



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Supportive Care in Patients with Critical Coronavirus Disease 2019



Daniel A. Sweeney, MD*, Atul Malhotra, MD

KEYWORDS

- COVID-19 • Critical care • Supportive care • Prone ventilation
- Noninvasive positive pressure ventilation • High flow nasal cannula • Lung

KEY POINTS

- The COVID-19 pandemic has emphasized the importance of previously validated supportive care measures for critically ill patients, especially those with ARDS.
- For the patient with COVID-19 and ARDS, prone ventilation, low tidal volume ventilation, and ECMO consideration should be standard of care.
- Noninvasive positive pressure ventilation or high-flow nasal cannula may prevent the subsequent need for intubation.
- Prone ventilation in nonintubated patients has not been consistently shown to prevent the need for intubation.
- Providers should use well-established supportive care measures for critically ill patients with COVID-19, including chemical DVT prophylaxis, conservative fluid management, and strategies to minimize delirium.

INTRODUCTION

The mortality rate for patients with coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU) is approximately 30%.^{1,2} Since the start of the pandemic therapeutic advances, including vaccines, monoclonal antibodies, antiviral agents, and immunomodulating therapies, have resulted in fewer patients with COVID-19 being hospitalized and requiring ICU admission. However, current therapeutics have not been consistently helpful once a patient with COVID-19 progresses to the point of requiring critical care support, with only baricitinib in a placebo-controlled trial and dexamethasone in an open-label trial demonstrating benefit in patients receiving mechanical ventilation.^{3,4} Even vaccines, which have drastically reduced the burden of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection worldwide,

Division of Pulmonary, Critical Care, Sleep Medicine and Physiology, Department of Medicine, University of California, San Diego, 9300 Campus Point Drive, La Jolla, CA 92037-7381, USA

* Corresponding author.

E-mail address: dasweeney@health.ucsd.edu

Infect Dis Clin N Am 36 (2022) 777–789

<https://doi.org/10.1016/j.idc.2022.08.003>

0891-5520/22/© 2022 Elsevier Inc. All rights reserved.

id.theclinics.com

do not measurably reduce either length of stay or mortality for fully vaccinated patients compared with unvaccinated patients who are admitted to the ICU.⁵ In light of the dearth of therapeutic options for critically ill patients with COVID-19, optimization of supportive care is paramount. Although there has been great interest in expanding the application of prone ventilation to include nonintubated patients with COVID-19, current randomized trial data do not support its routine use. Rather, the pandemic experience has served to reinforce the importance of applying supportive critical care strategies that have been previously been proved to be beneficial in the management of patients with severe pneumonia and acute respiratory distress syndrome (ARDS). Accordingly, this article aims to highlight important aspects of supportive care for the critically ill patient with COVID-19, with an emphasis on a stepwise approach to the use of respiratory support for patients based on their severity of respiratory illness.

NONINVASIVE RESPIRATORY SUPPORT FOR CRITICALLY ILL PATIENTS WITH CORONAVIRUS DISEASE 2019

The need for additional respiratory support beyond low-flow oxygen therapy (<15 L/min [LPM]) is often the reason for admission to the ICU. For patients with COVID-19 who are hypoxemic (oxygen saturation <92%) despite receiving low-flow oxygen, but not requiring urgent intubation, the 3 advanced respiratory support options are continuous positive airway pressure (CPAP), noninvasive positive pressure ventilation (NIPPV, also known as noninvasive ventilation [NIV] or by its trade name, “BiPAP”) or high-flow nasal cannula (HFNC). Although the data are limited, NIPPV and HFNC, both of which raised concerns for the potential to aerosolize viral particles, have not been shown to pose an increased risk of infection to health care workers who adhere to standards of personal protective equipment use.^{6,7} Before discussing how to choose between CPAP, BiPAP, or HFNC for a particular patient, it is worth reviewing technical aspects of these respiratory support modalities.

Continuous Positive Airway Pressure

CPAP uses a tight-fitting nasal or face mask and delivers oxygen to a patient with a continuous positive pressure in the system during both patient inspiration and oxygenation. As such, CPAP is not a “ventilatory” mode because it does not provide additional pressure support during inspiration. Instead, the continuous airway pressure aids in oxygenation by preventing the collapse of alveoli during expiration. The clinician sets both the fraction of inspired oxygen (F_{iO_2}) and the continuous pressure ranging from 4 to 20 cm H_2O .

