in oxygenation may be seen with a recruitment maneuver (98). While not usually detrimental over the long term, if the patient is already severely hypoxemic, worsening the oxygenation, even transiently, may lead to further hemodynamic instability.

There have been appropriate concerns regarding the safety of recruitment maneuvers in terms of hemodynamics or worsening lung injury. However, it seems that the major deleterious effects arise from the rapid rise in pressure, as opposed to a more gentle, sustained pressure (37,99). A 2017 study found no improvement in patients treated with recruitment maneuvers and a subsequent best PEEP trial (97). However, there were substantial limitations to this study as the peak inspiratory pressures used for the recruitment maneuvers were high, at 60 cm H_2O, and barotrauma and hemodynamic instability were common in this study (97).

Previous studies using more gentle recruitment maneuvers have found more favorable outcomes. A small study of incremental increases in inspiratory pressures found that it is possible to open the lung in the majority of patients, and the hemodynamic effects were only transient. They evaluated patients by CT scan of the chest, finding a strong relationship between arterial oxygenation and the percentage of derecruitment (100). A meta-analysis of 10 randomized controlled trials found that recruitment maneuvers were associated with in-hospital mortality (RR = 0.84 [95 % CI 0.74–0.95]), although the quality of evidence was considered to be low because the recruitment maneuvers were largely performed in conjunction with other interventions. There was no difference in barotrauma rates (101).

Evidence regarding recruitment maneuvers therefore does not support routine use in all patients with hypoxemia, especially patients at an increased risk for hemodynamic instability. Patients in the ED are not always mechanically ventilated nor hemodynamically stable long enough for a maneuver before admission to the ICU. However, in circumstances where patients stay in the ED for a longer duration, such as when there are no available ICU beds, prolonged mechanical ventilation in the ED with gradual incremental increases in PEEP should be considered in patients with COVID-19 with refractory hypoxemia and derecruitment.

Prone Positioning

Prone positioning can significantly improve oxygenation in patients with ARDS as described above and should also be considered in intubated patients with refractory hypoxemia. Older studies found a risk of complications, including inadvertent line and endotracheal tube pulls, which can be life threatening (102). A multicentric, randomized control trial on 466 patients with severe ARDS with a PaO_2/FiO_2 ratio of $\leq$150 published in 2013 found the hazard ratio for death with prone positioning was 0.39 (95% CI 0.25–0.63) (16). A meta-analysis also found that the subgroup with moderate to severe ARDS had improved outcomes as well (103). As such, prone positioning is recommended for patients with COVID-19 with severe hypoxemic respiratory failure, unless there is a specific contraindication (55,104). The challenges of proning in the ED are substantial, and the decision to prone in the ED should be made on the institutional level and involve multidisciplinary training.

Inhaled Vasodilators

Inhaled pulmonary vasodilators can be useful in the management of severe hypoxemia in the ED. Pulmonary vasodilators, including inhaled nitric oxide and inhaled epoprostenol, are taken up in the functional lung units where they vasodilate the associated pulmonary vasculature. This redistributes blood flow to the good lung units

and away from poorly functioning lung units, thereby improving oxygenation by improving V/Q matching (105). In addition, vasodilation helps the right ventricle by decreasing the right ventricular afterload. Right ventricular dysfunction is strongly associated with poor outcomes in ARDS (106).

A study evaluating the response to inhaled epoprostenol assessed patients by their PaO_2/FiO_2 ratios, grouping them as <60, 60–90, and >90 mm Hg (107). In total, 62% of patients demonstrated a response, and the mean PaO_2/FiO_2 ratio increased by 33 mm Hg. The highest baseline PaO_2/FiO_2 group had the greatest improvement in PaO_2/FiO_2 of 51 $\pm$ 63 mm Hg and responder rate of 82% (107).

