



COVID-19: Lessons Learned

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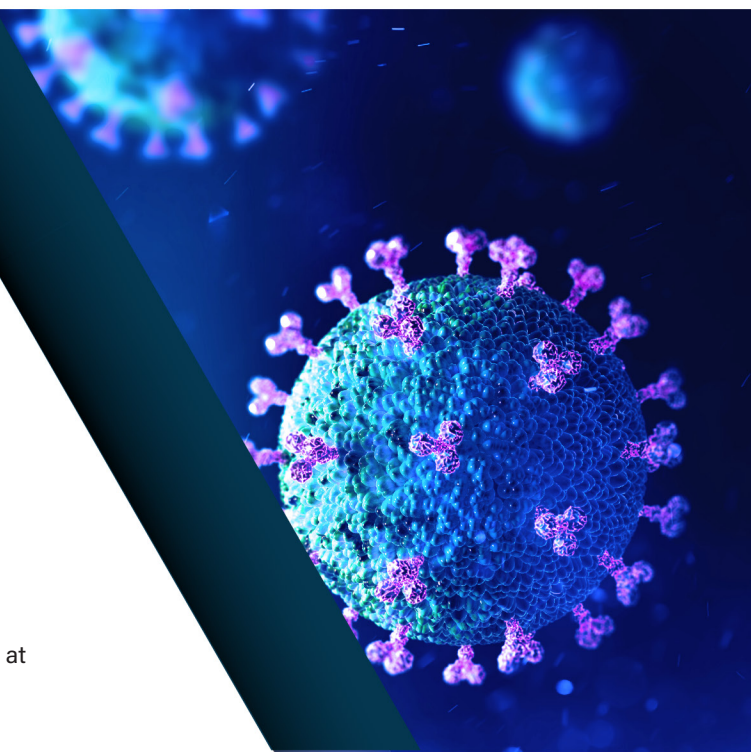
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OBJECTIVES

1. Describe the time course of the COVID-19 pandemic.
2. Discuss the role of face masks and vaccines in the prevention of COVID-19.
3. Discuss caregiver protection in the setting of various aerosol generating procedures.
4. Discuss the role of noninvasive respiratory support for treatment of patients with COVID-19.
5. Describe how to use a non-invasive ventilator for invasive ventilation.
6. Discuss the timing of intubation in patients with COVID-19.
7. Discuss the use of invasive mechanical ventilation in patients with hypoxemic respiratory failure with COVID-19.
8. Discuss the use of ECMO in patients with hypoxemic respiratory failure with COVID-19.
9. Discuss technical issues related to oxygen supply in the setting of a surge in demand.
10. Describe the physiology of happy hypoxemia.
11. Compare ARDS in those with and without COVID-19.
12. Discuss the role of prone positioning in patients with COVID-19.
13. Discuss issues with humidification in patients with COVID-19.
14. Discuss the risk of post-extubation stridor in patients with COVID-19.
15. Describe the role of the strategic national stockpile in the setting of COVID-19.
16. Discuss issues with the use of anesthesia machines for ventilation in the ICU.
17. Discuss the role of the respiratory therapist in care of patients with post-COVID syndrome.

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INTRODUCTION

Coronavirus disease 2019, now commonly called COVID-19, is caused by a novel coronavirus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2019). The virus was first described in December of 2019 in Wuhan, Hubei province, China.¹ Transmission of the virus from live animals to humans was initially traced to a seafood wholesale market. Despite widespread conjecture regarding its origin, the virus was found to be closely related to a previously described coronavirus in bats.^{2,3} Viral transmission from animals to humans demonstrates an emerging area of concern, as climate change and global human encroachment on native habitats place people and wild animals in ever closer proximity.

Initial descriptions of COVID-19 included presentation of patients with fever, cough, and progressive dyspnea.¹ Over time, the full spectrum of COVID-19 disease would range from mild symptoms similar to the common cold to viral sepsis, acute respiratory failure, severe hypoxemia, and death. SARS-CoV-2 proved to be rapidly transmitted via airborne particles and in the absence of vaccines and native immunity, spread quickly around the globe. More recent variants of the original virus appear to be even more readily transmissible, albeit with less severe disease and fewer hospitalizations in the presence of effective vaccines, improved understanding of the disease and novel drug treatments.⁴

COVID-19 represents the first severe respiratory failure pandemic since the 1918 influenza, which killed nearly a fifth of the world's population.⁵ The first wave of the COVID-19 pandemic overwhelmed healthcare systems around the world. Shortages of personnel, intensive care beds, ventilators, medications, personal protective equipment (PPE) and oxygen were real and covered daily in the lay press. Professional societies convened task forces and struggled to provide solutions and guide practice.⁶⁻⁸

Respiratory therapists found themselves at the forefront of the pandemic, providing direct care to patients with COVID-19 respiratory failure, managing equipment shortages, finding effective therapies, and reducing transmission to staff and other patients. During the pandemic, several concepts were advanced, many refuted, and a few found to show promise. From 2020 to 2022, the volume of publications covering the respiratory care of patients with COVID-19 is seemingly limitless. This guide aims to coalesce the literature on COVID-19 and provide evidence-based practices and the current understanding of aspects related to care of these critically ill patients. This will include the use of non-invasive respiratory support, invasive ventilation, prone positioning, aerosol-generating procedures, shared ventilation, issues related to oxygen therapy, silent hypoxemia, ventilator shortages, and long COVID. We provide the best evidence on these topics. As we have learned, COVID-19 will remain a public health concern for years to come and new problems and findings are surely forthcoming.

TIME COURSE OF THE PANDEMIC

Initial reports of COVID-19 emerged in December of 2019, hence the 19 attached to the coronavirus disease moniker. In the initial report from December 12, 2019, the clinical course of 3 patients with fever, cough, chest discomfort and diffuse opacities on chest radiograph are briefly described. One patient required mechanical ventilation and 2 patients survived to discharge. Bronchoalveolar lavage samples from these subjects demonstrated more than 85% identity with a bat SARS-like CoV genome that had previously been described. One of the patients worked at the Wuhan seafood market and the second was a frequent visitor.¹ This is the genesis story of COVID-19 and the highly contagious nature of the SARS-CoV-2 virus soon ignited a worldwide pandemic. Of note, Wuhan is a transportation hub in China with direct flights to many of the major cities in the United States and Europe.

By New Year's Eve of 2019, the World Health Organization (WHO) was notified of a spate of pneumonia cases in Wuhan with an unknown etiology. Initially, all cases were linked to the Hunan Seafood Wholesale Market. Early in January, WHO confirmed data from Chinese authorities identifying a novel coronavirus as the cause of the outbreak. The Centers for Disease Control (CDC) established an incident management structure and by mid-January 2020 was screening passengers on direct flights from Wuhan to major American cities (<https://www.cdc.gov/museum/timeline/covid19.html>, accessed June 13, 2022).

The first known US cases of COVID-19 were identified in the state of Washington on January 17, 2020. An initial cluster of cases were seen in a long-term care facility in King County.⁹ This initial report proved to be a harbinger of future findings, the increased risk of severe disease in the elderly and those with comorbidities. By mid-March 2020, 167 confirmed cases of COVID-19 were linked to the long-term care facility, with 101 residents, 50 caregivers and 16 visitors infected by the virus. Half of residents and staff required hospitalization, compared to only 6% for visitors, and the case fatality rate for residents was 34%.⁹

Additional reports from the Seattle area confirmed the presenting symptoms of cough, fever, and dyspnea. They also reported hypoxemic respiratory failure requiring mechanical

ventilation and hypotension requiring vasopressors, as well as, associated diabetes mellitus in over half the patients. The mortality rate was over 50%.¹⁰ Reports from the Evergreen Hospital outside Seattle provided confirmatory evidence. In a case series of 21 patients, co-morbidities were present in 86% of cases and shortness of breath, fever, and cough were the most common presenting symptoms. Fifteen subjects required mechanical ventilation and 75% received vasopressor support. The mortality rate was 52% with 38% of subjects still in the intensive care unit (ICU) at the time of the report.¹¹

On January 22, 2020, WHO confirmed spread of SARS-CoV was human to human but declined to declare the novel coronavirus a Public Health Emergency of International Concern. By January 31, 2020, Health and Human Services (HHS) declared SARS-CoV-2 a public health emergency and WHO declared the outbreak a Public Health Emergency. On February 11, 2020, coronavirus disease officially became COVID-19. On March 13, 2020, the President of the United States declared COVID-19 a nationwide emergency (<https://www.cdc.gov/museum/timeline/covid19.html>, accessed June 13, 2022).

In March of 2020, New York City (NYC) became the epicenter of the COVID-19 pandemic, owing in part to the unique population, available ICU beds per inhabitant, and housing. NYC not only has primarily multiple-unit housing, but also multiple generations living under the same roof. These factors conspired to create an ideal breeding ground for SARS-CoV-2, and also a nearly catastrophic surge overwhelming the healthcare system (<https://www1.nyc.gov/site/doh/COVID/COVID-19-data.page>, accessed June 13, 2022).

Goyal and colleagues¹² described the first 393 patients admitted to two NYC hospitals in March of 2020. In both hospitals, an early intubation strategy was used, in part to mitigate concerns related to virus spread during the use of noninvasive respiratory support. Symptomology of cough, fever, and dyspnea remained hallmarks of the disease and obesity was present in a third of patients. Mechanical ventilation was instituted in a third of patients (n=130) and at the time of publication only 43 (33%) of those patients had been extubated. At the time of publication, overall mortality rate

was 10% and mortality rate for patients requiring invasive ventilation was 15%. Of those patients requiring mechanical ventilation, nearly all required vasopressor support, detailing a disease of severe hypoxemic respiratory failure, pneumonia, and viral sepsis.¹²

Follow-up studies from NYC provided new and confirmatory findings. A study of patients treated in the Mt Sinai system demonstrated a requirement for ICU admission in 36% of patients and an overall mortality rate of 29%. Pre-existing conditions were associated with a nearly 50% increase in mortality compared to patients without those conditions. This population included a diverse population and confirmed a burden of COVID-19 in people of color.¹³⁻¹⁵

Richardson and co-workers¹⁶ published what became a controversial paper regarding the outcome of mechanically ventilated patients in NYC hospitals. In this case series of 5,700 patients, the reported mortality rate for mechanically ventilated patients was 88%, prompting widespread concern on social media and in the general public (<https://www.bloomberg.com/news/articles/2020-04-22/almost-9-in-10-COVID-19-patients-on-ventilators-died-in-study>, accessed June 13, 2022; <https://www.politifact.com/article/2020/apr/28/are-88-COVID-19-patients-ventilators-dying-its-not/>, accessed June 13, 2022). The authors quickly provided clarification, that while mortality of subjects who were discharged was high, more than 75% of the cohort remained hospitalized.¹⁷ Social media created a pandemic of misinformation, as well as, disinformation regarding mitigation strategies, risks, effective treatments, and equipment shortages. Among the lessons learned from COVID-19 is that a major goal in future pandemics will be to cultivate an informative and accurate social media strategy.¹⁸⁻²²

COVID-19 disease spread across the country in a sporadic fashion with hot spots in the South and Northeast, while other areas of the country were yet to be impacted. At the time, NYC was experiencing overwhelmed ICUs, ventilator shortages, and staffing crunches, Ohio had canceled elective surgeries and had open beds and half the ventilator fleet unused. In many ways, this allowed sharing of personnel and technology, preventing a simultaneous nationwide catastrophe.

Tracking the pandemic has been a challenge, but CDC has provided a treasure trove of data. Deaths from COVID-19 have been staggering. On May 28, 2020, 100,000 deaths were reported in the US. The US reached 200,000 deaths on September 22, 2020, and 300,000 deaths on December 14, 2020. By Christmas, 2020, one million vaccinations had been administered. February 21, 2021, marked half a million deaths in this country. In March of 2021, 100 million vaccines had been administered and soberingly, in May 2022, the death toll exceeded one million Americans. Table 1 compares data related to hospitalizations, deaths, and vaccines over the course of the pandemic.

New variants of the virus, vaccine uptake, and previous disease have all altered the course of infection rates, hospitalizations, and deaths. New pharmacologic treatments have been shown to improve outcomes and mitigation strategies have proven useful. COVID-19 is an ongoing pandemic and while great strides have been made, we must remain observant and cautious. Boosters and mitigation remain important, particularly for at-risk individuals.

Table 1. Cases, hospitalizations, deaths, and vaccinations in the US during the COVID-19 pandemic. On May 31, 2022, 258,586,526 Americans had received at least one dose of vaccine (78% of the population). Data from <https://COVID.cdc.gov/COVID-data-tracker>

	March 1, 2020	Sept 1, 2020	Peak 2020	March 1, 2021	Sept 1, 2021	March 1, 2022	Peak 2022
New Cases (7-day average)	18 7	39,075 42,489	246,614 218,004	61,328 165,742	135,103 134,224	42,498 54,891	475,193 809,496
Hospitalizations - New Admissions (7-day moving average)	unknown	4,067	15,121	5,646	7,103	4,291	22,920
Deaths daily (7-day moving average)	0	864	3,425	1,788	1,992	1,788	2,712
Vaccinated Americans > 5 years of age (7-day moving average)	0	0	405,469 (Dec 31)	2,209,444	663,920	285,668	505,271

Key Points

- SARS-CoV-2 emanated from live animals and spread to humans in a seafood market in Wuhan, China.
- SARS-CoV-2 infection can lead to COVID-19 with a range of symptoms from mild illness to viral sepsis and ARDS.
- The most common presenting symptoms of COVID-19 are cough, fever, and dyspnea.
- Despite early reports, the mortality rate from COVID-19 in mechanically ventilated patients is similar to ARDS and sepsis unrelated to COVID-19.
- In May, 2022, the death rate from COVID-19 exceeded 1 million in the US.
- Misinformation on social media was a pandemic within the pandemic, spreading fear and unsubstantiated claims.

VACCINES, TESTING, MASKS, AND THERAPEUTICS

Vaccination

Vaccination is the best protection against COVID-19. All currently approved or authorized COVID-19 vaccines are safe and effective in reducing the risk of severe illness (<https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html#vaccine-table>, accessed June 13, 2022). Vaccination also reduces the spread of disease, which helps protect those who get vaccinated and the community at large. Vaccines effectively prevent serious illness and reduce the need for hospitalization. Several COVID-19 vaccines are authorized or approved for use in the United States to prevent COVID-19: Pfizer-BioNTech and Moderna are COVID-19 mRNA vaccines and are preferred. These vaccines teach cells how to make proteins to trigger an immune response. Another option in some situations is the Johnson & Johnson Janssen COVID-19 vaccine. However, the FDA limits its use due to the risk of life-threatening blood clots (<https://www.fda.gov/news-events/press-announcements/coronavirus-COVID-19-update-fda-limits-use-janssen-COVID-19-vaccine-certain-individuals>, accessed June 13, 2022). Novavax vaccine uses copies of the SARS-CoV-2 spike protein to instruct the body's cells to make the protein that prompts an immune response.

There is some decline in vaccine effectiveness against infection over time. Therefore, a booster shot is needed either 6 months after the initial Pfizer or Moderna vaccination, or 2 months after the initial Johnson & Johnson's Janssen vaccine. A second booster is recommended for persons 50 years or older, and those who are moderately or severely immunocompromised. CDC does not recommend mixing the primary vaccine series. Adults may get a different vaccine for a booster than they got for their primary series.