Noninvasive Positive Pressure Ventilation

NIVPP delivers 2 levels of pressure: an expiratory pressure (EPAP, analogous to CPAP) and an inspiratory pressure (IPAP), additional pressure provided to the patient with each breath. In addition, the clinician sets a backup respiration rate (in the event the patient does not spontaneously breathe or to ensure a certain number of breaths per minute) and the F_{iO_2} . An example of initial NIVPP settings include IPAP = 10 cm H_2O , EPAP = 5 cm H_2O , backup respiration rate = 10 breaths per minute, and F_{iO_2} = 100%. Patient oxygenation can be further improved by increasing the EPAP to prevent alveolar collapse. NIVPP is a ventilatory mode. Increasing the inspiratory pressure while maintaining the same expiratory pressure (IPAP – EPAP = “delta”) will increase the patient’s tidal volume. Although hypoxemia is a cardinal feature of pneumonia, increasing the delta will serve to improve ventilation and

CO₂ removal if hypercapnia requires correction, for example, in patients with concomitant asthma or chronic obstructive pulmonary disease (COPD).

High-Flow Nasal Cannula

HFNC systems deliver warmed and humidified oxygen (FiO₂ = 21%–100%) via nasal cannula at flow rates ranging from greater than or equal to 15 to 60 LPM. Typical HFNC settings are FiO₂ between 50% and 100% and a flow rate between 20 and 60 LPM. Both FiO₂ and flow rates are adjusted to improve a patient's oxygen saturation, because increasing the flow rate above the patient's intrinsic minute ventilation prevents entrainment of room air and thus ensures that the patient is receiving the set FiO₂; moreover, high flow rates provide a modest amount of end expiratory pressure that may further improve oxygenation by recruiting more alveoli. The flow rate can also be increased to relieve dyspnea and tachypnea, because HFNC serves to reduce anatomic dead space, thus reducing the work of breathing and aiding in CO₂ clearance.

Choosing Between Continuous Positive Airway, Noninvasive Positive Pressure Ventilation, and High-Flow Nasal Cannula Therapies for the Treatment of Patients with Coronavirus Disease 2019

Before the SARS-CoV-2 pandemic, the use of NIVPP and HFNC for the treatment of pneumonia was supported by limited clinical trial data.^{8,9,10} In a study comparing the 2 modalities for the treatment of hypoxic respiratory failure (254 of 310 patients or 82% of trial participants with pneumonia), HFNC was associated with a greater number of ventilator-free days ($P = .02$) and a lower 90-day mortality rate ($P = 0.006$).¹⁰

For the treatment of patients with COVID-19, HFNC (vs low-flow oxygen therapy) has been shown in a retrospective study ($n = 379$) and in a randomized controlled trial ($n = 220$) to reduce the need for endotracheal intubation, but not impact mortality.^{11,12} However, unlike the pre-pandemic experience, NIVPP may be superior to HFNC for the treatment of patients with COVID-19. In the Helmet Noninvasive Ventilation versus High-flow Oxygen Therapy in Acute Hypoxemic Respiratory Failure (HENIVOT) trial ($n = 109$), patients receiving NIPPV via a helmet device, compared with patients receiving HFNC therapy, were less likely to require mechanical ventilation (a secondary study outcome, 30% vs 51%, $P = .03$), although there was no difference in the number of days free of respiratory support (the primary study outcome).¹³ Also, in the RECOVERY-RS trial ($n = 1273$), patients treated with CPAP compared with HFNC were less likely to reach the combined end point of endotracheal intubation or death within 30 days (36.3% vs 44.4%, $P = .03$), but this difference was due almost entirely to differences in intubation rates (33.4% vs 41.3%; odd ratio [OR], 0.71 [0.53–0.96]) and not mortality (16.7% vs 19.2%; OR, 0.84 [0.58–1.23]).¹⁴ It should be noted that device intolerance (5.8% vs 0.7% of participants), adverse events (34.2% vs 20.6% of participants), and serious adverse events (1.8% vs 0% of participants), including pneumothoraces and vomiting requiring emergent intubation, were more common in patients receiving CPAP, compared with patients receiving HFNC.

Based entirely on pre-pandemic data, both the Surviving Sepsis Campaign and the National Institutes of Health (NIH) COVID-19 Treatment Guidelines recommend HFNC over NIVPP (and do not comment on CPAP) for the treatment of patients with hypoxic respiratory therapy despite low-flow oxygen therapy.^{15,16} The authors maintain that there is equipoise regarding whether 1 noninvasive respiratory support strategy is superior for the treatment of patients with COVID-19. And considering the evidence supporting both modalities, the authors recommend that choice of an NIV strategy should be based on comorbidities, patient tolerance, and institutional norms. For example,

CPAP or NIVPP may be preferable to HFNC for patients with COVID-19 and either congestive heart failure or COPD. On the other hand, patients who find NIVPP or CPAP uncomfortable are better suited for treatment with HFNC. Finally, institutional experience and resources must be considered. Over the course of the pandemic many health care systems have developed familiarity and expertise with mostly treating patients with HFNC, CPAP, or NIVPP. Pending the results of the ongoing RENO-VATE study (NCT03643939) or future trials, the authors see no reason for these practice patterns to change.¹⁷