Inhaled epoprostenol and inhaled nitric oxide have similar efficacy and safety profiles (108). A retrospective study found no difference in the change in the partial pressure of arterial O_2/fraction of inspired O_2 ratio after 1 h of therapy (20.58 $\pm$ 91.54 vs. 33.04 $\pm$ 36.19; $p = 0.36$) (109). However, inhaled epoprostenol is 4.5 to 17 times cheaper than inhaled nitric oxide, making it more accessible (109).

While pulmonary vasodilators do not improve mortality, they can be beneficial in the short term, especially for patients with hypoxemia refractory to traditional therapies (110). Improvement in oxygenation can improve the safety of transporting the patient to a tertiary care center, moving the patient to the ICU, cannulating for extracorporeal membrane oxygenation (ECMO), or even awaiting for anticipated improvement of a reversible condition such as pneumonia that should be amenable to antibiotics (111,112). Inhaled pulmonary vasodilators are recommended as a rescue therapy in COVID-19 guidelines (104).

Medical Therapies for COVID-19

The preliminary results for the RECOVERY Trial, published in July 2020, provide the most compelling data for medical therapies for COVID-19. In this controlled study, 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. The 28-day mortality rate was 22.9% in the dexamethasone group and 25.7% in the usual care group, for an age-adjusted rate ratio of 0.83 (95% CI 0.75–0.93; $p < 0.001$). However, among patients on mechanical ventilation, the differences were more stark (RR = 0.64 [95% CI 0.51–0.81]). For those on supplemental oxygen without mechanical ventilation, the RR was 0.82 (95% CI 0.72–0.94). As such, dexamethasone should be prescribed to all patients with COVID-19 requiring supplemental oxygen.

Remdesivir, an antiviral medication, has been studied in a randomized controlled trials in COVID-19. A small study of 237 patients in China did not find any differences in outcomes, and a trial of 598 patients with moderate disease in the United States did not find any benefit to a 10 day course (113,114). A large randomized controlled trial of 1062 patients found a decreased time to symptom resolution, 10 days versus 15 days, in patients treated with remdesivir as compared to placebo (115). As such, remdesivir is a reasonable treatment for patients with COVID-19, but the clinical impact may be minimal.

Given the role of thromoboemboli in COVID ARDS, therapeutic anticoagulation has been suggested as a medical therapy. However, data do not support this as a routine approach. A large retrospective study found no difference in therapeutic and prophylactic anticoagulation as long as the therapy was started within 48 h of hospital admission (116). Guidelines recommend the use of venous thromboembolism prophylaxis with either unfractionated heparin or low molecular weight heparin in all hospitalized patients with COVID-19 without absolute contraindications (117,118). There are no data to support early initiation of thromboprophylaxis in the ED, however.

ECMO. When a patient continues to have refractory hypoxemia despite optimal ventilator and medical management, venovenous ECMO (VV-ECMO) should be considered for those without contraindications (119). ECMO centers are becoming regionalized and transport of patients, either before or after cannulation should be considered (120). Because transporting severely hypoxemic patients is associated with a risk of desaturation or other adverse events, ECMO cannulation before transfer should be strongly considered if resources are available (121,122).

A trial on patients with H1N1-related ARDS who were randomized to transfer to an ECMO center had lower mortality rates than patients who received conventional care (23.7% for ECMO-referred patients vs. 52.5% for non–ECMO-referred patients; RR = 0.45 [95% CI 0.26–0.79]; $p = 0.006$), even though only 86.3% of those transferred received ECMO (123).

A recent multicenter international trial randomized patients with severe ARDS to be placed directly on VV-ECMO or managed with conventional treatments. The 60-day mortality was 35% in the ECMO group and 46% in the conventional groups (RR = 0.76 [95% CI 0.55–1.04]; $p = 0.09$). Notably, crossover to ECMO occurred in 35 patients in the control group at a mean of 6.5 days in 28% of the control group, with 57% of those patients dying. The only difference in complications were that the ECMO group had more bleeding requiring transfusions, more thrombocytopenia, and fewer strokes (124). Although the trial was stopped early for failure to reach the predetermined outcomes, supporters of ECMO note that conventional therapies were deemed insufficient by treating clinicians over a quarter of the time. COVID-19 guidelines from the National Institute of Health do not recommend for or against ECMO, and the World Health

Organization guidelines state that referral to an ECMO center can be considered when other conventional treatments for acute respiratory failure fail (53,104).