Most people who get COVID-19 are unvaccinated, but some people who are fully vaccinated still get COVID-19. An infection in a fully vaccinated person is called a breakthrough infection. Vaccines are not 100% effective in the prevention of disease, but individuals with a breakthrough infection are less likely to develop serious illnesses than unvaccinated individuals who are infected. Fully vaccinated people who are infected and develop symptoms tend to have less severe symptoms than unvaccinated people. They are

much less likely to be hospitalized or die than unvaccinated people if infected with COVID-19. It is important to appreciate that persons with a breakthrough infection can be contagious.

Herd immunity occurs when a large portion of a community (the herd) becomes immune to a disease, making the spread of disease from person to person unlikely. As a result, the whole community becomes protected, not just those who are immune. Herd immunity is achieved through infection and vaccination. It is unknown what percentage of a community needs to be immune to achieve herd immunity for COVID-19. But it is likely a large fraction. For the highly contagious disease measles, over 90% of the population must be immune to interrupt the chain of transmission (<https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/herd-immunity-and-coronavirus/art-20486808>, accessed June 13, 2022).

Testing

COVID-19 testing is an important strategy to reduce the spread of the disease and to allow prompt treatment. Quickly identifying and isolating people who are infected reduces SARS-CoV-2 transmission in the community (<https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html>, accessed June 13, 2022). COVID-19 tests detect either the SARS-CoV-2 virus or antibodies produced after COVID-19 infection or vaccination. A viral test uses a nasal swap sample.

Two types of tests are used to detect SARS-CoV-2 infection. Rapid point-of-care (POC) tests can be performed or interpreted by someone other than the individual being tested or can be taken at home by the individual. They are easy to use and produce rapid results (within 30 minutes). Rapid POC tests are immunoassays that detect the presence of viral antigen, which indicates a current infection. Laboratory tests can take days to complete and use reverse transcription polymerase chain reaction (PCR) analysis and other nucleic acid amplification tests (NAATs) to detect and amplify the presence of viral nucleic acid. PCR testing is considered the gold standard.

Antigen tests perform best if the individual is tested when they are symptomatic. Due to the sensitivity of current FDA-authorized

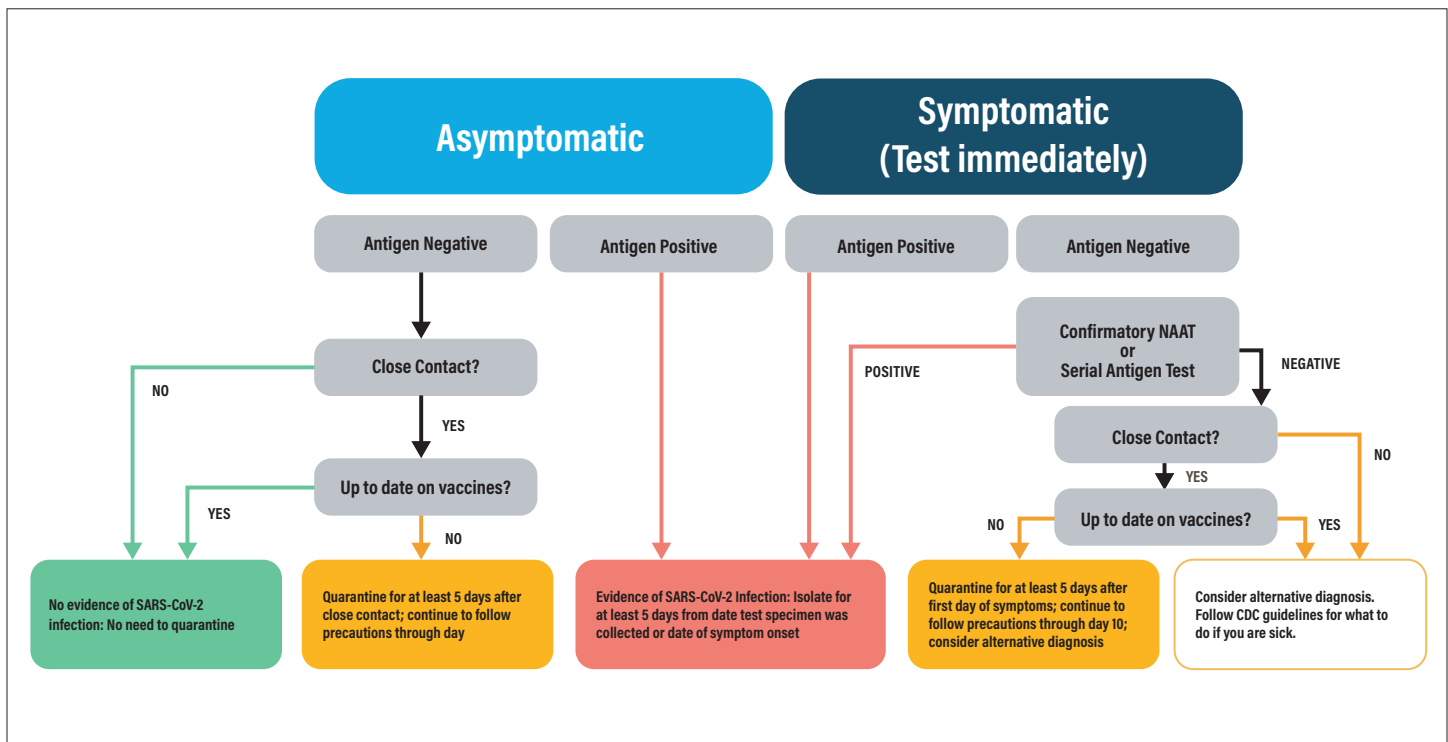


Figure 1. CDC algorithm for COVID testing. From <https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html>.

antigen tests, negative diagnostic testing results should be interpreted with caution depending on the circumstances. Negative test results should be considered presumptive, meaning they are preliminary results and should be confirmed with a PCR test. CDC has developed an algorithm for community testing (Figure 1) (<https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html>, accessed June 13, 2022).

Masks, social distance, and handwashing

Masks and specialized filtering masks such as N95 masks (respirators) provide different levels of protection depending on the type of mask and how they are used. Loosely woven cloth masks provide the least protection, layered finely woven products offer more protection, well-fitting disposable procedural (surgical) masks and KN95s offer even more protection, and a well-fitting NIOSH-approved respirator (N95) offers the highest level of protection. The CDC recommends that everyone 2 years of age and older should properly wear a well-fitting mask indoors in public and in areas where the COVID-19 community level is high, regardless of vaccination status (https://www.cdc.gov/coronavirus/2019-ncov/science/community-levels.html#anchor_47145, accessed June 13,

2022). In the United States, masks are required in healthcare facilities. If possible, maintain 6 feet away from any person with COVID-19 infection (social distance). To prevent the spread of any infectious disease, including COVID-19, wash your hands often with soap and water for at least 20 seconds.

Therapeutics

Several therapeutics have become available since the onset of the COVID-19 pandemic (<https://www.covid19treatmentguidelines.nih.gov>, accessed June 13, 2022 and <https://app.magicapp.org/#/guideline/nBkO1E>, accessed August 5, 2022.). These can be grouped as therapies used in the home for mild to moderate disease in patients not requiring supplemental oxygen, in hospitalized patients receiving supplemental oxygen, and in critically ill patients requiring respiratory support (figures 2 and 3). Symptom management includes using over-the-counter antipyretics for fever, analgesics for headache and myalgias, and antitussives for cough. Patients should rest and those with dyspnea may choose to rest in the prone position. Individuals should be advised to drink fluids to avoid dehydration. Ambulation and other forms of activities should be increased according to patient tolerance.

PATIENT DISPOSITION

PANEL'S RECOMMENDATIONS

Does Not Require Hospitalization or Supplemental Oxygen

All patients should be offered symptomatic management (AIII).

For patients who are at high risk of progressing to severe COVID-19, use 1 of the following treatment options:

Preferred Therapies

Listed in order of preference:

- Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)
- Remdesivir (BIIa)

Alternative Therapies

For use *ONLY* when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:

- Bebtelovimab (CIII)
- Molnupiravir (CIIa)

The Panel **recommends against** the use of **dexamethasone** or **other systemic corticosteroids** in the absence of another indication (AIII).

Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen

The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.

Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen

For those who are stable enough for discharge but who still require oxygen^b

There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.

Discharged From ED Despite New or Increasing Need for Supplemental Oxygen

When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured^d

The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not exceed** 10 days) with careful monitoring for AEs (BIII).

Since remdesivir is recommended for patients with similar oxygen needs who are hospitalized,ⁱ clinicians may consider using it in this setting. As remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Figure 2. Therapeutic management of non-hospitalized adults with COVID-19. From https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/clinical-management-summary/?utm_source=site&utm_medium=home&utm_campaign=highlights

The U.S. Food and Drug Administration has issued emergency use authorization of Paxlovid, which includes nirmatrelvir, a SARS-CoV-2 main protease inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. These drugs are indicated for the treatment of mild-to-moderate COVID-19 in patients 12 years of age and older weighing at least 40 kg who are at high risk for progression to severe COVID-19. Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir (two 150 mg tablets) must be co-administered with ritonavir (one 100 mg tablet) twice daily for 5 days. Treatment should begin as soon as possible after COVID-19 diagnosis and within 5 days of symptom onset.

The antiviral remdesivir is currently approved by the FDA for use in hospitalized patients with COVID-19 and in non-hospitalized patients with mild to moderate COVID-19 at high risk for disease

progression. In the outpatient setting, remdesivir is recommended only if Paxlovid is unavailable (Figure 3). Remdesivir requires infusions for 3 consecutive days, making its use in the outpatient setting impractical.

Remdesivir, dexamethasone, or remdesivir with dexamethasone should only be used for hospitalized patients requiring supplemental oxygen. The steroid dexamethasone is highly effective in hospitalized patients requiring supplemental oxygen, noninvasive respiratory support, or invasive mechanical ventilation. The immunomodulatory drugs baricitinib (a Janus kinase inhibitor) and tocilizumab (an anti-IL-6 receptor monoclonal antibody) are useful when added to remdesivir and dexamethasone. Sarilumab, another anti-IL-6 receptor monoclonal antibody, can also be used. Recommendations for anticoagulation therapy are shown in Figure 3.

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII).^a There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • Prophylactic dose of heparin, unless contraindicated (AI)
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • Remdesivir^{b,c} (e.g., for patients who require minimal supplemental oxygen) (BIIa) • Dexamethasone plus remdesivir^{b,c} (BIIb) • Dexamethasone (BI) For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug^d (e.g., baricitinib^e or tocilizumab^g) (CIIa).	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:^f • Therapeutic dose of heparin^g (CIIa) For other patients: • Prophylactic dose of heparin,^g unless contraindicated (AI)
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • Dexamethasone (AI) • Dexamethasone plus remdesivir^b (BIIb) For patients with rapidly increasing oxygen needs and systemic inflammation, add either baricitinib^e (BIIa) or IV tocilizumab^g (BIIa) to 1 of the options above.^{d,h}	For patients without evidence of VTE: • Prophylactic dose of heparin,^g unless contraindicated (AI)
Hospitalized and Requires MV or ECMO	Dexamethasoneⁱ (AI) For patients who are within 24 hours of admission to the ICU: • Dexamethasone plus IV tocilizumab (BIIa) If IV tocilizumab is not available or not feasible to use, IV sarilumab can be used (BIIa).	For patients without evidence of VTE: • Prophylactic dose of heparin,^g unless contraindicated (AI) If patient is started on therapeutic heparin before transfer to the ICU, switch to a prophylactic dose of heparin, unless there is a non-COVID-19 indication (BIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Weak Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion		

^aCorticosteroids that are prescribed for an underlying condition should be continued.

^bIf the patient progresses to requiring high-flow oxygen, NIV, MV, or ECMO, complete the full course of remdesivir (refer to Table A).

^cEvidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset). Clinical trials have not demonstrated a mortality benefit for remdesivir, but a large, placebo-controlled trial showed that the use of remdesivir reduced time to clinical recovery in hospitalized patients. See Rationale for the Use of Remdesivir below.

^dDrugs are listed alphabetically. There are no studies that directly compare the use of baricitinib and tocilizumab, and there is insufficient evidence to recommend a drug or class of drug (i.e., JAK inhibitors, anti-IL-6 receptor mAbs) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.

^eIf baricitinib and IV tocilizumab are not available or not feasible to use, **tofacitinib** can be used instead of baricitinib (BIIa) and **IV sarilumab** can be used instead of IV tocilizumab (BIIa).

^fContraindications for the use of therapeutic anticoagulation in patients with COVID-19 include platelet count <50 x 10⁹/L, Hgb <8 g/dL, the need for dual antiplatelet therapy, bleeding within

the last 30 days that required an ED visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding.

^gEither LMWH or UFH heparin can be used. In general, LMWH is preferred.

^hThe Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19, except in a clinical trial (AIII). Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.

ⁱThe combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated (CIII). The Panel **recommends against** the use of **remdesivir** monotherapy in these patients (AIIa).

Key: ECMO = extracorporeal membrane oxygenation; ED = emergency department; Hgb = hemoglobin; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; LMWH = low-molecular-weight heparin; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; UFH = unfractionated heparin; ULN = upper limit of normal; VTE = venous thromboembolism

Figure 3. Therapeutic management of adults hospitalized for COVID-19 based on disease severity. From https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/clinical-management-summary/?utm_source=site&utm_medium=home&utm_campaign=highlights

Evusheld is an investigational drug used in adults and adolescents for pre-exposure prophylaxis to prevent COVID-19 in persons who are not currently infected with SARS-CoV-2. It is used in those without recent close contact with a SARS-CoV-2 infected individual and who are moderately to severely immune compromised. Such individuals may not be able to mount an adequate immune response to COVID-19 vaccination. It also is used for those in whom vaccination with any available COVID-19 vaccine is not recommended.

The use of monoclonal antibodies (amlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab) has been paused because the products have reduced activity against the Omicron variant. The monoclonal antibody bebtelovimab can be used to treat mild-to-moderate COVID-19 in adults and pediatric patients, aged 12 years and older, who are at high risk for progression to severe COVID-19; it has been shown to be active against the omicron variant. In contrast, hydrochloroquin and ivermectin are not effective and should not be used. Convalescent plasma for treatment of COVID-19 is controversial.²³

Key points

- Vaccination is the best protection against COVID-19.
- COVID-19 testing is an important strategy to reduce the spread of disease and to allow prompt treatment.
- Masks, social distance, and handwashing reduce the spread of COVID-19.
- Symptom management includes using over-the-counter antipyretics for fever, analgesics for headache and myalgias, and antitussives for cough.
- Paxlovid is indicated for the treatment of mild-to-moderate COVID-19.
- Remdesivir is recommended only if Paxlovid is unavailable.
- Dexamethasone should be used in hospitalized patients requiring supplemental oxygen, noninvasive respiratory support, or invasive mechanical ventilation.