PRONING IN NONINTUBATED PATIENTS WITH CORONAVIRUS DISEASE 2019

Proning in the nonintubated (PINI) refers to the strategy of having hospitalized, nonintubated patients with hypoxic respiratory failure resting in the prone rather than the supine position for extended periods. This strategy is sometimes referred to as “awake” prone ventilation, even though this term is a misnomer because intubated patients could clearly be awake or sedated or asleep whether prone or not; similarly nonintubated patients could be awake or asleep. The proposed mechanisms of benefit of prone ventilation have been best studied for the treatment of intubated patients with ARDS before the SARS-CoV-2 pandemic (see section, “Prone ventilation for intubated patients”). Prepandemic, PINI investigations were limited to case series.¹⁸ A meta-analysis performed by Li and colleagues¹⁹ of 10 clinical trials ($n = 1985$ patients; in actuality 8 trials were analyzed because 2 trials had no events in either arm) involving patients with COVID-19 receiving PINI compared with supine position ventilation showed a reduction in the need for intubation (risk ratio [RR], 0.84; 95% confidence interval [CI], 0.72–0.97), but did not impact mortality (RR, 1.0; 95% CI, 0.70–1.44). Meta-regression analysis further revealed that PINI only reduced the need for intubation among patients receiving NIV modalities or being treated in the ICU. It should also be noted that the results of this meta-analysis are entirely due to results of a meta-trial (consisting of 6 national, randomized open-label trials) authored by Ehrmann and colleagues²⁰ ($n = 1121$), and more specifically patients enrolled in 1 particular national trial ($n = 430$) who had very different baseline characteristics and were managed differently than patients enrolled at other sites.²¹ When the meta-analysis performed by Li and colleagues¹⁹ is repeated excluding this national trial and incorporating the results of a more recent randomized trial performed by Alhazzani and colleagues²² ($n = 400$), there is no benefit of PINI on intubation rates (RR, 0.89; 95% CI, 0.77–1.03) (Fig. 1). Further complicating the interpretation of PINI clinical studies is that the duration of prone positioning varied across clinical trials. In a more recent prospective, multicenter cohort study of 335 patients in the ICU receiving HFNC (187 with PINI, 148 with nonprone positioning) showed that 6 hours or more of PINI reduced the rate of endotracheal intubation and that 8 hours or more of PINI reduced the risk of hospital mortality.²³ This result makes intuitive sense because the only randomized trial to show a mortality benefit of prone positioning in patients with ARDS receiving mechanical ventilations required that patients receive 16 hours of prone ventilation.²⁴ On the other hand, rather than a dose response, duration of PINI may actually represent a confounder whereby patients who can tolerate longer sessions of PINI are less severely ill. At present, the NIH COVID-19 Treatment Guidelines recommend a trial of PINI for patient with hypoxemia requiring HFNC and for whom endotracheal intubation is not indicated.¹⁶ Although it is unlikely that PINI is harmful, the benefit of this therapy is not established. If PINI is administered to a patient receiving CPAP, HFNC, or NIVPP the authors suggest that the duration of therapy be extended, ideally lasting 8 hours or more a day.

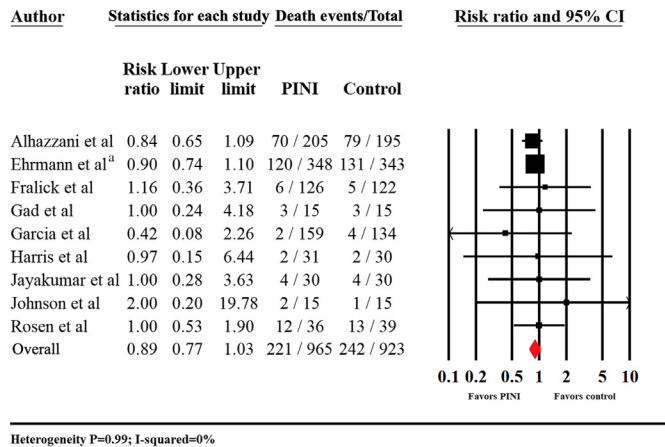
PINI and the risk of intubation in hospitalized patients with COVID-19

Fig. 1. Meta-analysis of 9 randomized trials showing the effect of PINI on the risk of intubation for hospitalized patients with COVID-19. ^aOf note, 5 of 6 national trials from the meta-trial led by Ehrmann and colleagues²⁰ were included in the analysis.

CLINICAL JUDGMENT SHOULD INFORM THE DECISION TO INTUBATE AND INITIATE MECHANICAL VENTILATION

Early in the pandemic, many health care systems adopted a strategy of early intubation of patients with COVID-19.²⁵ The rationale for this approach was based on 2 concerns: fear of aerosolizing SARS-CoV-2 with NIV (both NIVPP and HFNC) leading to hospital-acquired COVID-19 and the theoretic risk of patient self-inflicted lung injury.^{26,27} The risk of NIV leading to hospital-acquired COVID-19 is not supported by 2 clinical studies.^{6,7} An analysis of 245 patients in 11 ICUs showed that early intubation (defined as occurring during the first 2 calendar days of their ICU stay) was associated with increased risk of secondary infection and an increased 60-day mortality risk (hazard ratio [HR], 1.74; 95% CI, 1.07–2.83).²⁸ Traditionally, clinical data guide the decision to initiate mechanical ventilation in a patient with pneumonia, but clinical judgment dictates the ultimate decision.²⁹ The authors endorse the use of clinical judgment, rather than an early intubation policy or protocol, when deciding when to intubate a patient with COVID-19.