CONCLUSION

Management of severe refractory hypoxemia begins with adequate knowledge of the physiologic mechanisms of hypoxemia in the ED. Shunting, especially on a large scale with derecruitment, is a major cause of hypoxemia. Evidence supports the use of lung-protective ventilation, decreasing FiO_2 and proning patients with COVID-19, both nonintubated and intubated. Elevated PEEP can also be an effective tool for lung recruitment and should be individually adjusted with careful monitoring of hemodynamic stability. Inhaled vasodilators should be considered as a tool for short-term improvement in oxygenation. Neuromuscular blockade is not a routine recommendation, but was shown to have benefit in patients who cannot maintain patient-ventilator synchrony even with deep sedation. Finally, ECMO can be considered in patients with COVID-19 who have refractory hypoxemia despite all other advanced therapies, weighing the risks and benefits on an individual basis (**Table**).

Table. Evidence-Based Interventions for Hypoxemic Respiratory Failure Caused by COVID-19

Intervention	Evidence Base and Recommendations
High-flow nasal cannula oxygen	Improved mortality in RCT in non-COVID patients Effective in mild to moderate hypoxemia May be effective in some cases of severe hypoxemia Likely low risk of virus aerosolization in modeling studies Reasonable first-line treatment as long as HCWs are protected
Noninvasive positive pressure ventilation	High rates of failure in patients with non-COVID ARDS Small retrospective studies showing success in patients with moderate to severe COVID-19 Risk of aerosolization limits utility in many circumstances Not a first-line treatment, but may be considered based upon institutional protocols
Awake proning	Consistently improved oxygenation Mixed data regarding prevention of intubation Reasonable first-line treatment in alert, mobile patients
Intubation timing	Early studies indicated high mortality rates for intubated patients with COVID-19 Patients should be intubated based upon clinical judgement and local resources, but neither an early intubation nor late intubation strategy appears warranted
Lung-protective ventilation, tidal volume of 6–8 mL/kg PBW, plateau pressure $\leq$30 cm H_2O, PEEP titrated to compliance, and lowest FiO_2 to maintain SpO_2 92–96%	Well-supported in the critical care literature
Neuromuscular blockade	Recent RCT found no improvement in outcomes when used routinely Should be used if unable to maintain ventilator synchrony
Recruitment maneuvers	RCT stopped early for worse outcomes, but used high pressures with changes of 10 cm H_2O of PEEP at a time More gentle increases in pressure of 2–3 cm H_2O appear safer Can improve oxygenation in derecruited patient
Prone positioning	Multicenter RCT found improved mortality in non-COVID ARDS Recommended in patients with PaO_2/FiO_2 <150 Can be challenging in the ED and requires multidisciplinary training
Inhaled vasodilators	Observational studies demonstrating improved oxygenation, no improvement in mortality May be useful as an adjunct in cases of refractory hypoxemia
Medical therapies: dexamethasone, remdesivir, and anticoagulation	RCT of dexamethasone in patients with COVID-19 found reduced 28-day mortality for patients requiring respiratory support Dexamethasone should be administered to patients with COVID-19 requiring oxygen support Studies of remdesivir have had mixed results, with the most favorable results showing a 4-day reduction in symptoms Remdesivir is reasonable, but likely has minimal clinical impact Systemic anticoagulation has not been shown to improve outcomes over prophylactic dose Hospitalized patients should be given prophylactic dose anticoagulation
ECMO	Older RCT of patients with H1N1 influenza found reduced mortality when patients were transferred to an ECMO center More recent RCT of VV ECMO for non-COVID ARDS was stopped early for futility VV ECMO can be considered for refractory respiratory failure in patients without contraindications

ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; ED = emergency department; FiO_2 = fraction of inspired oxygen; HCW = health care worker; PaO_2 = pressure of arterial oxygen; PBW = predicted body weight; PEEP = positive end-expiratory pressure; RCT = randomized controlled trial; VV = venovenous.