HEALTHCARE PROVIDER RISKS

During the early pandemic, several respiratory care modalities, and procedures such as high-flow nasal cannula (HFNC), noninvasive ventilation (NIV), intubation, nebulization, bronchoscopy, and pulmonary function testing (PFT) were categorized as aerosol-generating procedures (AGP) (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html>, accessed June 13, 2022). This characterization prohibited the use of these treatments for patients with COVID-19 in many institutions. The delay or cancellation of these treatments resulted in a shortage of alternative devices and treatments such as critical care ventilators,²⁴ pressurized metered-dose inhalers (pMDI),²⁵ and dry powder inhalers (DPI). Therefore, it became necessary for clinicians to understand aerosol transmission risks associated with various respiratory care procedures—during the pandemic and in the future.²⁶

Per CDC, (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html>), an AGP is a treatment or procedure that generates more aerosols than during coughing, sneezing, speaking, or normal breathing. The CDC definition fails to recognize that not all aerosols generated during respiratory care procedures increase the likelihood of contamination and infection. In fact, only the so-called bioaerosols that contain micro-organisms carry the risk of transmission.²⁷

Procedures that irritate the airway of an infected individual, such as bronchoscopy, intubation, nasal-pharyngeal suctioning, open tracheal suctioning, or sputum induction, can stimulate cough and generate bioaerosols.²⁸ Thus those procedures are AGPs. In contrast, medical aerosols generated from aerosol devices, including nebulizers, do not carry micro-organisms unless contaminated.²⁹ A portion of the aerosol (10-30% for adults) generated by a nebulizer is inhaled and deposited in the airway, while the remaining aerosols are released or exhaled into the environment. The aerosols released into the environment have been termed fugitive aerosols.²⁹

Respiratory support devices such as HFNC or NIV do not cause patients to generate additional bioaerosols beyond their normal breathing. Rather, they carry the exhaled gas and aerosols from subjects further; measured as aerosol dispersion distance using a range of imaging techniques.³⁰ Thus, HFNC and NIV

treatments should not be considered AGPs (https://www.england.nhs.uk/wp-content/uploads/2022/04/C1632_rapid-review-of-aerosol-generating-procedures.pdf, accessed June 10, 2022), as they do not generate aerosols; they disperse aerosols. The imaging techniques used in some aerosol studies illustrate the maximum distance the aerosol can travel, but they do not capture the aerosol concentrations, nor the viral load (which may indicate infectivity).²⁷ Notably, aerosol concentrations and aerosol dispersion distances indirectly reflect transmission risks, while viral load in the air sample might directly reflect transmission risks.³⁰ Lastly, the risk of clinician infection depends on the amount of viral exposure, the judicious use of personal protective equipment (PPE), and indoor environmental controls.³¹⁻³³

HFNC

In the past 2 years, 10 studies using healthy volunteers³⁴⁻⁴³ and 2 studies examining patients^{44,45} investigated aerosol particle concentrations during HFNC. Aerosol dispersion was similar to breathing with a conventional nasal cannula or room air, but lower than coughing. Five studies measured the viral load of SARS-CoV-2 from air samples taken inside rooms of COVID-19 patients treated with HFNC.⁴⁵⁻⁴⁸ Two studies did not detect the virus in the air samples,^{45,47} while 3 studies found no differences in viral load when HFNC was and was not used.^{46,48,49} Westafer et al reported no significant differences in infection rates among clinical and non-clinical staff in their emergency department before and after using HFNC to treat COVID-19 patients.⁵⁰ Their study suggests that HFNC can be safely used for patients with COVID-19 and posed no additional risks for healthcare workers.

When compared to either NIV or HFNC devices, coughing has a higher transmission risk and is unpredictable and difficult to control. To reduce aerosol dispersion, a procedural mask can be placed over the patient's face during HFNC, which reduces aerosol particle concentrations and aerosol dispersion distances.^{35,41,42,51} Wearing a procedural mask is recommended for COVID-19 patients, especially when others are present, as a way to reduce transmission risks (Figure 4).



Figure 4. Patient wearing procedural mask over high flow nasal cannula to minimize aerosol dispersion.

CPAP/NIV

Similar to HFNC, 6 studies of healthy volunteers reported lower aerosol particle concentrations with CPAP/NIV than coughing.^{34, 35,40,41,43,52} Two clinical studies reported similar viral load in air samples with COVID-19 patients treated with CPAP/NIV compared to those not treated with CPAP/NIV.^{48,49} Like HFNC, CPAP/NIV should not be considered an AGP, but rather an aerosol dispersing procedure. During CPAP/NIV use, a bacteria/virus filter should be placed between the mask and exhalation valve in the single limb ventilator or at the expiratory port in the dual limb ventilator to reduce aerosol dispersion.⁵³ Vented masks should be avoided,⁵⁴ and the helmet interface with an expiratory port filter are recommended, if available and tolerated.⁵⁵

Nebulization

Three studies in healthy volunteers found significantly elevated aerosol particle concentrations during nebulization treatments.^{38, 53,56} This increase in aerosol particle concentrations is expected and represents fugitive aerosols, which do not carry viruses.²⁹ Thuresson

et al⁴⁸ did not detect any positive air samples inside the room with COVID-19 patients during nebulization treatments. However, it is possible that contaminated nebulizers, especially those with a contaminated medication cup, might generate aerosols that contain micro-organisms.²⁹ Thus, nebulizers at risk for contamination during use or while being stored should be avoided.

Device designs, like a small volume jet nebulizer in which the medication cup is in close contact with the patient's mouth, can be easily contaminated by saliva or secretions during the use.^{27,29} Additionally, since jet nebulizers are an open system, the medication cup can easily be contaminated during storage between treatments. Thus, jet nebulizers should be avoided for patients with airborne diseases, especially the repeated use of jet nebulizers should be prohibited when possible. If used, an expiratory filter should be attached to the end of the mouthpiece, and a filter facemask or a scavenger over an aerosol mask is recommended when the nebulizer is used with a facemask (Figure 5).⁵⁶ It should also be appreciated that inhaled medications such as bronchodilators are not indicated in patients with COVID-19 unless the patient has previous underlying respiratory disease.

Intubation

During intubation, sedatives and paralytics are often administered, which suppresses cough during the procedure. Once the endotracheal tube is inserted, a filter should be placed between the endotracheal tube and the manual resuscitator. By immediately placing the filter, the duration of exposure to the subject's open airway and exhaled gases is minimized. Three clinical studies⁵⁷⁻⁵⁹ and one porcine study⁶⁰ reported no significant increase in aerosol particle concentrations during intubation under controlled conditions. However, these clinical studies were conducted in an ultra-clean operating theater with high air exchange frequency, and patients were sedated and paralyzed.⁵⁷⁻⁵⁹ The aerosol transmission risk of intubation in these controlled environments is low. However, these findings may not apply to the critical care environment and



Figure 5. Filters and devices to reduce fugitive aerosol concentrations. From Harnois LJ, Alolaiwat AA, Jing G, Fink JB, Dhand R, Li J. Efficacy of various mitigation devices in reducing fugitive emissions from nebulizers. *Respir Care* 2022;67(4):394-403.

intubation of patients who are spontaneously breathing at high minute volumes and have copious secretions.²⁷ During the early pandemic, intubation boxes were developed to block the direct path of exhaled gas from a patient's airway to the surrounding environment.⁶¹ However, it has been reported that intubation boxes both reduce intubation success rates and also cause breaches of PPE. Consequently, intubation boxes are not recommended.

Bronchoscopy

Unlike intubation, patients maintain spontaneous breathing and cough during bronchoscopy. Though 2 studies reported no significant elevation of aerosol particle concentrations during bronchoscopy under procedural sedation,^{59,60} the transmission risk remains high since bronchoscopy examination usually lasts 10 to 30 minutes, which is much longer than intubation. Thus, bronchoscopy should indeed be categorized as an AGP (https://www.england.nhs.uk/wp-content/uploads/2022/04/C1632_rapid-review-of-aerosol-generating-procedures.pdf, accessed June 10, 2022). More studies are warranted, especially those with viral load measurement during bronchoscopy examinations.

PFT

Sheikh et al reported that PFT significantly increases aerosol particle concentrations.⁶² After adding a filter to the mouthpiece of the spirometer, aerosol particle concentrations were significantly reduced, but still higher than baseline.⁶²⁻⁶⁵ Interestingly, aerosol particle concentrations generated during PFTs with the filter attached to the mouthpiece are similar to aerosol particle concentrations during speaking, but lower than when coughing.^{62,63} After PFTs are completed, air in the procedure room should be cleared and returned to baseline. The duration for returning aerosol particle concentrations to baseline depend upon the room volume and air exchange frequency.⁶⁴ Filters are recommended to be attached to the mouthpiece or mask during PFTs, and an interval between subjects to reduce aerosol particle concentrations to the ambient background level in the room air is needed.

Cardiopulmonary Rehabilitation and Cardiopulmonary Exercise Test

There was a significant increase in aerosol particle concentrations among healthy volunteers without procedure masks during cardiopulmonary exercise testing.⁶⁶ Even though participants wore procedure masks, higher aerosol particle concentrations were observed during cardiopulmonary rehabilitation than that observed at baseline among healthy volunteers⁶⁷ and patients.⁶⁸ Thus, both cardiopulmonary rehabilitation and cardiopulmonary exercise tests are considered AGPs.

Infectivity of bioaerosols from infected patients depends on the phase of the disease. For those patients in the recovery phase, the viral load or infectivity of the bioaerosols generated might be lower, even for the same amount of aerosol generated. When patients are

coughing or sneezing, they should be encouraged to cover their mouth and nose with a tissue or a mask to reduce the chance of spreading bioaerosols in the surrounding environment. Additionally, aerosol particle concentrations decrease with distance. When possible, clinicians need to stay at a greater distance from patients when they are coughing or sneezing and keep time within close proximity at a minimum. Clinicians should always wear appropriate PPE in proximity to any patients or visitors who may be infected. Vaccination is recommended to protect healthcare providers and their family members.

Key points

- It is important to differentiate medical aerosols, fugitive aerosols, and bioaerosols.
- Respiratory care procedures that irritate the airway of an infected individual and stimulate a cough generate bioaerosols are aerosol-generating procedures.
- HFNC is not an aerosol-generating procedure.
- Wearing a procedure mask over the nasal cannula is recommended for patients with COVID-19 when in close contact with healthcare providers.
- NIV is not an aerosol-generating procedure and can be safely used for COVID-19 patients.
- A virus filter should be placed between the mask and exhalation valve in the single limb ventilator or at the expiratory port in the dual limb ventilator.
- Small volume jet nebulizers should be avoided, if possible, for COVID-19 patients.
- If a nebulizer is used, an expiratory filter should be attached to the exhalation port.
- If an aerosol facemask is used, place a scavenger over the facemask or use a filtered facemask.
- Intubation for COVID-19 patients with spontaneous breathing is an aerosol-generating procedure.
- Intubation boxes are not recommended due to increased intubation failure and PPE lapses.
- Filters are recommended to be attached to the mouthpiece or mask during PFTs. An interval is needed between subjects to reduce aerosol particle concentrations to the ambient background level in the room air.
- Wearing procedure masks for patients during cardiopulmonary rehabilitation and cardiopulmonary exercise tests are recommended.
- When patients are coughing or sneezing, they should be encouraged to cover their mouth and nose with a tissue or a mask.
- When possible, clinicians need to stay at a greater distance from patients when patients are coughing or sneezing, and keep time within proximity at a minimum.

NONINVASIVE RESPIRATORY SUPPORT

Noninvasive respiratory support refers to NIV, CPAP, and HFNC. Each of these therapies has been applied in the setting of hypoxemic respiratory failure. But only NIV provides support for ventilation by applying an inspiratory pressure greater than expiratory pressure. Conventional clinical reasoning has suggested that NIV is used primarily for hypercapnic respiratory failure, with CPAP and HFNC used primarily for hypoxemic respiratory failure. Recommendations from clinical practice guidelines for NIV are listed in Table 2⁶⁹ and recommendations for HFNC are listed in Table 3.⁷⁰⁻⁷² The World Health Organization has made conditional recommendations for the use of HFNC, CPAP, and NIV rather than standard oxygen therapy for hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure who do not need emergent intubation (<https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2022-1>, accessed August 5, 2022).

Noninvasive ventilation

The use of NIV for hypoxemic patients with ARDS is controversial. A sub-study of the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study examined the practice of NIV in 436 patients with ARDS.⁷³ NIV was used in 15% of patients with ARDS. NIV failure occurred in 22% of mild, 42% of moderate, and 47% of patients with severe ARDS. Use of NIV was independently associated with increased ICU mortality: hazard ratio 1.45 (95% confidence interval 1.16-1.81). In a propensity-matched analysis, ICU mortality was higher with NIV than with invasively ventilated patients with a $\text{PaO}_2/\text{FIO}_2$ less than 150. Given the uncertainty of the evidence, authors of a clinical practice guideline for NIV were unable to offer a recommendation on the use of NIV for de novo acute respiratory failure (i.e., ARDS).⁶⁹ Similarly, they were unable to offer a recommendation for NIV use in the setting of pandemic viral illness due to the uncertainty of the evidence. Recommendations from the Society of Critical Care Medicine suggest a trial of NIV only if HFNC is not available and there is no urgent need for intubation, with close monitoring and short-interval assessment for worsening of respiratory failure.⁷⁴

High NIV failure rates have been reported in subjects with COVID-19.⁷⁵ Thus, if NIV is instituted for a patient with COVID-19 hypoxemic respiratory failure, it is important to monitor the patient

closely and intubate promptly when there are signs of impending NIV failure. High tidal volumes in patients with hypoxemic respiratory failure are predictive of failure.^{76,77} A tidal volume >9 mL/kg and $\text{PaO}_2/\text{FIO}_2 \leq 200$ at 1 hour after initiation are predictive of NIV failure. The HACOR score has been used to identify NIV failure (Table 4). It assesses heart rate, acidosis, consciousness, oxygenation, and respiratory rate (breathing frequency). The highest possible score is 25 points. At 1 hour of NIV, the odds ratio of NIV failure is 1.73 for every 1-point increase in HACOR score. HACOR score improves in patients with NIV success

A variety of interfaces are available for NIV (Figure 6).⁷⁸ The oronasal mask or total face mask is usually used in the setting of acute respiratory failure. These interfaces are preferred over a nasal interface in the setting of COVID-19 due to the risk of bioaerosol dispersion with mouth leak. A total face mask might be preferred because the risk of facial skin breakdown is lower compared to an oronasal mask.⁷⁹ The helmet received attention following the

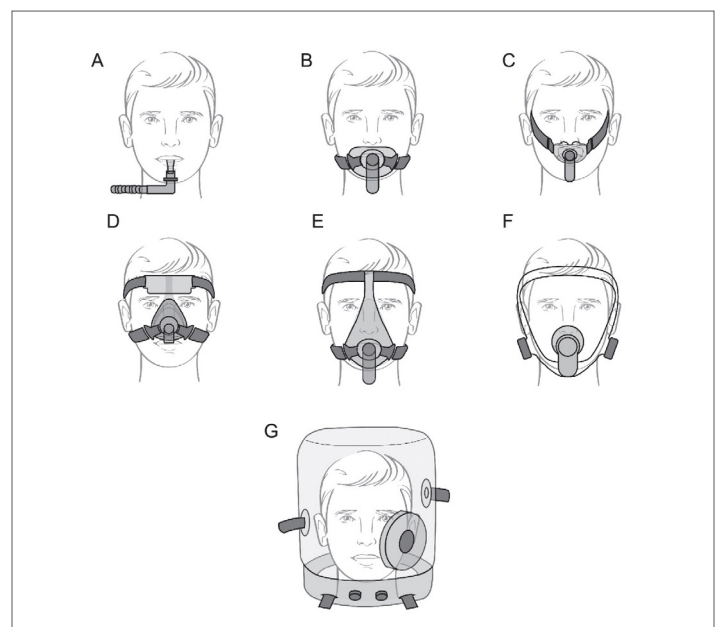


Figure 6. Types of noninvasive ventilation interfaces. A: Mouthpiece, B: oral (lip-seal mouthpiece) mask, C: nasal pillows, D: nasal mask; E: oro-nasal mask, F: total face mask, and G: helmet. From Cui X, Jung H, Lee W, Kim SH, Yun R, Kim S, You H, Huh S. Ergonomics and personalization of noninvasive ventilation masks. *Respir Care* 2022;67(1):87-101.