PATIENTS WITH CORONAVIRUS DISEASE 2019 RECEIVING MECHANICAL VENTILATION: TREATING ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is diagnosed when a patient has acute respiratory failure, a PaO_2 : FiO_2 ratio less than 300 mm Hg, and chest radiography showing bilateral infiltrates in the absence of congestive heart failure.³⁰ Patients with COVID-19 who clinically deteriorate and require mechanical ventilation almost certainly have ARDS and should be treated with previously proven strategies for patients with non-COVID-19 ARDS. In general, ventilator strategies to support patients with ARDS are designed to minimize the so-called ventilator-induced lung injury caused by the overdistension of ventilated lung units (ie, volutrauma) and the repetitive opening and closing of alveoli during the respiratory cycle (ie, atelectrauma).³¹ Since the start of the pandemic there have been no compelling data suggesting that patients with ARDS secondary to SARS-CoV-2

infection should be treated differently than those with prepandemic ARDS in terms of mechanical ventilatory support.

Low Tidal Volume Mechanical Ventilation

In a landmark trial, a low tidal volume (6 mL tidal volume/kg ideal body weight) was shown to reduce mortality compared with a high tidal volume (12 mL tidal volume/kg ideal body weight) for the treatment of ARDS.³² Thus, 6 mL/kg has become the default tidal volume setting for patients with ARDS; however, clinicians should be mindful to try and minimize the plateau pressure (measured during an inspiratory pause, it is an estimate of the mean alveolar pressure) and driving pressures (computed as the plateau pressure minus positive end expiratory pressure).^{33,34} It is generally accepted that the plateau pressure should ideally be less than 32 mm H₂O and that driving pressure should be less than 15 cm H₂O.^{34,35}

Prone Ventilation for Intubated Patients

Prone ventilation has a multitude of beneficial effects on the pulmonary system in ARDS, including recruitment of alveoli, improvement in ventilation and perfusion, and lung compliance.^{30,36} The PROSEVA study, a multicenter randomized controlled trial involving 466 patients with severe ARDS demonstrated that prone ventilation for 16 h/d compared with ventilation in the supine position improved 28-day mortality (16% vs 32.8%, $P < .001$).²⁴ It is important to note that a subsequent meta-analysis showed that the mortality benefit of prone ventilation for the treatment of ARDS was only detectable when patients were concomitantly receiving low tidal volume ventilation.³⁷ Thus, patients with ARDS are best treated with low tidal volume ventilation, while simultaneously receiving prone ventilation.

Paralysis

Chemical paralysis may have a role in ensuring that an individual patient is synchronous with the ventilator and safely maintained in the prone position; however, the routine use of neuromuscular blocking agents has not been consistently shown to improve outcomes in the treatment of patients with ARDS. Paralysis was unlikely to have affected the results of the PROSEVA trial because patients in both study arms were similarly treated with neuromuscular blocking agents (91% of patients receiving prone ventilation and 82% of supine patients). And whereas a study by Papazian and colleagues³⁸ ($n = 340$) showed that a 48-hour course of a continuous infusion of a neuromuscular blocking agent increased survival among intubated patients with ARDS, a subsequent, larger trial ($n = 1006$) by Moss and colleagues was stopped at the second interim analysis due to futility.³⁹ Thus, use of paralytics should be individualized in ARDS rather than given routinely.⁴⁰

Extracorporeal Membrane Oxygenation as a Rescue Therapy

Despite the use of low tidal volume and prone positioning, patients with ARDS remain susceptible to ventilator-induced lung injury, refractory hypoxemia, and/or refractory hypercapnia. With extracorporeal membrane oxygenation (ECMO), blood is removed from the patient via a large venous catheter, pumped through an extracorporeal membrane in which carbon dioxide is removed and oxygen is delivered, and returned via another large catheter to the right atrium. Patients receiving ECMO therapy are placed on minimal mechanical ventilatory settings eliminating any ventilator-induced lung injury with the hope that lung function will recover over time. Although simple in concept, the actual delivery of ECMO and ECMO-related care requires expertise, costly resources, and is associated with a host of risks and potential complications

for an already critically ill patient.⁴¹ Before the SARS-CoV-2 pandemic, in 2 randomized controlled trials, ECMO was not shown to be superior to conventional respiratory care for the treatment of patients with ARDS.^{42,43} The Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial ($n = 180$) was particularly interesting because it showed that patients with ARDS who were *transferred* to a tertiary center specializing in ECMO experienced a 16% survival benefit without severe disability. However, the relative improvement in outcome may have been due to better general care provided at a center of excellence because only 75% of patients in the study arm received ECMO.