CASE CONCLUSION

The patient is encouraged to self-prone, which he tolerates. His oxygenation improves and he is able to wean back to 6 L nasal cannula. He receives 6 mg dexamethasone. Overnight, the patient boards in the ED awaiting an inpatient bed, and by the morning is again requiring nonrebreather to maintain oxygen saturation of >92% despite self-proning. Risks and benefits of intubation are discussed with the patient and, via video chat, his family. The patient affirms his desire for intubation if his oxygenation continues to worsen. HFNC is considered, but the patient's work of breathing significantly decompensates before initiation and the patient is intubated. He is placed on lung-protective ventilation, with a tidal volume of 6 mL/kg and a resultant plateau pressure of 29 cm H_2O. An arterial blood gas is checked a half-hour later and results as 7.25/65/330. The ventilator is adjusted with a higher respiratory rate and his FiO_2 is decreased to 40% before he is transferred upstairs to his ICU bed.

REFERENCES

1. Wilcox SR, Seigel TA, Strout TD, et al. Emergency medicine residents' knowledge of mechanical ventilation. J Emerg Med 2015; 48:481–91.
2. Wilcox SR, Strout TD, Schneider JI, et al. Academic emergency medicine physicians' knowledge of mechanical ventilation. West J Emerg Med 2016;17:271–9.
3. Mudumbai SC, Barr J, Scott J, et al. Invasive mechanical ventilation in California over 2000-2009: implications for emergency medicine. West J Emerg Med 2015;16:696–706.
4. Fuller BM, Ferguson IT, Mohr NM, et al. A quasi-experimental, before-after trial examining the impact of an emergency department mechanical ventilator protocol on clinical outcomes and lung-protective ventilation in acute respiratory distress syndrome. Crit Care Med 2017;45:645–52.
5. Fuller BM, Ferguson IT, Mohr NM, et al. Lung-Protective Ventilation Initiated in the Emergency Department (LOV-ED): a quasi-experimental, before-after trial. Ann Emerg Med 2017;70: 406–4184.
6. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9.
7. Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. JAMA 2020;323:1499–500.
8. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81.
9. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–8.
10. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016; 315:788.
11. Fan E, Beitler JR, Brochard L, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? Lancet Respir Med 2020;8:816–21.
12. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526–33.
13. Gattinoni L, Coppola S, Cressoni M, et al. Covid-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201:1299–300.
14. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354:1775–86.
15. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region - case series. N Engl J Med 2020;382:2012–22.
16. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013; 368:2159–68.
17. Haudebourg AF, Perier F, Tuffet S, et al. Respiratory mechanics of COVID-19- versus non-COVID-19-associated acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;202: 287–90.
18. Grieco DL, Bongiovanni F, Chen L, et al. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. Crit Care 2020;24:529.
19. Gattinoni L, Chiumello D, Caironi P, et al. Intensive care medicine COVID-19 pneumonia: different respiratory treatment for different phenotypes? Intensive Care Med 2020;46:1099–102.
20. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2014;2: 611–20.
21. Wilson JG, Calfee CS. ARDS subphenotypes: understanding a heterogeneous syndrome. Crit Care 2020;24:102.
22. Delucchi K, Famous KR, Ware LB, et al. Stability of ARDS subphenotypes over time in two randomised controlled trials. Thorax 2018;73:439–45.
23. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology 2020;77:198–209.
24. Tian S, Hu W, Niu L, et al. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 2020;15:700–4.
25. Hariri LP, North CM, Shih AR, et al. Lung histopathology in COVID-19 as compared to SARS and H1N1 influenza: a systematic review. Chest 2020. [Epub ahead of print].
26. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120–8.
27. Konopka KE, Nguyen T, Jentzen JM, et al. Diffuse alveolar damage (DAD) resulting from coronavirus disease 2019 infection is morphologically indistinguishable from other causes of DAD. Histopathology 2020;77:570–8.
28. Radermacher P, Maggiore SM, Mercat A. Fifty years of research in ARDS. Gas exchange in acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;196:964–84.
29. Albert RK, Jobe A. Gas exchange in the respiratory distress syndromes. In: Comprehensive Physiology. Hoboken, NJ: John Wiley & Sons, Inc.; 2012:1585–617.
30. Gattinoni L, Protti A, Caironi P, et al. Ventilator-induced lung injury: the anatomical and physiological framework. Crit Care Med 2010;38(10 suppl):S539–48.
31. Cressoni M, Chiumello D, Carlesso E, et al. Compressive forces and computed tomography–derived positive end-expiratory pressure in acute respiratory distress syndrome. Anesthesiology 2014;121:572–81.
32. Cressoni M, Cadringher P, Chiurazzi C, et al. Lung inhomogeneity in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2013;189:149–58.
33. Lang M, Som A, Mendoza DP, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis 2020;20:1365–6.