Table 2. Clinical practice guidelines for noninvasive ventilation for acute respiratory failure. From Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50(2).

1. Suggest NIV not be used in patients with hypercapnia who are not acidotic in the setting of a COPD exacerbation. (Conditional recommendation, low certainty of evidence.)
2. Recommend NIV for patients with acute respiratory failure leading to acute or acute-on-chronic respiratory acidosis ($\text{pH} \leq 7.35$) due to COPD exacerbation. (Strong recommendation, high certainty of evidence.)
3. Recommend a trial of NIV in patients considered to require endotracheal intubation and mechanical ventilation unless the patient is immediately deteriorating. (Strong recommendation, moderate certainty of evidence.)
4. Recommend either NIV or CPAP for patients with acute respiratory failure due to cardiogenic pulmonary edema. (Strong recommendation, moderate certainty of evidence.)
5. Suggest that CPAP or NIV be used for patients with acute respiratory failure due to cardiogenic pulmonary edema in the pre-hospital setting. (Conditional recommendation, low certainty of evidence.)
6. Given the uncertainty of evidence, unable to offer a recommendation on the use of NIV for acute respiratory failure due to asthma.
7. Suggest early NIV for immunocompromised patients with acute respiratory failure. (Conditional recommendation, moderate certainty of evidence.)
8. Given the uncertainty of evidence, unable to offer a recommendation on the use of NIV for de novo acute respiratory failure.
9. Suggest NIV for patients with post-operative acute respiratory failure. (Conditional recommendation, moderate certainty of evidence.)
10. Suggest offering NIV to dyspneic patients for palliation in the setting of terminal cancer or other terminal conditions. (Conditional recommendation, moderate certainty of evidence.)
11. Suggest NIV for chest trauma patients with acute respiratory failure. (Conditional recommendation, moderate certainty of evidence.)
12. Given the uncertainty of evidence, unable to offer a recommendation for NIV in the setting of acute respiratory failure due to pandemic viral illness.
13. Suggest that NIV be used to prevent post-extubation respiratory failure in high-risk patients. (Conditional recommendation, low certainty of evidence.)
14. Suggest that NIV should not be used to prevent post-extubation respiratory failure in non-high-risk patients. (Conditional recommendation, very low certainty of evidence.)
15. Suggest that NIV should not be used in the treatment of patients with established post-extubation respiratory failure. (Conditional recommendation, low certainty of evidence.)
16. Suggest NIV be used to facilitate weaning from mechanical ventilation in patients with hypercapnic respiratory failure. (Conditional recommendation, moderate certainty of evidence.)

Table 3. Clinical practice guidelines for high flow nasal cannula.

From Oczkowski S, Ergan B, Bos L, Chatwin M, Ferrer M, Gregorett C, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. Eur Respir J 2022 Vol. 59 Issue 4.

1. Suggest the use of HFNC over conventional oxygen therapy in adults acute hypoxemic respiratory failure (conditional recommendation, moderate certainty of evidence).
2. Suggest the use of HFNC over NIV in patients with acute hypoxemic respiratory failure (conditional recommendation, very low certainty of evidence).
3. Suggest use of HFNC over conventional oxygen therapy during breaks from NIV in patients with acute hypoxemic respiratory failure (conditional recommendation, low certainty of evidence)
4. Suggest the use of either conventional oxygen therapy or HFNC in postoperative patients at low risk of respiratory complications (conditional recommendation, low certainty of evidence).
5. Suggest either HFNC or NIV in post-operative patients at high risk of respiratory complications (conditional recommendation, low certainty of evidence).
6. Suggest HFNC over conventional oxygen therapy in non-surgical patients after extubation at low or moderate risk of extubation failure (conditional recommendation, low certainty of evidence).
7. Suggest the use of NIV over HFNC after extubation for patients at high risk of extubation failure unless there are relative or absolute contraindications to NIV (conditional recommendation, moderate certainty of evidence).
8. Suggest a trial of NIV prior to use of HFNC in patients with COPD and acute hypercapnic respiratory failure (conditional recommendation, low certainty of evidence).

From Rochweg B, Einav S, Chaudhuri D, Mancebo J, Mauri T, Helviz Y, et al. Intensive Care Med 2020;46(12):2226-2237.

1. Recommend using HFNC compared to conventional oxygen therapy for patients with hypoxemic respiratory failure (strong recommendation, moderate certainty evidence).
2. Suggest HFNC as compared to conventional oxygen therapy following extubation for patients who are intubated more than 24 h and have any high-risk feature (conditional recommendation, moderate certainty evidence).
3. No recommendation regarding use of HFNC in the peri-intubation period. For patients who are already receiving HFNC, we suggest continuing HFNC during intubation (conditional recommendation, moderate certainty).
4. In high risk and/or obese patients undergoing cardiac or thoracic surgery, we suggest using HFNC compared to conventional oxygen therapy to prevent respiratory failure in the immediate postoperative period (conditional recommendation, moderate certainty evidence). We suggest against prophylactic HFNC use to prevent respiratory failure in other postoperative patients (conditional recommendation, very low certainty evidence).

From: Qaseem A, Etzeandia-Ikobaltzeta I, Fitterman N, Williams JW, Kansagara D. Appropriate Use of High-Flow Nasal Oxygen in Hospitalized Patients for Initial or Postextubation Management of Acute Respiratory Failure: A Clinical Guideline from the American College of Physicians. Ann Intern Med 2021;174(7):977-984.

1. Suggests that clinicians HFNC rather than NIV in hospitalized adults for the management of acute hypoxemic respiratory failure (conditional recommendation; low-certainty evidence).
2. Suggests that clinicians use HFNC rather than conventional oxygen therapy for hospitalized adults with post-extubation acute hypoxemic respiratory failure (conditional recommendation; low-certainty evidence).

Table 4. The HACOR Score. At 1 hour of NIV, odds ratio of NIV failure is 1.73 for every 1-point increase in HACOR score of test cohort.

Variable	Category	Assigned Points
Heart rate	≤ 120	0
	< 120	1
pH	≥ 7.35	0
	7.30 – 7.34	2
	7.25 – 7.29	3
	< 7.25	4
Glasgow Coma Score	15	0
	13-14	2
	11-12	5
	≤ 10	10
PaO₂/FIO₂	> 200	0
	176 – 200	2
	151 – 175	3
	126 – 150	4
	101 – 125	5
	≤ 100	6
Respiratory rate	≤ 30	0
	31 – 35	1
	36 – 40	2
	41 – 45	3
	> 45	4

publication by Patel et al⁸⁰ reporting a significant reduction of intubation rate and 90-day mortality with helmet NIV in subjects with ARDS. Use of the helmet has been described in patients with COVID-19⁸¹⁻⁸³ and emergency use authorization was granted by the Food and Drug Administration for patients with COVID-19. However, the helmet has not received widespread use in the United States.

NIV can be delivered with bilevel ventilators or critical care ventilators. In the past, leak compensation was better with bilevel devices, but leak compensation is comparable in modern ICU ventilators with an NIV mode.⁸⁴ Bilevel ventilators use a valveless leak port, which is undesirable in the setting of COVID-19 due to the risk of bioaerosol dispersion. A filter can be used over the leak port and between the patient and the circuit. However, this can have unintended consequences related to ventilator performance and patient-ventilator interactions.^{85,86} Thus, in the setting of COVID-19 it is desirable to use a critical care ventilator in NIV mode with filtration of the exhaled gas.

Although the use of NIV in patients with COVID-19 is controversial, there is no controversy related to the use of NIV for indications such as COPD exacerbation and acute cardiogenic pulmonary edema.⁶⁹ For patients who present with these conditions, NIV should be strongly considered whether or not they also have COVID-19.

Continuous positive airway pressure

Despite that CPAP improves oxygenation in patients with acute hypoxemic respiratory failure, it might not reduce the need for endotracheal intubation.⁸⁷ In a parallel group, adaptive, randomized clinical trial of hospitalized subjects with COVID-19-related acute hypoxemic respiratory failure, Perkins et al⁸⁸ compared CPAP (n=377), HFNC (n=415), or conventional oxygen therapy (n=356). The composite endpoint of intubation or death within 30 days was significantly lower with CPAP (36%) versus conventional oxygen therapy (44%, P=.03), but was not significantly different from HFNC (44%, P=.83). Adverse events occurred in 34% of participants in the CPAP group, 21% in the HFNC group, and 14% in the conventional oxygen therapy group. Given the greater patient comfort with HFNC and the ease of administration, patients and clinicians are likely to prefer HFNC. If CPAP therapy is used, the HACOR score might be useful to assess failure.⁸⁹

High flow nasal cannula

Compared to NIV and conventional oxygen therapy, Frat et al⁹⁰ reported a significant reduction in 90-day mortality using HFNC in subjects with acute hypoxemic respiratory failure (the majority of whom had pneumonia). This was followed by considerable clinical interest in the use of HFNC for patients with acute hypoxemic respiratory failure. Interestingly, Frat et al⁹⁰ reported the worst clinical outcomes with NIV. Clinical practice guidelines support the use of HFNC in patients with hypoxemic respiratory failure.⁷⁰⁻⁷² For adults with COVID-19 and acute hypoxemic respiratory failure, the SCCM suggests using HFNC over conventional oxygen therapy or NIV.⁷⁴ However, available evidence does not support use of HFNC for patients with COVID-19 and mild hypoxemia.⁹¹

At the outset of the COVID-19 pandemic, there were doubts about the use of HFNC. There was skepticism about its effectiveness, but even greater concerns for dispersion of bioaerosols and the potential for contamination of healthcare providers. However, the risk to healthcare providers with the use of HFNC was likely an overreaction. Bem et al⁴⁴ reported that HFNC does not result in overall increased aerosol formation as compared to conventional oxygen therapy. Over time the use of HFNC for hypoxemic patients with COVID-19 became better accepted, supported by both narrative⁹² and systematic reviews.^{93,94} Gershengorn et al⁹⁵ constructed dynamical (deterministic) simulation models of HFNC and mechanical ventilation use for COVID-19. They found that use of HFNC coupled with early mechanical ventilation when supply is sufficient, results in fewer deaths and greater ventilator availability.

Due to high failure rates related to noninvasive respiratory support strategies,⁷⁵ it is important to promptly identify failure and the need for endotracheal intubation. The ROX index is a validated method to identify HFNC failure:⁹⁶

$$\text{ROX} = (\text{SpO}_2/\text{FIO}_2)/\text{breathing frequency}$$

Patients with a ROX ≥ 4.88 after 2, 6 and 12 h of HFNC are less likely to be intubated. Patients with a ROX < 2.85, 3.47 and 3.85 after 2, 6, and 12 h of therapy, respectively, are more likely to fail. For the intermediate ROX, a decrease in the score over time suggests that intubation should be considered (Figure 7). Several studies have reported benefits for the use of ROX in subjects with COVID-19 receiving HFNC.⁹⁷⁻¹⁰⁰ A high tidal volume might also be predictive of HFNC failure,¹⁰¹ but it is difficult to monitor tidal volume in this patient population.

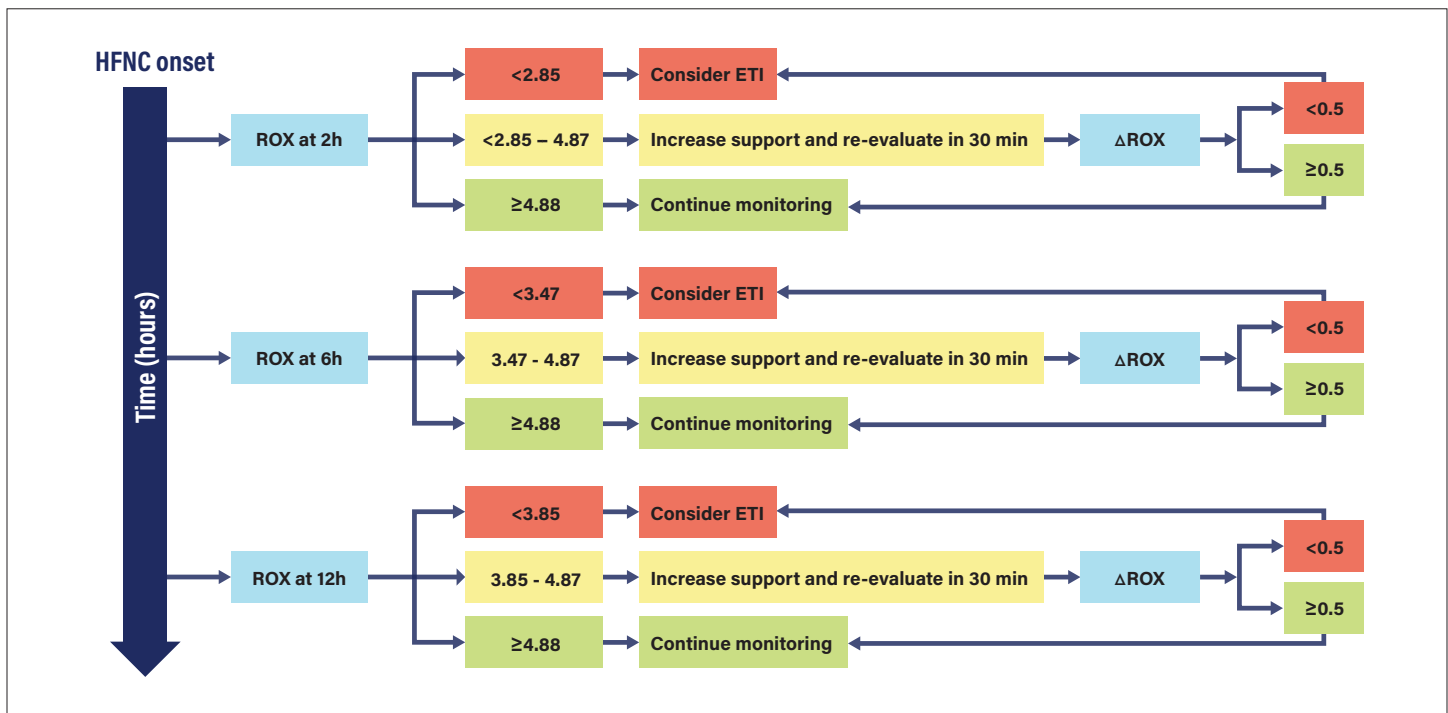


Figure 7. An algorithm for use of ROX to determine success or failure of high flow nasal cannula therapy. From Ricard JD, Roca O, Lemiale V, Corley A, Braunlich J, Jones P, et al. Use of nasal high flow oxygen during acute respiratory failure. *Intensive Care Med* 2020;46(12):2238-2247.