Our current understanding of the effectiveness of ECMO for the treatment of ARDS secondary to SARS-CoV-2 is limited in the absence of randomized controlled clinical trials. Retrospective data from one study showed that patients with COVID-19 who were treated with ECMO had an estimated 60-day mortality of 31%, which is similar to ECMO-treated patients before the start of the pandemic.^{42,44} In a subsequent, larger trial ($n = 4812$) that included patients from later in the pandemic, the investigators describe a mortality rate for patients with COVID-19 treated with ECMO of greater than 50%.⁴⁵ Possibly the most compelling evidence supporting the use of ECMO in the treatment of COVID-19 can be found in a study performed by Gannon and colleagues⁴⁶ that compared the mortality rates of 35 patients who were accepted for transfer by a tertiary center and treated with ECMO, versus 55 patients who were also deemed to be eligible candidates for treatment, but because of hospital capacity strain were not transferred to the tertiary center and subsequently did not receive ECMO. The in-hospital mortality rate for those patients who underwent ECMO was 42.9%, versus 89.1% for those patients who were unable to receive ECMO (adjusted HR, 0.23; 95% CI, 0.12–0.43; $P < .001$). However, the findings of this small, retrospective study must be interpreted cautiously in the context of a health system that may have been overwhelmed during the pandemic.

The authors recommend that patients with COVID-19 who are intubated and failing standard ARDS respiratory supportive strategies be referred for ECMO early in their clinical course especially because determining eligibility varies across centers. Most ECMO programs evaluate patients based on expert opinion in conjunction with established criteria that takes into consideration patient age, body mass index, duration of mechanical ventilation, comorbidities (neurologic function specifically), and extrapulmonary organ dysfunction.⁴⁷ The authors further urge clinicians taking care of patients with COVID-19 to engage preferentially with high-volume ECMO centers, because programs with less experience are more likely to have higher mortality rates.⁴⁵

GENERAL CRITICAL CARE SUPPORTIVE CARE

The experience of the SARS-CoV-2 pandemic has served to reinforce the importance of many established supportive measures used to treat all critically ill patients.

Anticoagulation

Rates of deep venous thromboembolism and pulmonary embolism among critically ill patients with COVID-19 are comparable to those among critically ill patients without COVID-19.⁴⁸ Moreover, a large ($n = 1098$) open-label adaptive clinical trial, in which critically ill patients with COVID-19 were randomized to either therapeutic-dose anticoagulation with heparin or pharmacologic thromboprophylaxis, was stopped early for futility.⁴⁹ Although not statistically significant, major bleeding occurred more often in patients assigned to receive therapeutic dose anticoagulation compared with patients who were treated with usual care pharmacologic thromboprophylaxis. In light

of these data, the authors agree with the NIH COVID-19 Treatment Guidelines recommending pharmacologic thromboprophylaxis and not routine therapeutic-dose anticoagulation for critically ill patients with COVID-19 (NIH).¹⁶

Fluid Management

There are inherent risks for critically ill patients who are either under or over fluid resuscitated. To date, there are no randomized clinical trials comparing different fluid management strategies for critically ill patients with COVID-19. For the treatment of non-COVID-19-related ARDS, conservative rather than liberal fluid management strategy was shown to increase the number of ventilator-free days (14.6 vs 12.1, $P < .0001$) (a secondary study outcome) albeit without any mortality benefit (the primary study outcome).⁵⁰ Considering respiratory failure is the cause or is present in more than 80% of patients who die of COVID-19, the authors recommend a conservative fluid strategy for patients with COVID-19 receiving mechanical ventilation.⁵¹ Estimating the fluid status of a critically ill patient can be challenging; besides daily weight and fluid balance measures, point-of-care ultrasonography can be a useful adjunct to aid in guiding diuretic or fluid resuscitation decisions for the critically ill patient with COVID-19.^{52,53}