34. Tomashefski JF, Davies P, Boggis C, et al. The pulmonary vascular lesions of the adult respiratory distress syndrome. Am J Pathol 1983;112:112–26.
35. Fan BE, Ng J, Chan SSW, et al. COVID-19 associated coagulopathy in critically ill patients: a hypercoagulable state demonstrated by parameters of haemostasis and clot waveform analysis. J Thromb Thrombolysis 2020. [Epub ahead of print].
36. Patel BV, Arachchillage DJ, Ridge CA, et al. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. Am J Respir Crit Care Med 2020;202:690–9.
37. Kallet RH, Lipnick MS, Burns G. The nature of recruitment and derecruitment and its implications for management of ARDS. Respir Care 2020. [Epub ahead of print].
38. Mosier JM, Joshi R, Hypes C, et al. The physiologically difficult airway. West J Emerg Med 2015;16:1109–17.
39. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. Ann Emerg Med 2012;59:165–1751.
40. Cochi SE, Kempker JA, Annangi S, et al. Mortality trends of acute respiratory distress syndrome in the United States from 1999 to 2013. Ann Am Thorac Soc 2016;13:1742–51.
41. Chen L, Xia HF, Shang Y, et al. Molecular mechanisms of ventilator-induced lung injury. Chin Med J (Engl) 2018;131:1225–31.
42. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of intensive care medicine/society of critical care medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253–63.
43. Cornejo RA, Diaz JC, Tobar EA, et al. Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2013;188:440–8.
44. Pelosi P, Brazzi L, Gattinoni L. Prone position in acute respiratory distress syndrome. Eur Respir J 2002;20:1017–28.
45. Elharrar X, Trigui Y, Dols AM, et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. JAMA 2020;323:2336–8.
46. Scaravilli V, Grasselli G, Castagna L, et al. Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: a retrospective study. J Crit Care 2015;30:1390–4.
47. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. Acad Emerg Med 2020;27:375–8.
48. Padrão EM, Valente FS, Besen BA, et al. Awake prone positioning in COVID-19 hypoxemic respiratory failure: exploratory findings in a single-center retrospective cohort study. Acad Emerg Med 2020;27:1249–59.
49. Weatherald J, Solverson K, Zuege DJ, et al. Awake prone positioning for COVID-19 hypoxemic respiratory failure: a rapid review. J Crit Care 2020;61:63–70.
50. Ni YN, Luo J, Yu H, et al. Can high-flow nasal cannula reduce the rate of endotracheal intubation in adult patients with acute respiratory failure compared with conventional oxygen therapy and noninvasive positive pressure ventilation? A systematic review and meta-analysis. Chest 2017;151:764–75.
51. Ni YN, Luo J, Yu H, et al. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. Am J Emerg Med 2018;36:226–33.
52. Makdee O, Monsomboon A, Surabenjawong U, et al. High-flow nasal cannula versus conventional oxygen therapy in emergency department patients with cardiogenic pulmonary edema: a randomized controlled trial. Ann Emerg Med 2017;70:465–4722.
53. World Health Organization. Clinical management of COVID-19. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed December 30, 2020.
54. Frat J-PP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185–96.
55. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet Respir Med 2020;8:433–4.
56. Rello J, Pérez M, Roca O, et al. High-flow nasal therapy in adults with severe acute respiratory infection. A cohort study in patients with 2009 influenza A/H1N1v. J Crit Care 2012;27:434–9.
57. Wax RS, Christian MD. Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. Can J Anesth 2020;67:568–76.
58. Sivaloganathan AA, Nasim-Mohi M, Brown MM, et al. Noninvasive ventilation for COVID-19-associated acute hypoxaemic respiratory failure: experience from a single centre. Br J Anaesth 2020;125:e368–71.
59. Remy KE, Lin JC, Verhoef PA. High-flow nasal cannula may be no safer than non-invasive positive pressure ventilation for COVID-19 patients. Crit Care 2020;24:169.
60. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. Eur Respir J 2019;53:1802339.
61. Kotoda M, Hishiyama S, Mitsui K, et al. Assessment of the potential for pathogen dispersal during high-flow nasal therapy. J Hosp Infect 2020;104:534–7.
62. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. Eur Respir J 2020;55:2000892.
63. Agarwal A, Basmaji J, Muttalib F, et al. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. Can J Anesth 2020;67:1217–48.
64. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 2009;302:1872–9.
65. Rodríguez A, Ferri C, Loeches IM, et al. Risk factors for noninvasive ventilation failure in critically ill subjects with confirmed influenza infection. Respir Care 2017;62:1307–15.
66. Mukhtar A, Lotfy A, Hasanin A, et al. Outcome of non-invasive ventilation in COVID-19 critically ill patients: a retrospective observational study. Anaesth Crit Care Pain Med 2020;39:579–80.
67. Brewster DJ, Chrimes N, Do TB, et al. Consensus statement: Safe Airway Society principles of airway management and tracheal intubation specific to the COVID-19 adult patient group. Med J Aust 2020;212:472–81.
68. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA 2020;323:2329–30.
69. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. Ann Intensive Care 2020;10:78.
70. Rola P, Farkas J, Spiegel R, et al. Rethinking the early intubation paradigm of COVID-19: time to change gears? Clin Exp Emerg Med 2020;7:78–80.
71. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323:2052–9.
72. Ziehr DR, Alladina J, Petri CR, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med 2020;201:1560–4.
73. Auld SC, Caridi-Scheible M, Blum JM, et al. ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. Crit Care Med 2020;48:E799–804.
74. Matta A, Chaudhary S, Bryan Lo K, et al. Timing of intubation and its implications on outcomes in critically ill patients with coronavirus disease 2019 infection. Crit Care Explor 2020;2:e0262.