Noninvasive respiratory support and prone

NIV,¹⁰²⁻¹⁰⁴ CPAP¹⁰⁵, and HFNC¹⁰⁶⁻¹¹¹ have been used with awake prone position in individuals with COVID-19. This is feasible and can result in an improvement in oxygenation and reduced need for intubation. In a multinational open-label meta-trial, Ehrmann et al¹⁰⁶ randomized subjects receiving HFNC to awake prone positioning (n=567) or standard care (n=559). They found that prone positioning with HFNC reduced the incidence of treatment failure and the need for intubation. There was no signal of harm. The authors¹⁰⁶ suggest routine use of awake prone positioning of patients with COVID-19 who require HFNC. A nonrandomized controlled trial of awake prone positioning reported no clinical benefit among patients with COVID-19-associated hypoxemic respiratory failure; clinical outcomes at study day 5 were worse among patients recommended to receive awake prone positioning intervention, suggesting potential harm.¹⁰⁸ However, it should be noted that only about 25% of patients in this study were receiving HFNC.

Sequential use of NIV and HFNC

Sequential use of NIV and HFNC has been reported, in which the use of NIV and HFNC is alternated. This might be particularly useful in patients who are poorly tolerant of NIV.¹¹²⁻¹¹⁴ Sequential NIV and HFNC might also reduce the risk of facial skin breakdown. Increasingly, devices are available that provide both NIV and HFNC in the same devices, making sequential use of NIV and HFNC easy to implement at the bedside.

Thille et al¹¹⁴ randomized patients at high risk of extubation failure (i.e., older than 65 years or with an underlying cardiac or respiratory disease) to either sequential HFNC and NIV or HFNC alone. NIV was initiated immediately after extubation with the first session of at least 4 hours and a minimum duration of at least 12 hours/day during the 48 hours following extubation. Continuous application of NIV was promoted throughout the night. The use of sequential HFNC and NIV immediately after extubation significantly decreased the risk of reintubation compared with HFNC alone.

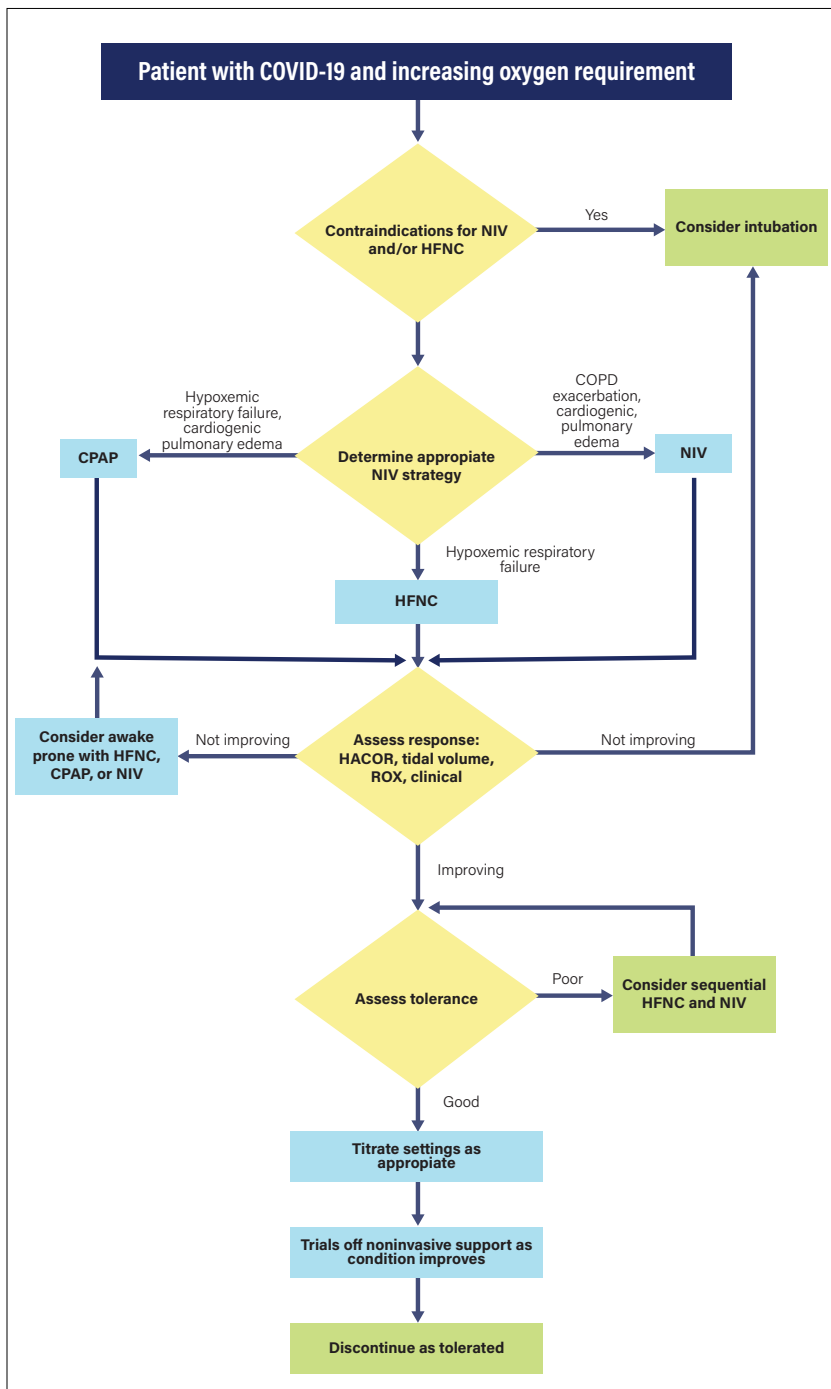


Figure 8. An algorithm can be used to guide use of NIV and HFNC in patients with COVID-19.

An algorithm for clinical application

Based on available evidence, an algorithm can be used to guide use of NIV and HFNC in patients with COVID-19 (Figure 8).¹¹⁵

Key points

- NIV should be used cautiously in patients with hypoxemic respiratory failure, including those with COVID-19.
- NIV should not be withheld for disorders where it has high evidence to support its use (COPD exacerbation, acute cardiogenic pulmonary edema, etc.), even if the patient has COVID-19.
- CPAP may be effective in patients with COVID-19 and hypoxemic respiratory failure.
- HFNC is beneficial in patients with COVID-19 and hypoxemic respiratory failure.
- Patients receiving noninvasive respiratory support should be monitored closely for signs of failure (HACOR for NIV/CPAP, ROX for HFNC).
- Noninvasive respiratory support is beneficial when combined with prone position.

USE OF BILEVEL VENTILATORS FOR INVASIVE MECHANICAL VENTILATION

Bilevel ventilators commonly used for NIV can be used for invasive ventilation. Some are cleared by the FDA for this use. When critical care ventilators are unavailable, such as can occur in a surge in demand during a pandemic, bilevel ventilators can be deployed for invasive ventilation. Bilevel ventilators do not have all the capabilities of full-featured critical care ventilators. It is prudent to triage bilevel ventilators for less acutely ill patients, thus freeing critical care ventilators for those patients who would best benefit.

Bilevel ventilators use settings such as inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) rather than the more traditional pressure control and PEEP. The difference between IPAP and EPAP is the level of pressure control (or pressure support) and EPAP is equivalent to PEEP. Volume-targeted adaptive pressure modes can be used, but it is unclear whether these are superior to a fixed IPAP. An issue with adaptive pressure modes is that they reduce support with increased respiratory demand and that it is more difficult to assure lung protective ventilation with these modes. To assure a precise FIO_2 and deliver a high FIO_2 , it is desirable to use a bilevel ventilator with an integral oxygen blender. Particularly in patients with an artificial airway, it is important to adequately humidify the inspired gas. For patient safety, alarms must be set appropriately.

Key Points

- Bilevel ventilators can be used for invasive ventilation.
- When used for invasive ventilation, bilevel ventilators should be triaged to the least sick patients.

WHEN TO INTUBATE

Acute hypoxemic respiratory failure (Type 1) is a $\text{PaO}_2 < 60$ mm Hg versus acute ventilatory failure (Type 2), which is a $\text{PaCO}_2 > 50$ mm Hg.¹¹⁶ Because these failure thresholds are not inherently life-threatening, it is the context in which failure occurs that determines whether a trial of HFNC or NIV is attempted, versus invasive mechanical ventilation (e.g., age, comorbidities, presence/severity of respiratory/metabolic acidosis, hemodynamic and/or neurologic instability, etc.). Thus, unambiguous intubation triggers have never been defined for the myriad situations when clinicians encounter acute respiratory failure.¹¹⁷

Because most severely hypoxemic patients with COVID-19 and severe hypoxemia develop acute respiratory distress syndrome (ARDS),¹¹⁸ it is important to recognize that ARDS resolution typically is prolonged (i.e., resumption of unassisted breathing usually occurs at 8-10 days and frequently extends to 15-19 days).^{119,120} This potentially limits the utility of HFNC and/or NIV for refractory hypoxemia because elevated work of breathing, and prolonged exposure to toxic FIO_2 (i.e., > 0.8) often persists despite these therapies. This is based upon evidence that NIV failure in ARDS is high (particularly when $\text{PaO}_2/\text{FIO}_2$ remains < 150) and that delayed intubation under these conditions is associated with increased mortality.^{73,121,122}

General recommendations for managing hypoxemic failure in patients with COVID-19 (when deemed safe and feasible) is to delay intubation (i.e., ≤ 24 h) by initiating stepwise trials of HFNC to NIV, or a combination of both.^{117,123} This should be done only in a closely monitored unit with immediate endotracheal intubation available so that acute decompensation can be detected rapidly. A systematic review found no difference in either mortality or duration of mechanical ventilation in COVID-19 when intubation was done early (≤ 24 h) or delayed (> 24 h) after ICU admission, regardless of whether or not intubation was preceded by HFNC or NIV.¹²⁴ However, this study did not specifically assess the impact of delayed intubation on outcomes within the context of hypoxemia severity or duration, and the relative effectiveness of noninvasive therapies. Although the study supports

first attempting noninvasive respiratory support, it does not address whether prolonged use in patients not initially (or only transiently) responding to HFNC or NIV might negatively impact outcomes in patients with COVID-19.

Key points

- ARDS resolution typically is prolonged so that effective use of non-invasive respiratory support is limited to a subset of patients meeting specific characteristics and responses to these therapies.
- In select patients with COVID-19, delaying intubation up to 24 hours by stepwise addition of non-invasive therapies in a closely monitored care unit is reasonable.
- NIV failure rate is high in patients whose $\text{PaO}_2/\text{FIO}_2$ is < 150 .

THE ROLE OF TRACHEOSTOMY

Tracheostomy in critically ill patients may increase patient comfort, thereby reducing the need for sedation, which may hasten ventilator liberation.¹²⁵⁻¹²⁸ In acute respiratory failure, the decision for tracheostomy is typically based upon the likelihood of prolonged mechanical ventilation (i.e., ≥ 3 weeks).¹²⁵ As an elective surgical procedure, tracheostomy requires clinical stability. Therefore, because COVID-19 acute respiratory failure usually presents as (or evolves into) ARDS,¹¹⁸ wherein 30 to 70% of cases require > 5 days before meeting liberation readiness criteria (i.e., PEEP and FIO_2 requirements consistent with safety criteria for performing tracheostomy),¹²⁰ early tracheostomy in patients with COVID-19 likely is 7 to 14 days. In non-COVID acute respiratory failure, conversion to tracheostomy typically is not performed within the first 2 weeks following intubation (3-14%), but thereafter increases to 35% (15-21 days) and 65% after 3 weeks.¹²⁹ In patients with ARDS, early tracheostomy occurs at a median (IQR) of 14 (7-21) days.¹³⁰ Although the overall use of tracheostomies varies considerably across studies (13-24%),^{129,130} it appears to be needed in only a minority of mechanically ventilated patients.

Timing of tracheostomy

The role of tracheostomy during COVID-19 centers on 2 opposing issues. Delayed tracheostomy was advocated to reduce clinician exposure to aerosol-generating procedures,¹³¹ so that delaying tracheostomy to about 14 days would reduce clinician exposure to a time when SARS-CoV-2 viral load is markedly reduced.¹³² In contrast, arguments favoring earlier tracheostomy were motivated by reports that patients with COVID-19 ARDS required advanced respiratory support for a median of 13 (7-23) days.¹³¹ Because tracheostomy has been associated with reduced sedation and facilitation of liberation, it was reasoned that early tracheostomy might reduce intensive care unit burden during the pandemic.

Nonetheless, it was recommended that postponing tracheostomy for 3 weeks and limited to clinically stable patients (e.g., $\text{PaO}_2/\text{FIO}_2 > 200$) testing negative for COVID-19, and in

whom there was objective evidence of difficult weaning (i.e., failure of ≥ 3 consecutive spontaneous breathing trials).¹³³ Of note, the cumulative pass rate by the third spontaneous breathing trial in non-COVID ARDS is 70-80%.¹²⁰ In a review of COVID-19 institutional guidance documents on tracheostomy, only 25% recommended its performance within 10 days compared to days 14 to 19 (57%) or ≥ 20 (19%).¹³⁴ Others have concluded that tracheostomy should be delayed for at least 10 days, and performed only in patients no longer requiring high FIO_2 , high PEEP, or high ventilation requirements.¹³¹

Tracheostomy Outcomes

Studies examining tracheostomy during COVID-19 reported usage of 16-18%.^{135,136} Percutaneous dilatational technique was favored (55-78% usage) over open surgical technique (22-45%).^{135,137,138} In a majority of studies tracheostomy was performed at an average of 12-18 days, in contrast to an average of 21-22 days in others.^{135-137,139-146} Few studies examined whether tracheostomy decreased the use or dosage of sedatives and analgesics. All found substantial reductions (65%) in or discontinuation of sedation along with marked analgesic reductions (about 50%).^{137,140,145} However, these reductions sometimes transpired over 7 days (making their association with tracheostomy highly questionable);¹⁴⁵ whereas the impact on weaning either was not reported,¹³⁷ or was negligible.¹⁴⁰

Likewise, the overall impact tracheostomy had on liberation could not be assessed as none of these studies described weaning and sedation practices. Average weaning durations in early vs. late tracheostomy were 11-12 days and 6-11 days respectively, with an overall mechanical ventilation duration of 12 ± 7 days regardless of tracheostomy timing.^{139,142,144} Decannulation reported in a large number of studies^{136,137,139,140,142,143} was accomplished in 13 to 99% of survivors at an average of 13-17 days,^{137,140,147} and sometimes substantially longer (27 days).¹⁴³

Complications

Tracheostomy-associated complications varied widely across studies (3-30%) regardless of sample size and were predominantly associated with minor bleeding in most instances (2-18%) with an overall incidence usually under 10%.^{135-137,139-142,144-146} Bleeding likely was accentuated by the heightened need for anticoagulation in treating COVID-19. Incidences of other complications were low: pneumothorax/subcutaneous emphysema (0.2-5%), accidental tube dislodgement (3-4%) or secretion obstruction (5%).

Risk of Clinician Infection

Recommendations for enhanced personal protection during tracheostomy in COVID-19 include that the procedure is performed in a negative-pressure room with personnel using a powered air-purifying (PAPR) device, a fit-tested filtering facepiece (FFP3), or an N95 face mask along with face shield/eye goggles and an additional surgical mask, caps, boots, fluid-repellent disposable gown and double gloves.^{131,135,144} The majority of studies (88%) that assessed healthcare worker COVID-19 infection reported no infections among the surgical team,^{135-137,139,140,143-145} with only one study that reported an infection rate of 0.4%.¹⁴⁶

In summary, the use and timing of tracheostomy in COVID-19 are consistent with established clinical practices for patients with acute respiratory failure requiring prolonged mechanical ventilation. Most clinicians have favored the percutaneous dilatational technique. The efficacy of tracheostomy in facilitating weaning remains unknown because corresponding weaning and sedation practices were not reported. The most common procedure-related adverse event was minor bleeding, likely enhanced by an increased need for anticoagulation therapy in treating COVID-19. The use of enhanced personal protection practices and environment controls essentially eliminated procedure-related clinician infection.