Minimizing Risk Factors for Delirium

Unfortunately, critically ill patients with COVID-19 have been at high risk for developing delirium, with a reported incidence of greater than 50%.^{54,55} In part, this finding may represent an unintended consequence of both the supportive care measures (eg, the frequent use of deep sedation in conjunction with paralytic agents) and hospital infection prevention policies aimed at protecting both health care workers and family members and friends of patients. As with all critically ill patients, clinicians should screen all mechanically ventilated patients for delirium using a validated tool such as the The Confusion Assessment method for the ICU (CAM-ICU).⁵⁶ Limiting the use of sedative/anxiolytics, especially benzodiazepines, has been the cornerstone of minimizing delirium in the ICU.⁵⁷ For example, it may not be necessary to administer neuromuscular blocking agents (and therefore concomitant high-dose sedatives) when patients are undergoing prone ventilation. As previously described, therapeutic paralysis has not been shown to be definitively beneficial in the treatment of patients with ARDS in the pre-pandemic era; likewise, there are no clinical trials in patients with COVID-19 supporting the routine use of neuromuscular blockade. In an observational study of 156 patients, similar improvement in $\text{PaO}_2 : \text{FiO}_2$ and $\text{O}_2\text{Sat} : \text{FiO}_2$ ratios were noted postinitiation of prone ventilation in patients being treated with and without paralysis.⁴⁰ Furthermore, there were no adverse events associated with prone positioning performed without neuromuscular blockade. Restrictive hospital visitation policies instituted during the pandemic may also have added to the overall burden of delirium experienced by critically ill patients. Although not consistent, there is pre-pandemic evidence to suggest that flexible and extended visiting hours can lower the incidence of delirium and anxiety among critically ill patients.⁵⁸ Performed during the pandemic, a study comparing rates of delirium among patients with COVID-19 before and after the implementation of an ICU visitor ban did not show a significant increase in the overall incidence of delirium (27.4% vs 30.9%, respectively, $P = .162$); however, a restrictive visitor policy was associated with an increase of hyperactive and mixed subgroups of delirium and high anxiety levels.⁵⁹ Thus, evolving hospital visitor policies designed to continue to prevent hospital transmission of SARS-CoV-2 should be tempered by the potential importance of patient-visitor interactions.

SUMMARY

The early adoption of supportive care strategies for the management of ARDS, developed during the pre-pandemic era, may have been responsible for the improvement in critical care outcomes noted during the early phase (March to May, 2020) of the pandemic. Anecdotally, those of us who have taken care of critically ill patients throughout the pandemic have marveled at how proficient ICU teams of nurses and respiratory therapists have become at routinely repositioning patients with COVID-19, some of whom have chest tubes and are simultaneously receiving continuous renal replacement therapy. In addition to prone ventilation and adherence to low tidal volume ventilation, the expansive use of other measures such as NPPV, and HFNC, have the potential to reduce the need for intubation, if not possibly mortality, for critically ill patients with COVID-19. And although PINI is intriguing, its clinical benefit for patients with COVID-19 has not been established; whether longer durations of therapy (>8 hours) could be beneficial remains to be proven. Finally, the experience of the pandemic has also resulted in recognition of the importance of providing quality critical adjunctive therapies such as deep vein thrombosis prophylaxis, attention to fluid management, and minimizing sedation and neuromuscular blockade for the purpose of reducing the risk of delirium. Despite these early advances, mortality rates among critically ill patients with COVID-19 are largely unchanged over the later phases of the pandemic.^{60,61} Although the development of therapeutics to treat patients with severe disease specifically needs to be the primary strategy, supportive care—either by expanding the use of current strategies or developing new approaches—can serve an adjunctive role to improve clinical outcomes for critically ill patients with COVID-19.

CLINICAL CARE POINTS

- Lung size does not change with either weight loss or weight gain. Ideal body weight and not actual body weight in kilograms should be used when choosing a low tidal volume for the treatment of mechanically ventilated patients with COVID-19 and ARDS.
- The nomenclature of respiratory supportive care is inherently confusing. NIV, NIPPV, bilevel, and BiPAP (a trade name) are synonymous and describe a system that uses 2 different pressures—IPAP and EPAP. CPAP as the name implies delivers one continuous pressure. HFNC delivers oxygen flow rates ranging from greater than or equal to 15 to 60 LPM as opposed to low-flow or nasal cannula oxygen, which delivers oxygen from 1 to 14 LPM.
- For patients receiving HFNC, the F_{iO_2} should be titrated based on the patient's pulse oximetry, whereas the flow rate should be titrated based on the clinical assessment of the patient including presence of dyspnea and breathing pattern.
- Not all patients with COVID-19 and ARDS who are intubated and receiving prone ventilation require chemical paralysis; rather, the decision to administer neuromuscular blocking agents should be individualized based on patient safety and ability to maintain synchrony with the ventilator.
- Basic tenants of supportive critical care established before the pandemic remain relevant for the management of patients with severe COVID-19

DISCLOSURE

D.A. Sweeney has nothing to declare. A. Malhotra is funded by the National Institutes of Health. He reports income related to medical education from Livanova, Jazz,

Equillium, and Corvus, unrelated to the content of this manuscript. ResMed provided a philanthropic donation to UC San Diego.