75. Driver BE, Klein LR, Carlson K, et al. Preoxygenation with flush rate oxygen: comparing the nonrebreather mask with the bag-valve mask. Ann Emerg Med 2018;71:381–6.
76. Baillard C, Fosse J-P, Sebbane M, et al. Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. Am J Respir Crit Care Med 2006;174:171–7.
77. Bailly A, Ricard JD, Le Thuaut A, et al. Compared efficacy of four preoxygenation methods for intubation in the ICU: retrospective analysis of McGrath Mac Videolaryngoscope Versus Macintosh Laryngoscope (MACMAN) trial data. Crit Care Med 2019;47: e340–8.
78. Russotto V, Cortegiani A, Raineri SM, et al. Respiratory support techniques to avoid desaturation in critically ill patients requiring endotracheal intubation: a systematic review and meta-analysis. J Crit Care 2017;41:98–106.
79. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351:327–36.
80. Guérin C, Papazian L, Reignier J, et al. Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials. Crit Care 2016;20: 384.
81. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372:747–55.
82. Barnes T, Zochios V, Parhar K. Re-examining permissive hypercapnia in ARDS: a narrative review. Chest 2018;154:185–95.
83. Wilcox SR, Richards JB, Fisher DF, et al. Initial mechanical ventilator settings and lung protective ventilation in the ED. Am J Emerg Med 2016;34:1446–51.
84. Angotti LB, Richards JB, Fisher DF, et al. Duration of mechanical ventilation in the emergency department. West J Emerg Med 2017; 18:972–9.
85. Al Ashry HS, Richards JB, Fisher DF, et al. Emergency department blood gas utilization and changes in ventilator settings. Respir Care 2018;63:36–42.
86. Owyang CG, Kim JL, Loo G, et al. The effect of emergency department crowding on lung-protective ventilation utilization for critically ill patients. J Crit Care 2019;52:40–7.
87. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome. JAMA 2008;299:637.
88. Çoruh B, Luks AM. Positive end-expiratory pressure. When more may not be better. Ann Am Thorac Soc 2014;11:1327–31.
89. Rincon F, Kang J, Maltenfort M, et al. Association between hyperoxia and mortality after stroke. Crit Care Med 2014;42:387–96.
90. Page D, Ablordeppey E, Wessman BT, et al. Emergency department hyperoxia is associated with increased mortality in mechanically ventilated patients: a cohort study. Crit Care 2018;22:9.
91. Forel J-M, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006;34:2749–57.
92. Fanelli V, Morita Y, Cappello P, et al. Neuromuscular blocking agent cisatracurium attenuates lung injury by inhibition of nicotinic acetylcholine receptor-α1. Anesthesiology 2016; 124:132–40.
93. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363: 1107–16.
94. Moss M, Huang DT, Brower RG, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 2019;380:1997–2008.
95. Beitler JR, Sands SA, Loring SH, et al. Quantifying unintended exposure to high tidal volumes from breath stacking dyssynchrony in ARDS: the BREATHE criteria. Intensive Care Med 2016;42: 1427–36.