Key points

- What constitutes early tracheostomy criteria for patients with COVID-19 is airway conversion between 7 to 14 days.
- The use of enhanced personal protection practices and environmental controls essentially eliminated incidences of procedure-related clinician infection.
- Most complications associated with tracheostomy in patients with COVID-19 involve minor bleeding that is likely attributable to higher use of anticoagulants.

THE ROLE OF ECMO IN COVID-19 ASSOCIATED ARDS

Guidelines and protocols for extracorporeal membrane oxygenation (ECMO) in severe ARDS, including COVID-19, emphasizes: 1) initiation < 7 days from starting mechanical ventilation in those with potentially reversible respiratory failure, 2) persistent $\text{PaO}_2/\text{FIO}_2 < 80$ with either $\text{PEEP} \geq 10$ cm H_2O and $\text{FIO}_2 \geq 0.80$, or PEEP requirements ≥ 15 cm H_2O , 3) uncompensated respiratory acidemia ($\text{pH} < 7.15$), $\text{pH} < 7.25$ and $\text{PaCO}_2 > 60$ mm Hg, or $\text{pH} < 7.20$ and $\text{PaCO}_2 > 80$ mm Hg, and 4) Pplat to > 35 cm H_2O despite lung-protective ventilation.¹⁴⁸⁻¹⁵⁰ These and other protocols emphasize that hypoxemia thresholds persist for > 6 h (or > 3 h if $\text{PaO}_2/\text{FIO}_2 < 50$), and persist despite the use of ancillary therapies to support gas exchange (i.e., prone position, inhaled vasodilators, and neuromuscular blockade).^{150,151} In appropriately selected patients, initiation of ECMO (or transfer to an ECMO center) should occur without delay. In addition, updated guidelines that have reviewed mobile ECMO (to facilitate the transfer of patients to ECMO centers) found it to be both feasible and safe.¹⁵² Evidence from RCTs and emulated target trials suggest a beneficial effect of ECMO for patients with severe ARDS due to COVID-19.¹⁵³ A higher benefit is seen when selecting patients early in the course of invasive ventilation, with severe hypoxemia, or receiving a higher intensity of mechanical ventilation. ECMO is likely best delivered in specialized centers.

The most frequently used techniques are veno-venous (V-V) ECMO to enhance oxygenation and CO_2 elimination, extracorporeal carbon dioxide removal (ECCO₂R) to enhance or achieve ultra-lung-protective ventilation by lowering PaCO_2 alone, and veno-arterial (V-A) ECMO to enhance systemic O_2 delivery in patients with cardiac failure.¹⁵⁴ Both V-V ECMO and ECCO₂R are the primary modalities used in patients with acute respiratory failure (single-organ) whereas V-A ECMO is used in patients with acute respiratory failure with right or left ventricular dysfunction.¹⁵⁴ ECMO is a relatively limited resource so that the added stress of the COVID-19 pandemic necessitated contingency capacity and triage guidelines (Tables 5 and 6).¹⁵⁰

Relative usage, timing, titration, and duration of ECMO

During COVID-19, ECMO has been used in 1-36% of mechanically ventilated patients with median usage of 8% (4.5-18%).^{151,155-161} V-V ECMO has been used in 92-100% of cases.^{151,155,157-160,162-167} Across studies, ECMO tended to begin 3 to 6 days following mechanical ventilation initiation, with an average duration of 13 to 20 days. When reported, ECMO blood flow support was within established parameters,¹⁵⁴ averaging 4 to 5 L/min with sweep flows of 4-6 L/min to keep $\text{PaCO}_2 < 45$ mm Hg.^{157,159, 162,167,168}

Ventilator Management and Ancillary Therapies Before and During ECMO

Ventilator management guidelines for patients with COVID-19 receiving ECMO suggest targeting a PEEP of 10-15 cm H_2O and $\text{Pplat} < 25$ cm H_2O (or driving pressure < 15 cm H_2O), reducing respiratory frequency to 4 to 10 breaths/min and targeting a $\text{SpO}_2 > 85\%$ with an $\text{FIO}_2 < 0.5$.¹⁵⁰ Recommended alternative management is using established lung protective ventilation protocols that were incorporated during previous ECMO trials (e.g., Express or ARDSNet).¹⁶⁹⁻¹⁷¹

Rigid adherence to lung-protective ventilation goals prior to initiating ECMO has been followed across studies, with an average V_T of 6 mL/kg and Pplat of 30 cm H_2O with remarkably little variation. At ECMO initiation, the average $\text{PaO}_2/\text{FIO}_2$ was usually 67-75 with corresponding average PEEP of 11-15 cm H_2O , FIO_2 of 0.9 to 1, arterial pH of 7.28-7.30 and PaCO_2 of 57-65 mm Hg.^{151,155-160, 162,164-167,172,173} ECMO allowed further reductions in ventilator settings with some studies reporting substantial decreases in FIO_2 (to about 0.5), peak or tidal airway pressures (6-8 cm H_2O), V_T (1-3 mL/kg), but only modest reductions in PEEP (2 cm H_2O).^{155,159,164,167}

As recommended prior to initiating ECMO, ancillary therapies widely used include neuromuscular blockade (80-98%), prone position (68-94%), inhaled vasodilators (32-79%), and vasopressors (41-82%).^{151,155-160,162-164,166,167,172} Studies in which prone positioning continued after initiating ECMO found small but significant reductions in PaCO_2 (about 2 mm Hg) and driving pressure (1 cm H_2O) with more substantial improvements in $\text{PaO}_2/\text{FIO}_2$ (25).¹⁷⁴

Table 5. Extracorporeal membrane oxygenation therapy contingency capacity categorizations during COVID-19. Adapted from 2020 Interim consensus guidelines of the Extracorporeal Life Support Organization (ELSO).

Contingency	Description	Guidance
Conventional Capacity	Normal capacity to provide ECMO	Usual criteria in place to administer V-V and V-A ECMO in selected COVID-19 and non-COVID patients.
Tier 1	Expanded ECMO capacity	Triage ECMO to maximize resource:benefit by: • Use of V-V or V-A ECMO in younger patients with COVID with single organ failure • Judicious application of ECMO for patients without COVID using established criteria • ECPR not offered for any patient
Tier 2	Expanded ECMO capacity nearing or at the saturation point	More restrictive ECMO criteria in place for all potential indications: • Only V-V ECMO offered to younger patients with COVID and single organ failure • Prioritize ECMO for non-COVID indications in which there is a higher probability for survival • Both V-A and ECPR ECMO are removed as care options.
Crisis	Expanded ECMO capacity is overwhelmed	• ECMO therapy no longer feasible for both COVID and non-COVID patients alike. • Assess therapeutic futility in patients currently undergoing therapy for withdrawal of ECMO support to again create capacity in the system.

Key: ECMO = extracorporeal membrane oxygenation, ECPR = extracorporeal cardiopulmonary resuscitation, V-A = venoarterial, V-V = venovenous.

Table 6. Contraindications for the use of extracorporeal membrane oxygenation in COVID-19 associated acute respiratory distress syndrome. Adapted from 2020 Interim consensus guidelines of the Extracorporeal Life Support Organization (ELSO).

Absolute	Relative
• Advanced age • Clinical frailty score > 3 • Mechanical ventilation > 10 days • Significant underlying comorbidities (eg, cirrhosis, dementia, metastatic cancer, etc.) • Severe multiorgan dysfunction syndrome • Severe acute neurologic injury • Uncontrolled bleeding • Contraindications for anticoagulation therapy • Inability to receive blood products • Ongoing cardiopulmonary resuscitation	• Age ≥ 65 years • Body Mass Index ≥ 40 • Immunocompromised • Medical-legal surrogate consent not available

ECMO Outcomes and Complications

Assessing mortality in COVID-19 observational studies is complicated by numerous factors including small sample sizes and uncontrolled confounding variables (e.g., advanced age, comorbidities, use of other potentially effective therapies, etc.). Prior to COVID-19, the largest randomized controlled ECMO trial in very severe ARDS reported a mortality of 35%.¹⁴⁹ By comparison, most of the larger COVID-19 ECMO studies reported mortality of 35-55%,^{163,164,166,167} the exception being one study reporting hospital mortality of 71%.¹⁶¹ The overall mortality including the outlier study was 43%. This is similar to mortality observed clinically in non-COVID severe ARDS irrespective of ECMO therapy use (46%).¹¹⁹

A follow-up investigation into the outlier study found that mortality was largely attributed to older age (mortality > 80% in those ≥ 60 years), later ECMO initiation (50% after 7 days of mechanical ventilation) and a high incidence of renal failure (60%).¹⁷⁵ However, it was also suggested that the lack of stringent ECMO guidelines for ARDS (as used in other studies) may have allowed for a too liberal usage in a country for which ECMO was widely available.¹⁷⁵

Both patient-related adverse events and equipment-related issues were reported across most studies. The most commonly reported patient-related issue during ECMO was significant bleeding (4-42% incidence),^{151,157-160,162,166-168,172} followed by hemorrhagic or ischemic cerebral vascular accident (4-29% and 1-14% incidences, respectively),^{159,160,162-164,166-168,173} ischemic limb (6% incidence),¹⁶⁰ and other incidences of thromboembolism (11-24%).^{157,159,160,162,166} The frequency of these occurrences did not necessarily reflect an artifact related to the small study size. As coagulopathy is a common feature of COVID-19, specific concern regarding higher incidences of both catheter and circuit-related venous thrombosis during ECMO including its apparent correspondence to both pulmonary embolism and intracranial hemorrhage/infarction has been expressed.¹⁷⁶⁻¹⁷⁸

The most common equipment-related problem was the need for circuit replacement (4-41% incidence),^{134,158,167,168,172} and apparent cannula-associated blood stream infection (6-32% incidence),^{158, 159,166,167,173} whereas other issues were reported in only 6-13% of studies: cannula repositioning (4-43% incidence),^{151,157} oxygenator replacement (9-24% incidence),^{160,164} circuit air embolism (1-13% incidence),^{163,172} and pump replacement (1% incidence).¹⁶⁴

In summary, ECMO has been used in a minority of COVID-19 associated ARDS with V-V ECMO used in more than 90% of cases and initiated < 7 days after instituting invasive mechanical ventilation. On average, ECMO was required for 2-3 weeks. Across studies lung-protective ventilation was strictly adhered to and incorporation of ancillary therapies failed to improve gas exchange prior to initiating ECMO therapy. Mortality in profoundly hypoxemic COVID-19 ARDS subjects ranged from 35-55%. However, there was a relatively higher incidence of bleeding and clotting complications during ECMO therapy in COVID-19 that likely reflected the prevalence of coagulation disorders associated with SARS-CoV-2 infection.

Key points

- In cases of severe refractory ARDS, ECMO therapy should be initiated within 7 days of mechanical ventilation and only in those with potentially reversible, single organ failure.
- Prior to initiating ECMO, ancillary therapies should be attempted first (e.g., neuromuscular blockade, prone position, inhaled vasodilators, and vasopressors).
- Ventilator management guidelines for COVID-19 patients receiving ECMO include targeting PEEP of 10-15 cm H₂O and Pplat < 25 cm H₂O, a breathing frequency of 4-10 breaths/min, and FIO₂ < 0.5.

OXYGEN THERAPY AND SHORTAGES

Oxygen is one of the most common drugs provided within the healthcare system.¹⁷⁹ Under typical circumstances, caregivers rarely need to be concerned with the ready availability of oxygen at the bedside. Liquid systems commonly installed in a hospital contain hundreds of liters of liquid oxygen and the systems are routinely refilled using electronic monitoring. Two papers in RESPIRATORY CARE over the years have considered the potential oxygen shortages during a natural disaster or pandemic.^{180,181} During the COVID-19 pandemic, these theoretical concerns were manifested in low and middle income countries as well as in the United States.¹⁸²

Hospital Oxygen Systems

Chatburn and Branson reviewed hospital-based liquid oxygen (LOX) systems and the vulnerabilities during a pandemic.¹⁸³ The basics of the hospital-based liquid system are described here. Hospital liquid systems typically consist of 1 or 2 primary liquid vessels and a smaller reserve vessel (Figures 9 and 10). Each liquid vessel has an array of evaporating coils that appear as a tall aluminum radiator. As liquid flows through the coils, liquid oxygen evaporates, often leaving a small amount of ice on the coils even



Figure 9. A typical hospital liquid oxygen system. There are 2 main liquid vessels and 1 reserve smaller vessel to the right. The evaporating coils, where liquid oxygen is converted to gas are in the foreground and in this figure have no ice accumulation.

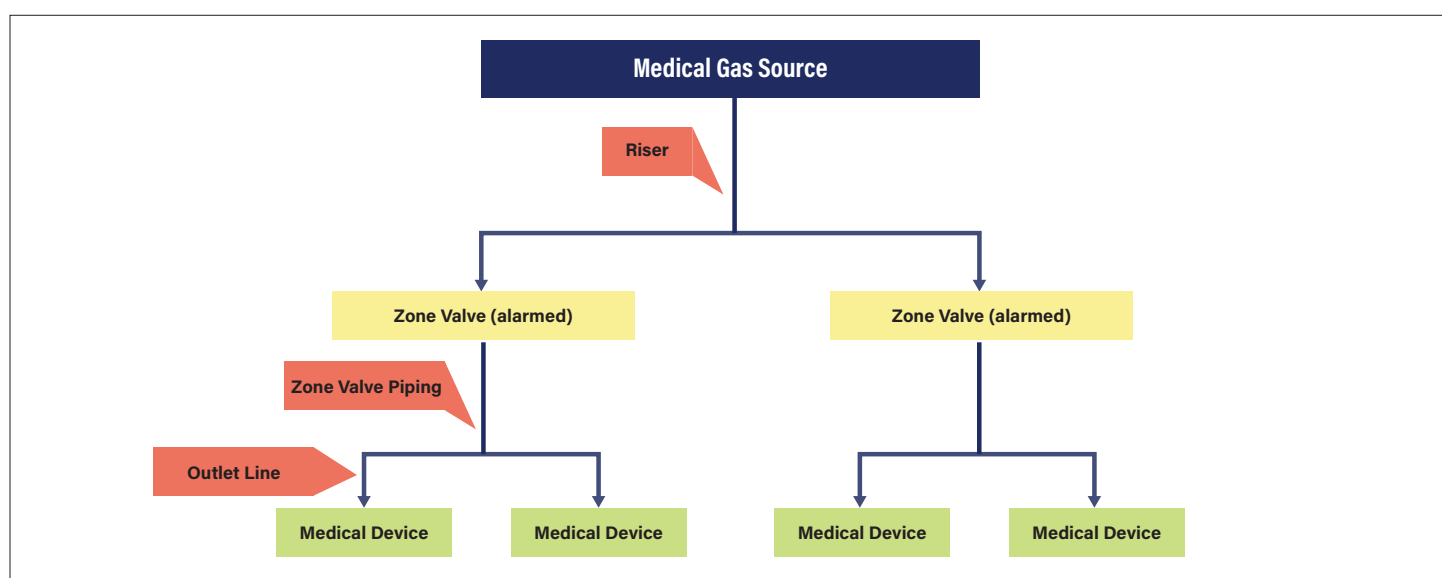


Figure 10. A schematic of a hospital-based oxygen system. From Chatburn RB, Branson RD. Shortages and vulnerabilities of hospital oxygen systems. *Respir Care* 2022;67(8):in press.

in the summer. Gas is delivered to the hospital via a series of pipes of varying sizes depending upon the position in the system and intended endpoint. The diameter of pipes serving the ICU are larger than those intended for the general floor unit. Table 7 describes pipe diameters and available flows.