REFERENCES

1. Auld SC, Caridi-Scheible M, Robichaux C, et al. Declines in Mortality Over Time for Critically Ill Adults With Coronavirus Disease 2019. *Crit Care Med* 2020;48(12): e1382–4.
2. Carbonell R, Urgeles S, Rodriguez A, et al. Mortality comparison between the first and second/third waves among 3,795 critical COVID-19 patients with pneumonia admitted to the ICU: A multicentre retrospective cohort study. *Lancet Reg Health Eur* 2021;11:100243.
3. Ely EW, Ramanan AV, Kartman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. *Lancet Respir Med* 2022;10(4):327–36.
4. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021;384(8):693–704.
5. Whittaker R, Brathen Kristofferson A, Valcarcel Salamanca B, et al. Length of hospital stay and risk of intensive care admission and in-hospital death among COVID-19 patients in Norway: a register-based cohort study comparing patients fully vaccinated with an mRNA vaccine to unvaccinated patients. *Clin Microbiol Infect* 2022;28(6):871–8.
6. Westafer LM, Soares WE 3rd, Salvador D, et al. No evidence of increasing COVID-19 in health care workers after implementation of high flow nasal cannula: A safety evaluation. *Am J Emerg Med* 2021;39:158–61.
7. Costa W, Miguel JP, Prado FDS, et al. Noninvasive ventilation and high-flow nasal cannula in patients with acute hypoxemic respiratory failure by covid-19: A retrospective study of the feasibility, safety and outcomes. *Respir Physiol Neurobiol* 2022;298:103842.
8. Confalonieri M, Potena A, Carbone G, et al. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med* 1999;160(5 Pt 1): 1585–91.
9. Ferrer M, Esquinas A, Leon M, et al. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med* 2003; 168(12):1438–44.
10. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372(23):2185–96.
11. Ospina-Tascon GA, Calderon-Tapia LE, Garcia AF, et al. Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: A Randomized Clinical Trial. *JAMA* 2021;326(21):2161–71.
12. Demoule A, Vieillard Baron A, Darmon M, et al. High-Flow Nasal Cannula in Critically Ill Patients with Severe COVID-19. *Am J Respir Crit Care Med* 2020;202(7): 1039–42.
13. Grieco DL, Menga LS, Cesarano M, et al. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENI-VOT Randomized Clinical Trial. *JAMA* 2021;325(17):1731–43.

14. Perkins GD, Ji C, Connolly BA, et al. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. *JAMA* 2022; 327(6):546–58.
15. Alhazzani W, Evans L, Alshamsi F, et al. Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update. *Crit Care Med* 2021;49(3):e219–34.
16. Panel. C-TG. Coronavirus Disease 2019 (COVID-19) treatment Guidelines. National Institutes of Health. Available at: <https://www.covid19treatmentguidelines.nih.gov/>. Accessed April 7, 2022.
17. High-Flow Nasal Oxygen Cannula Compared to Non-Invasive Ventilation in Adult Patients With AcuTE Respiratory Failure (RENOVATE). Available at: <https://clinicaltrials.gov/ct2/show/NCT03643939>. Accessed April 9, 2022.
18. Weatherald J, Solverson K, Zuege DJ, et al. Awake prone positioning for COVID-19 hypoxemic respiratory failure: A rapid review. *J Crit Care* 2021;61:63–70.
19. Li J, Luo J, Pavlov I, et al. Awake prone positioning for non-intubated patients with COVID-19-related acute hypoxaemic respiratory failure: a systematic review and meta-analysis. *Lancet Respir Med* 2022. [https://doi.org/10.1016/S2213-2600\(22\)00043-1](https://doi.org/10.1016/S2213-2600(22)00043-1).
20. Ehrmann S, Li J, Ibarra-Estrada M, et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. *Lancet Respir Med* 2021;9(12):1387–95.
21. McGuire WC, Pearce AK, Malhotra A. Prone positioning might reduce the need for intubation in people with severe COVID-19. *Lancet Respir Med* 2021;9(12): e110.
22. Alhazzani W, Parhar KKS, Weatherald J, et al. Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA* 2022. <https://doi.org/10.1001/jama.2022.7993>.
23. Esperatti M, Busico M, Fuentes NA, et al. Impact of exposure time in awake prone positioning on clinical outcomes of patients with COVID-19-related acute respiratory failure treated with high-flow nasal oxygen: a multicenter cohort study. *Crit Care* 2022;26(1):16.
24. Guérin C, Reignier J, Richard J-C, et al. Prone Positioning in Severe Acute Respiratory Distress Syndrome. *N Engl J Med* 2013;368(23):2159–68.
25. Goyal P, Choi JJ, Pinheiro LC et al. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med* 2020;382(24):2372–4.
26. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020;46(6): 1099–102.
27. Haymet A, Bassi GL, Fraser JF. Airborne spread of SARS-CoV-2 while using high-flow nasal cannula oxygen therapy: myth or reality? *Intensive Care Med* 2020; 46(12):2248–51.
28. Dupuis C, Bouadma L, de Montmollin E, et al. Association Between Early Invasive Mechanical Ventilation and Day-60 Mortality in Acute Hypoxemic Respiratory Failure Related to Coronavirus Disease-2019 Pneumonia. *Crit Care Explor* 2021;3(1): e0329.
29. Tobin MJ. The criteria used to justify endotracheal intubation of patients with COVID-19 are worrisome. *Can J Anaesth* 2021;68(2):258–9.
30. Pearce AK, McGuire WC, Malhotra A. Prone Positioning in Acute Respiratory Distress Syndrome. *NEJM Evid* 2022;1(2). EVIDra2100046.

31. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N Engl J Med* 2017;377(6):562–72.
32. Acute Respiratory Distress Syndrome N, 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(18):1301–8.
33. Amato MBP, Meade MO, Slutsky AS, et al. Driving Pressure and Survival in the Acute Respiratory Distress Syndrome. *N Engl J Med* 2015;372(8):747–55.
34. Tobin MJ. Culmination of an Era in Research on the Acute Respiratory Distress Syndrome. *N Engl J Med* 2000;342(18):1360–1.
35. MacIntyre N. Ventilator Management Guided by Driving Pressure: A Better Way to Protect the Lungs? *Crit Care Med* 2018;46(2):338–9.
36. Guerin C, Albert RK, Beitler J, et al. Prone position in ARDS patients: why, when, how and for whom. *Intensive Care Med* 2020;46(12):2385–96.
37. Beitler JR, Shaefi S, Montesi SB, et al. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med* 2014;40(3):332–41.
38. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363(12):1107–16.
39. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. *N Engl J Med* 2019;380(21):1997–2008.
40. Cotton S, Husain AA, Meehan M, et al. A2508 - The Influence of Paralytics on the Safety and Efficacy of Prone Positioning in Covid19 ARDS. presented at: American Thoracic Society; 2021; Session TP48 - TP048 COVID: ARDS clinical studies.
41. Brodie D, Slutsky AS, Combes A. Extracorporeal Life Support for Adults With Respiratory Failure and Related Indications: A Review. *JAMA* 2019;322(6):557–68.
42. Combes A, Hajage D, Capellier G, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. *N Engl J Med* 2018;378(21):1965–75.
43. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;374(9698):1351–63.
44. Schmidt M, Hajage D, Lebreton G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med* 2020;8(11):1121–31.
45. Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. *Lancet* 2021;398(10307):1230–8.
46. Gannon WD, Stokes JW, Francois SA, et al. Association Between Availability of ECMO and Mortality in COVID-19 Patients Eligible for ECMO: A Natural Experiment. *Am J Respir Crit Care Med* 2022. <https://doi.org/10.1164/rccm.202110-2399LE>.
47. Badulak J, Antonini MV, Stead CM, et al. Extracorporeal Membrane Oxygenation for COVID-19: Updated 2021 Guidelines from the Extracorporeal Life Support Organization. *ASAIO J* 2021;67(5):485–95.
48. Gallastegui N, Zhou JY, Drygalski AV, et al. Pulmonary Embolism Does Not Have an Unusually High Incidence Among Hospitalized COVID19 Patients. *Clin Appl Thromb Hemost* 2021;27. 1076029621996471.

49. Investigators R-C, Investigators AC-a, Investigators A, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med* 2021; 385(9):777–89.
50. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354(24):2564–75.
51. Kazory A, Ronco C, McCullough PA. SARS-CoV-2 (COVID-19) and intravascular volume management strategies in the critically ill. *Proc (Bayl Univ Med Cent)* 2020;0(0):1–6.
52. Koratala A, Ronco C, Kazory A. Need for Objective Assessment of Volume Status in Critically Ill Patients with COVID-19: The Tri-POCUS Approach. *Cardiorenal Med* 2020;10(4):209–16.
53. Thalappillil R, White RS, Tam CW. POCUS to Guide Fluid Therapy in COVID-19. *J Cardiothorac Vasc Anesth* 2020;34(10):2854–6.
54. Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med* 2021;9(3):239–50.
55. Williamson CA, Faiver L, Nguyen AM, et al. Incidence, Predictors and Outcomes of Delirium in Critically Ill Patients With COVID-19. *Neurohospitalist* 2022; 12(1):31–7.
56. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286(21):2703–10.
57. Pandharipande P, Cotton BA, Shintani A, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma* 2008;65(1):34–41.
58. Rosa RG, Tonietto TF, da Silva DB, et al. Effectiveness and Safety of an Extended ICU Visitation Model for Delirium Prevention: A Before and After Study. *Crit Care Med* 2017;45(10):1660–7.
59. Kim B, Cho J, Park JY, et al. Delirium and Anxiety Outcomes Related to Visiting Policy Changes in the Intensive Care Unit During the COVID-19 Pandemic. *Original Research. Front Aging Neurosci* 2022;14. <https://doi.org/10.3389/fnagi.2022.845105>.
60. Anesi GL, Jablonski J, Harhay MO, et al. Characteristics, Outcomes, and Trends of Patients With COVID-19-Related Critical Illness at a Learning Health System in the United States. *Ann Intern Med* 2021;174(5):613–21.
61. Auld SC, Harrington KRV, Adelman MW, et al. Trends in ICU Mortality From Coronavirus Disease 2019: A Tale of Three Surges. *Crit Care Med* 2022;50(2):245–55.