96. de Matos GF, Stanzani F, Passos RH, et al. How large is the lung recruitability in early acute respiratory distress syndrome: a prospective case series of patients monitored by computed tomography. Crit Care 2012;16:R4.
97. Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome. JAMA 2017;318:1335.
98. Fan E, Checkley W, Stewart TE, et al. Complications from recruitment maneuvers in patients with acute lung injury: Secondary analysis from the lung open ventilation study. Respir Care 2012; 57:1842–9.
99. Guerin C, Debord S, Leray V, et al. Efficacy and safety of recruitment maneuvers in acute respiratory distress syndrome. Ann Intensive Care 2011;1:9.
100. Borges JB, Okamoto VN, Matos GFJ, et al. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. Am J Respir Crit Care Med 2006;174:268–78.
101. Suzumura EA, Figueiró M, Normilio-Silva K, et al. Effects of alveolar recruitment maneuvers on clinical outcomes in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. Intensive Care Med 2014;40:1227–40.
102. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome. JAMA 2009;302:1977.
103. Munshi L, Del Sorbo L, Adhikari NKJ, et al. Prone position for acute respiratory distress syndrome. A systematic review and meta-analysis. Ann Am Thorac Soc 2017;14(suppl 4): S280–8.
104. National Institutes of Health website. Care of critically ill patients with COVID-19. Available at: https://covid19treatmentguidelines.nih.gov/critical-care/. Accessed December 30, 2020.
105. Tabrizi MB, Schinco MA, Tepas JJ, et al. Inhaled epoprostenol improves oxygenation in severe hypoxemia. J Trauma Acute Care Surg 2012;73:503–6.
106. Repessé X, Vieillard-Baron A. Right heart function during acute respiratory distress syndrome. Ann Transl Med 2017;5:295.
107. Kallet RH, Burns G, Zhuo H, et al. Severity of hypoxemia and other factors that influence the response to aerosolized prostacyclin in ARDS. Respir Care 2017;62:1014–22.
108. Ammar MA, Bauer SR, Bass SN, et al. Noninferiority of inhaled epoprostenol to inhaled nitric oxide for the treatment of ARDS. Ann Pharmacother 2015;49:1105–12.
109. Torbic H, Szumita PM, Anger KE, et al. Inhaled epoprostenol vs inhaled nitric oxide for refractory hypoxemia in critically ill patients. J Crit Care 2013;28:844–8.
110. Searcy RJ, Morales JR, Ferreira JA, et al. The role of inhaled prostacyclin in treating acute respiratory distress syndrome. Ther Adv Respir Dis 2015;9:302–12.
111. Wilcox SR, Ries M, Bouthiller TA, et al. The importance of ground critical care transport. J Intensive Care Med 2017;32:163–9.
112. Reily DJ, Tollok E, Mallitz K, et al. Successful aeromedical transport using inhaled prostacyclin for a patient with life-threatening hypoxemia. Chest 2004;125:1579–81.
113. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569–78.
114. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 2020;324: 1048–57.
115. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. N Engl J Med 2020;383: 1813–26.
116. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76:1815–26.
117. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020; 18:1859–65.
118. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18:1023–6.