Table 7. Size of piping system and maximum flow through each internal diameter pipe. From Chatburn RB, Branson, RD. Shortages and vulnerabilities of hospital oxygen systems. *Respir Care* 2022;67(8):in press.

Pipe Size Diameter (inch)	Pressure Drop/100 Ft (psig)	Capacity (L/min)
1 ¼	1.02	2,700
1 ½	1.02	4,300
2	0.64	7,000
2 1/2	0.60	12,000
3	0.53	18,000

The major advantage of the LOX system is that a liter of liquid oxygen evaporates into 860 L of gaseous oxygen. Most hospitals use some type of monitoring to assure that the vessel never falls to less than 50% of its volume. Under normal conditions, LOX deliveries are made by truck and, in the absence of damage to highway infrastructure (flood, earthquake), LOX deliveries are assured. LOX is manufactured by fractional distillation and the supply is plentiful.

In the event of failure of the main LOX system, the reserve vessel is utilized. If piping to the hospital is disrupted by construction or natural disaster, the hospital system is required to have a secondary input where a mobile liquid system can be connected. In 2000, Stoller et al¹⁸⁴ reported that less than two-thirds of hospitals had an external connector to backfill the hospital's oxygen system. Equally problematic, they found that most backfill connectors used the same delivery piping as the primary LOX system. In this case, damage to the delivery pipe during construction would not only prevent gas from the primary LOX system from reaching the hospital, but it also defeats the backfill system.

Emergency backup systems are available, including room-size oxygen concentrators, banked cylinders, and portable liquid systems.¹⁸⁰ The COVID-19 pandemic stressed oxygen systems because of the unusually high oxygen requirements of so many patients. Oxygen deliveries had to be more frequent to meet demands. In smaller facilities these issues were more pronounced.¹⁸²

Understanding piping systems

Schematics for piping systems are complex and vary from hospital to hospital. The main supply from the primary and reserve LOX are large in diameter and capable of delivering high flows at 50 psig. These pipes typically contain check valves to prevent backflow to the LOX. As the piping system moves vertically through the floors of the hospital, the pipes are known as risers. At each floor, piping turns horizontally to feed the bed spaces on that floor. These pipes are known as laterals. Each lateral has a zone valve that allows that portion of the piping system to be isolated. The zone valve can be closed in the event of fire downstream from the lateral. In some cases, the zone valve is closed, and oxygen cylinders are used to back-fill the floor during the loss of delivery from the LOX.

The laterals connect to the outlet lines which feed the individual outlets at each bed. In the ICU, there may be 3 or 4 oxygen outlets at each care station. On the general wards, one oxygen outlet is typically provided. By the time respiratory therapists provide any type of oxygen therapy at the bedside, the plan for the system and the construction has taken place. During this pandemic, the issue of piping became important because of expansion of ICU capacity.

When many patients with hypoxemic respiratory failure requiring oxygen therapy were admitted, the ICU was overwhelmed. Surge capacity, adding additional ICU beds, included use of the post-anesthesia care unit, tent hospitals and use of general wards for ICU level care. A floor or ward designed for the general care and low flow oxygen might now include the care of several patients receiving HFNC at 40 to 60 L/min. Within the piping system there are choke points. Choke points represent narrowing of the gas delivery system and increased resistance reducing flow distal to the choke point, negatively impacting high gas consumption therapies.

The main choke points identified were the riser lines (e.g., 1.25 inches in diameter) coming from the medical gas source, the zone valves and lateral lines (e.g., 0.75-inch diameter) and outlet lines that connect to the medical devices (e.g., 0.5-inch diameter). The higher the flow through these lines, and the smaller the diameter, the greater the pressure drop. When the pressure drop is large enough, zone valve alarms are triggered (typically < 45 psig). This is also important because air-oxygen blenders and ventilators are calibrated to function at a range around 50 psig. Gas delivery outside this range may result in inaccurate gas delivery or additional alarms.



Figure 11. Progressive icing of coils of a hospital-based oxygen system with increased oxygen use during the pandemic. From Chatburn RB, Branson RD. Shortages and vulnerabilities of hospital oxygen systems. *Respir Care* 2022;67(8):in press.



Icing of coils

Ice accumulation occurs on LOX evaporating coils even in summer months and icing may be greater during winter months. The degree of icing also increases with the demand for the oxygen system. Figure 11 demonstrates the degree of icing on the vaporizing coils during the pandemic at the Cleveland Clinic. Even with differences in the season, during the peak admissions in Northeast Ohio, the icing demonstrated nearly complete coverage of the vaporizing coils.

While some ice accumulation of the vaporizing coils is expected, under high demands the liquid oxygen can travel further up the coils before evaporating into a gas. At extremes, it is possible that liquid oxygen can travel to the in-line pressure regulator freezing the components and rendering them inoperative. In the worst-case situation, freezing of the regulator can restrict oxygen flow to the hospital resulting in catastrophic failure. Figure 12 demonstrates the icing of the pipeline carrying oxygen from the vaporizing coils and a mitigation strategy, warm water irrigation spray to melt the ice.

Calculating oxygen usage

Calculating oxygen usage by low flow and high flow oxygen appliances is simple. The oxygen flow in L/min multiplied by 1,440 minutes in a day determines the daily oxygen usage of a given device. HFNC requires an understanding of both flows in L/min and FIO_2 . Despite the enthusiasm for HFNC during the pandemic, its use contributed importantly to oxygen usage. A non-rebreathing mask at 15 L/min can provide a high FIO_2 and historically was designed to not only increase the inspired oxygen but to conserve oxygen. These high flow devices were introduced during the time when oxygen was commonly provided from an H-cylinder wheeled to the patient's room. Oxygen conservation was a priority. HFNC at



Figure 12. Excessive icing of the piping system leading to the hospital (Top). A mitigation strategy was the use of warm water irrigation sprinklers to intermittently melt ice accumulation.

Table 8. Oxygen flow, expected delivered FIO_2 and maximum oxygen usage. From Chatburn RB, Branson, RD. Shortages and vulnerabilities of hospital oxygen systems. *Respir Care* 2022;67(8):in press.

Device Type	Device	Flow or minute ventilation (L/min)	Expected FIO_2	Maximum O_2 usage (L/min)
Adjustable O_2 flow	Nasal cannula	1-6	0.22 - 0.4	6
	Simple mask	5-10	0.35 - 0.5	10
Adjustable FIO_2	Entrainment mask	2-15	0.24 - 0.6	15
	High flow nasal cannula	10-60	0.21 - 1	60
	Invasive ventilation (no leak)	5-15	0.21 - 1	15
	Non-invasive ventilation with 40 L/min leak	45-55	0.21 - 1	55
Non-adjustable FIO_2	Partial rebreathing mask	≥ 10 L/min	0.4 - 0.7	15
	Non-rebreathing mask	≥ 10 L/min	0.6 - 0.7	15

60 L/min uses 4 times the oxygen at an FIO₂ of 1 than a non-rebreathing mask at 15 L/min. Oxygen usage of common oxygen therapy devices are shown in Table 8.

Ventilator oxygen usage has historically been calculated using a standard formula accounting for FIO₂ and minute ventilation. Modern ventilators often include constant flow during the expiratory time to stabilize PEEP and improve triggering, which increases gas consumption above the delivered minute ventilation. NIV systems with fixed and unintentional leaks and invasive ventilators with leak compensation further complicate calculating total gas consumption.

Table 9 provides some useful equations for calculating oxygen use by different devices. Determining the oxygen consumed by an entire hospital is more complicated and includes oxygen flow to manual resuscitators, anesthesia machines, and ventilators. The Open Critical Care group has developed some accurate and sophisticated calculators to assist in this endeavor (<https://opencriticalcare.org/oxygen-supply-demand-calculator/>, accessed June 13, 2022).

COVID-19 has reawakened respiratory therapists to the importance of understanding the hospital oxygen system and the nuances of ventilator function. Oxygen shortages in the US were real and while we are unaware of exhaustion of oxygen in any US hospitals, there were clearly concerns for that eventuality.

Key Points

- Hospital-based liquid oxygen systems have a large but finite capacity.
- Oxygen shortages were caused by increased numbers of patients requiring high oxygen flows and high FIO₂.
- The icing of the evaporation coils is associated with increased oxygen use and can result in reduced oxygen flows.
- HFNC and NIV with a leak at high FIO₂ are the greatest oxygen consumers.
- Increasing ICU capacity to general floors, which are not intended for high oxygen use, may limit the number of patients served by the oxygen system.

Table 9. Equations for calculating oxygen use by mechanical ventilators.
Standard mechanical ventilation Device O₂ consumption rate in L/min = (Minute ventilation x (FIO₂ - 0.21))/0.79
Mechanical Ventilation with an expiratory or bias flow. Device O₂ consumption rate in L/min = (Minute ventilation + (bias flow x rate x expiratory time/60) x (FIO₂ - 0.21))/0.79
Mechanical ventilation with an intentional or unintentional leak. Device O₂ consumption rate in L/min = (Minute ventilation + (bias flow x rate x expiratory time/60) + leak) x (FIO₂ - 0.21)/0.79

HAPPY HYPOXIA – THE SILENT HYPOXEMIA PHENOMENON

During the first year of the pandemic, several reports described what many believed was a uniquely COVID-19 related phenomenon, silent or happy hypoxia.^{185,186} Concern was raised because some of these patients suddenly became hemodynamically unstable and died, while others rapidly recovered from COVID-19 without incident.¹⁸⁶⁻¹⁹² Confusion regarding this phenomenon is based upon several factors: 1) the definition of severe hypoxemia and its relationship to compensatory cardiovascular and splenic function, 2) the erroneous conflation of severe hypoxemia with tissue hypoxia, 3) the imprecise, conditional relationship between arterial oxygen saturation (SaO_2), pulse oximetry saturation (SpO_2), and PaO_2 , and 4) a misunderstanding of the relationships between hypoxemia, respiratory drive, and dyspnea. All of these factors inform the therapeutic response to severe hypoxemia in clinical practice.

Hypoxemia is defined solely upon PaO_2 and is classified as mild (PaO_2 50 to 60 mm Hg), moderate (PaO_2 40 to 50 mm Hg), severe ($\text{PaO}_2 < 40$ mm Hg) and profound ($\text{PaO}_2 < 30$ mm Hg).¹⁹³ Under normal physiologic conditions, this translates into an SaO_2 of 81 - 90%, 76 - 80%, 50 - 75% and $< 50\%$, respectively. In contrast, hypoxia occurs at the tissue level leading to end-organ damage and with few exceptions (i.e., asphyxia, carbon monoxide, or cyanide poisoning) signifies the failure of compensatory mechanisms. An additional problem likely contributing to the perception of silent hypoxemia is a reliance upon SpO_2 monitoring. As hypoxemia worsens (particularly when $\text{SaO}_2 < 80\%$), SpO_2 substantially underestimates the corresponding SaO_2 by as much as 7%,¹⁹² particularly in the presence of anemia.¹⁹⁴

Hypoxemia-Induced Compensatory Mechanisms

The primary compensatory mechanisms during hypoxemia are increased cardiac output and hyperventilation. The hypoxic ventilatory response commences when PaO_2 is ≤ 60 mm Hg,¹⁹⁵ and is characterized by tachypnea, hyperventilation, tachycardia, and increased cardiac output. The magnitude of these responses increases with worsening hypoxemia.^{193,195,196} Also present during acute hypoxemia is a graded, catecholamine-induced surge in

blood volume (via splenic contraction) that is magnified further by the presence of hypercapnia.^{197,198}

The magnitude of hypoxic ventilatory response is mediated by the corresponding PaCO_2 such that a normal PaCO_2 of 39 mm Hg enhances the ventilatory response to hypoxemia, whereas mild hyperventilation (i.e., PaCO_2 of 34 mm Hg) blunts the response. Hypoxemia becomes the primary stimulus for the respiratory drive only when PaO_2 approaches 45 mm Hg. When PaO_2 is < 30 mm Hg breathing becomes erratic followed by apnea from brain stem hypoxia.

Hypoxemia and sudden clinical deterioration in COVID-19

Advanced age and comorbidities significantly increase the risk for sudden deterioration as hypoxemia worsens because of diminished adrenergic response and limited cardiovascular reserve. Older adults (e.g., > 65 years) and those with cardiovascular disease and/or diabetes have blunted cardiovascular and ventilatory responses to hypoxemia and hypercapnia (i.e., a 40-50% response reduction compared to young adults).^{199,200} This increases the likelihood of metabolic acidosis and cardiovascular failure that is further magnified in those with profound shunt physiology (ie. ARDS).¹⁹³ These risk factors must be considered in deciding whether to first initiate a trial of HFNC or NIV or to proceed directly to intubation in a patient with worsening hypoxemia unresponsive to standard oxygen therapy.

Hypoxemia and dyspnea in COVID-19

Hypoxemia is a relatively poor stimulus for dyspnea compared to hypercapnia, elevated work of breathing, and irritant receptor stimulation arising from the lung parenchymal injury. Even during severe hypoxemia (i.e., PaO_2 40 mm Hg), if PaCO_2 is normal (40 mm Hg) 30% of individuals do not experience significant dyspnea.²⁰¹ Individual responses to severe hypoxemia range from profound dyspnea and panic, to calmness and a sense of well-being.¹⁹³ Four factors likely explain the perception of silent hypoxemia in COVID-19 including: 1) compensatory mild hypocapnia (which

reduces respiratory drive and dyspnea),²⁰² 2) normal work of breathing (because of preserved lung compliance in early COVID-19),²⁰³³) blunted respiratory drive response to both hypoxemia and hypercapnia in older adults and those with diabetes, and 4) the negative bias in pulse oximeters as hypoxemia worsens.

Evidence supporting silent hypoxemia in COVID-19 is of low quality. The exception is a large prospective case-controlled study²⁰⁴ of 470 subjects with a baseline $\text{SpO}_2 < 80\%$, and in whom dyspnea was standardized using the American Thoracic Society definition.²⁰⁵ Only 5% of hypoxemic subjects with a median SpO_2 of 76% (60%-79%) at room air presented with apparent silent hypoxemia; 91% were tachypneic. These subjects also presented with similar degrees of hypocapnia reported in severely hypoxemic, healthy research subjects who also experienced minimally detectable levels of dyspnea when allowed to set their own PaCO_2 .²⁰²

The so-called silent hypoxemia is not unique to COVID-19; moreover, it can be explained by known mechanisms that prevent/ameliorate dyspnea. In the only well-controlled study, the incidence of silent hypoxemia during COVID-19 was no greater than that previously reported in the medical and physiologic literature. Of note, during the first wave of the pandemic, a substantial percentage of hospitalized COVID-19 subjects were older, and many had diabetes as a comorbidity, likely contributing to a perceived prevalence of silent hypoxemia. It is much more important for clinicians to focus on preventing and aggressively treating severe (or rapidly progressing) hypoxemia in patients particularly vulnerable to sudden, life-threatening decompensation (i.e., older adults and those with pre-existing cardiovascular disease and/or diabetes).