119. Tramm R, Ilic D, Davies AR, et al. Extracorporeal membrane oxygenation for critically ill adults. Cochrane Database Syst Rev 2015;1:CD010381.
120. Broman LM. Inter-hospital transports on extracorporeal membrane oxygenation in different health-care systems. J Thorac Dis 2017;9:3425–9.
121. Wilcox SR, Saia MS, Waden H, et al. Improved oxygenation after transport in patients with hypoxemic respiratory failure. Air Med J 2015;34:369–76.
122. Heuer JF, Mirschel M, Bleckmann A, et al. Interhospital transport of ARDS patients on extracorporeal membrane oxygenation. J Artif Organs 2019;22:53–60.
123. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA 2011;306:1659–68.
124. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965–75.

ARTICLE SUMMARY

1. Why is this topic important?

During the global COVID-19 pandemic there has been an incredible outpouring of research and collaboration among emergency physicians to share their evolving knowledge of managing the disease. A current review helps to focus this information and place it into context for practicing emergency physicians.

2. What does this review attempt to show?

This is a review of the current literature regarding the management of severe hypoxemic respiratory failure in the emergency department for patients who are presumed to have COVID-19. This review summarizes recent evidence for COVID-19 and places it in the context of known evidence-based management of hypoxemic respiratory failure in the emergency department.

3. What are the key findings?

COVID-19 is known to cause severe hypoxemia through acute respiratory distress syndrome (ARDS) in which hypoxemia is the result of mismatched ventilation and perfusion, or shunt. While recent data have noted low compliance among patients with COVID-19 with severe hypoxemia and differing phenotypes among COVID-19, these variations are consistent with preexisting data on variable presentations of ARDS. Before intubation, stable patients with hypoxemia who can tolerate repositioning should be placed in prone position while awake and a trial of high-flow nasal cannula can be considered if well-fitted nasal cannulae and appropriate precautions are available. Patients on supplemental oxygen should be started on dexamethasone. Remdesivir should be considered but has limited evidence of benefit in improving outcomes. Intubated patients should be managed with lung-protective volume and low-pressure ventilation appropriate to ARDS, with increasing positive end-expiratory pressure as tolerated in stable patients and consideration of proning and neuromuscular blockade for patients with prolonged mechanical ventilation in the emergency department. Venovenous extracorporeal membrane oxygenation should be considered early in patients with severe hypoxemia refractory to other advanced therapies

4. How is patient care impacted?

Trials of awake proning and high-flow nasal cannula in appropriate patients may improve hypoxemia and delay or avoid even intubation. Management of ventilated patients in the emergency department with ARDS-appropriate ventilation is associated with improved outcomes.