Hypoxemia, Oximetry and Skin Pigment

The impact of darker skin pigment on accuracy of pulse oximetry has been known for decades.^{193,206} Dark pigment absorbs more of the two wavelengths of light with a resulting reporting of SpO_2 that is greater than SaO_2 . Consequently, a dark-skinned Black patient may have an SpO_2 of 92%, but an actual SaO_2 of 86% and, in the presence of fever, a PaO_2 as low as 50 mm Hg. In the midst of COVID, a paper from the NEJM reported the results of a retrospective review of racial bias of oximeters.²⁰⁷ This data confirmed the work of Jubran and Tobin 30 years previously.²⁰⁸

This was followed by a number of studies linking the overestimation of SpO_2 by oximetry and misclassification of disease severity and delayed care in patients of color.²⁰⁸⁻²¹⁰ As an example, the ROX index and $\text{SpO}_2/\text{FIO}_2$ used to classify ARDS in the absence of PaO_2 might suggest a dark-skinned patient has better oxygenation than the true SaO_2 . As a result, escalation to HFNC,

intubation or ECMO might be delayed in Black patients leading to increased mortality. This has been termed occult hypoxemia.

Tobin and Jubran²¹¹ correctly point out that oximeters, as inanimate objects are incapable of racial bias. Rather, devices have a statistical bias, mean and standard deviation based on oximeter accuracy. Okunola and colleagues²¹² suggest a road map for solving the issues of oximeter inaccuracies in patients with dark skin pigment. This includes the inclusion of greater skin pigment diversity in subjects during the creation of algorithms used by oximeters to translate light absorption to SpO_2 .

This explanation does not change the fact that darker skinned patients may have more profound hypoxemia than the oximeter portends. This may also help explain the observed happy hypoxic syndrome, mistakenly attributed to COVID-19. From a clinical standpoint it suggests that clinicians obtain arterial blood for analysis in dark-skinned patients to determine blood oxygenation and correlate it to SpO_2 .

Key points

- Hypoxemia becomes the primary stimulus governing respiratory drive only when PaO_2 approaches 45 mm Hg.
- Mild hypocapnia (PaCO_2 about 35 mm Hg) effectively blunts hypoxic ventilatory drive.
- Sudden clinical deterioration associated with severe hypoxemia ($\text{PaO}_2 < 40$ mm Hg) is caused by the failure of cardiovascular compensatory response and occurs most frequently in older patients and those with comorbidities.
- Dyspnea is related to the heightened respiratory drive, but hypoxemia is itself a poor stimulus for dyspnea.
- The natural blunting of respiratory drive among older patients and in those with diabetes likely explains the apparent silent hypoxemia observed during the initial wave of the COVID-19 pandemic.
- Patients with darker skin pigment may have an overestimation of SpO_2 , resulting in occult hypoxemia and delayed intervention.
- Arterial blood gas analysis may be warranted in dark skinned patients to measure blood oxygenation directly.

ARDS VS COVID ARDS – IS THERE A DIFFERENCE?

Another controversy that arose was whether COVID-19 induced acute respiratory failure differed from ARDS, inviting some to question if current evidence-based lung-protective ventilation practices should be modified. Early reports from China found that 65-85% of COVID-19 ICU admissions met ARDS criteria.^{168,213} In contrast, initial reports from Southern Europe described 2 distinct manifestations of acute hypoxemic respiratory failure differentiated by the degree of alterations in lung mechanics, functional residual capacity (FRC) and radiographic presentation. These were prematurely designated as phenotypes. The less severe form that accounted for 70%-80% of cases were designated as Type L for low lung elastance (i.e., preserved compliance > 50 mL/cm H₂O). Initially referred to as non-ARDS, it was quickly reclassified as atypical ARDS. The more severe presentation, Type H for high lung elastance (low lung compliance < 40 mL/cm H₂O) was referred to as classic ARDS accounting for only 20%-30% of cases.^{214,215}

A review of the first year of the pandemic suggests the more likely explanation for these apparent phenotypes was differences in the timing from infection and symptom onset to clinical presentation, and perhaps a slower evolution of viral pneumonia from discrete lobar disease to ARDS.¹¹⁸ This was recognized by a declaration that COVID-19 phenotypes represented a time-related disease spectrum.²⁰³

Furthermore, it was hypothesized that patients who progressed from atypical ARDS to classic ARDS over time did so from patient self-inflicted lung injury (P-SILI). The mechanism for PSILI is prolonged high- V_T /high transpulmonary pressure from spontaneous breathing induced by abnormally high levels of respiratory drive caused by viral-induced carotid bodies hypersensitivity to hypoxemia.^{216,217} Concern that P-SILI may exacerbate acute lung injury was one of the main drivers for early (preemptive) intubation to insure the achievement of lung protective ventilation. Lower PEEP and liberalized V_T up to 8 mL/kg were advocated for those with preserved lung volumes and compliance. The rationale was that lung de-recruitment and intrapulmonary shunt were not the primary source of hypoxemia. Thus modest liberalization in V_T when lower

PEEP was indicated would likely prevent (or ameliorate) patient-ventilator asynchrony and associated double-triggering that would result in V_T greater than 12 mL/kg.²¹⁸

The question of whether COVID-19 acute hypoxemic respiratory failure is ARDS can be addressed by reviewing clinical studies of COVID-19 on its radiographic and pathology findings that measured lung mechanics, PEEP requirements, ability to achieve lung-protective ventilation, lung recruitment potential, oxygenation, and duration of mechanical ventilation and associated mortality.¹¹⁸ Pathology reports in subjects succumbing early or late in the course of COVID-19 associated respiratory failure observed temporal changes consistent with that found in non-COVID-19 ARDS.^{219,220} These are early findings of an exudative pattern with prominent interstitial and alveolar infiltration and hyaline membrane formation coupled with varying degrees of alveolar hemorrhage and extensive endothelial injury and thrombosis. Those who died at 2 to 3 weeks, or beyond, had prominent fibroproliferation typically found in the later stage of non-COVID-19 ARDS. Likewise, radiographic findings over the same time course were largely consistent with those observed in non-COVID-19 ARDS.²²¹

In studies reporting mechanical ventilation data, the average compliance was similar to non-COVID ARDS during lung-protective ventilation (≤ 40 mL/cm H₂O) as were average PEEP requirements (10-16 cm H₂O).¹¹⁸ Likewise, over 90% of studies reported an average $V_T < 8$ mL/kg. Lung recruitment potential in COVID-19 was similar to that observed in non-COVID-19 ARDS. At the onset of invasive ventilation, the average PaO₂/FIO₂ was 101 to 198.

In COVID-19 subjects with complete data (i.e., status at hospital discharge) overall mortality was ~50% but was ~40% in those without multiorgan dysfunction syndrome. By comparison mortality in moderate to severe non-COVID ARDS ranges from 37 to 50%.¹¹⁹ The average duration of mechanical ventilation among COVID-19 survivors ranged from 6 to 18 days with most reporting averages exceeding 12 days. These findings were like those reported in ARDS.

In summary, there is no apparent distinction between COVID-19 acute hypoxemic respiratory failure and ARDS as it

meets the classic criteria of injury mechanism (viral pneumonia), severity of oxygenation defect and both pathologic and radiographic presentation. Moreover, PEEP requirements, altered lung mechanics, and recruitment potential fell within the parameters found in non-COVID-19 ARDS, as did mechanical ventilation duration and mortality. Confusion early during the pandemic may have been influenced by a somewhat slower progression of pneumonia from lobar to multi-lobar infection.

Key points

- Speculation regarding the existence of phenotypes in those with COVID-19 acute respiratory failure likely reflects an apparent slower progression of pneumonia, and perhaps differences related in the time from infection and symptom onset to clinical presentation.
- There does not appear to be a distinct physiologic difference between ARDS due to sepsis and ARDS due to SARS-CoV-2 infection.
- Treatment of ARDS in subjects with COVID-19 should follow lung protective approaches from previously published guidelines.
- COVID-19 ARDS is often associated with profound hypoxemia requiring high FIO_2 .
- There are no salient differences when comparing COVID-19 ARDS to non-COVID ARDS in terms of radiographic and pathology findings, lung mechanics, mechanical ventilation requirements, duration of mechanical ventilation and associated mortality.

PRINCIPLES OF LUNG PROTECTIVE VENTILATION

Pathophysiologic Rationale

The principles of lung protective ventilation are based upon the interactions between acute lung injury (i.e., alterations in lung and chest wall mechanics and host response to tissue injury) and how volume, pressure and oxygen variables are set during mechanical ventilation that either ameliorate or exacerbate lung injury, and furthermore impact mortality by reducing or increasing the risk of multiorgan failure.²²²

Under normal conditions when vigorous breathing generates high transpulmonary pressures and large V_T , the corresponding elevations in strain and stress are distributed evenly throughout the lungs, thereby preventing tissue injury (i.e., the lungs exhibit liquid behavior). However, because acute lung injury is heterogeneous in nature with multiple foci of damage, the lungs exhibit solid behavior, whereby strain and stress are unevenly distributed.²²³ In consequence, neighboring regions of normal lung tissue are repetitively exposed to high levels of tidal strain and stress that further disseminates lung injury and inflammation.²²⁴ In addition, repetitive opening and closing of collapsed tissue causes shearing injury at the interfaces with neighboring patent alveoli and by breaking foam menisci and displacing fluid when obstructed small airways are recruited.²²⁴

Moreover, in ARDS the lungs release proinflammatory mediators either commensurate with or disproportionate to the degree of injury (i.e., hyperinflammatory phenotype).²²⁵ These mediators subsequently are distributed throughout the lungs (enhancing any further inflammatory response to injury),²²⁶ and distant highly vascularized exchange organs (e.g., kidneys, gastrointestinal, liver) causing secondary, reciprocating injury between these organs systems (i.e., organ cross talk) leading to multiorgan failure and increased mortality risk.^{227,228}

Lung Protective Ventilation Targets

The substantial improvement in ARDS mortality in the 21st century is almost exclusively due to lung protective ventilation, which rests upon three crucial aspects. First is using a physiologic V_T (i.e.,

4 - 8 mL/kg) commensurate to the size of the aerated (functional) lung in order to minimize abnormal amounts of lung strain and stress.²²⁹ This is accomplished by limiting P_{plat} , a surrogate for peak alveolar pressure, to ≤ 30 cm H₂O, and ideally to ≤ 26 cm H₂O. Doing so both maximizes protection of the right heart and limits abnormal stress development across different lung regions.^{226,230} It is also accomplished by limiting the magnitude of change in tidal stress or driving pressure (ΔP) to ≤ 15 cm H₂O.²³¹ ΔP is particularly important when high PEEP levels are used to counter high chest wall compressive forces that obviate P_{plat} targets ≤ 30 cm H₂O.

Recruitment of the lungs to reestablish FRC towards normal is needed to: 1) reduce regions of abnormal strain and stress, 2) reduce shearing injury and 3) improve oxygenation so that FI_{O_2} can be reduced to non-toxic levels (i.e., ≤ 0.6). In a sizable majority of moderate to severe ARDS cases this can be accomplished with PEEP of 10 to 15 cm H₂O.²³² This is largely because a V_T of 6 mL/kg in this PEEP range typically results in a P_{plat} range of 25 to 30 cm H₂O which coincidentally results in a substantial degree of recruitment in the middle and lower lung zones.²³² Moreover, PEEP of 15 cm H₂O is usually sufficient to prevent de-recruitment in dorsal lung regions.

Although formal recruitment maneuvers are controversial and appear unnecessary in most ARDS cases, a reasonable argument can be made for limited use, particularly in the exudative phase of ARDS when severe hypoxemia is exacerbated either by extraordinarily high chest wall compressive forces (e.g., morbid obesity, ascites, and thoracic anasarca) or secondary lobar collapse.²³² Recruitment maneuvers at a P_{plat} of 40 to 45 cm H₂O and PEEP of 20 to 25 cm H₂O are likely sufficient to achieve adequate oxygenation (i.e., PaO_2 of 55 - 80 mm Hg) at an $FI_{O_2} \leq 0.6$ in all but the most extraordinarily severe, uncommon presentations of ARDS. A systematic review and meta-analysis found that, in patients with moderate to severe ARDS, higher PEEP without recruitment maneuvers was associated with a lower risk of death than lower PEEP. A higher PEEP with prolonged recruitment maneuvers was associated with increased risk of death when compared with a higher PEEP without recruitment maneuvers.²³³

Finally, prolonged exposure to hyperoxia causes acute lung injury and likely exacerbates ARDS. Mammals breathing an $\text{FIO}_2 \geq 0.8$ for a prolonged period (> 3-4 days) develop acute lung injury indistinguishable from ARDS, as well as secondary bacterial pneumonia that frequently is a sequela of ARDS.²³⁴ Whether humans succumb to hyperoxia over time (as most mammals) is unknown and impossible to test. However, both within and across multiple species of mammals there exist phenotypes in which hyperoxic acute lung injury is almost always fatal.²³⁴ These facts underscore the importance of limiting the exposure to severe hyperoxia and targeting an $\text{FIO}_2 \leq 0.6$ to achieve adequate (not optimal) oxygenation.

In summary, lung protective ventilation consists of titrating V_T to 4 to 8 mL/kg to achieve a $\text{Pplat} \leq 30$ cm H_2O (ideally ≤ 26 cm H_2O) and $\Delta P \leq 15$ cm H_2O . Sufficient PEEP levels in most cases are 10 to 15 cm H_2O that allow adequate oxygenation (PaO_2 of 55-80 mm Hg) - at a non-toxic $\text{FIO}_2 \leq 0.6$) and prevents lung de-recruitment.

Key points

- Ventilator-induced lung injury in ARDS is primarily caused by heterogeneously distributed lung injury causing uneven distribution of lung stress and strain, particularly when excessive tidal volume or PEEP is applied to injured lungs with reduced amounts of aeratable tissue.
- Ventilator-induced lung injury magnifies systemic inflammation by causing endothelial injury in distant organs (e.g., the kidneys) in a process called reciprocal organ crosstalk.
- The 3 pillars of lung protective ventilation are: 1) use of a normal (physiologic) tidal volume (4 - 8 mL/kg) that limits Pplat to < 30 cm H_2O or driving pressure (Pplat -PEEP) to ≤ 15 cm H_2O , 2) sufficient PEEP to re-establish FRC towards normal (e.g., 10-15 cm H_2O), and minimizing the toxic effects of oxygen by achieving an adequate PaO_2 on an $\text{FIO}_2 < 0.60$.

PRONE POSITIONING

Awake prone positioning

Prior to the COVID-19 pandemic, awake prone positioning (APP) for non-intubated patients was reported to improve oxygenation in 5 case series or small cohorts.²³⁵ During the COVID-19 pandemic, clinicians sought measures to improve oxygenation and avoid intubation, especially during surges when ventilators were in short supply. As a noninvasive, easy-to-implement, and no-cost treatment, APP fits well for this situation and has been broadly utilized since the COVID-19 pandemic began.

As of May 2022, 10 randomized controlled trials (RCTs)^{106, 235-244} and one quasi-RCT¹⁰⁸ have compared APP with standard care (supine position) for patients with COVID-19 induced acute hypoxemic respiratory failure (AHRF). All RCTs did not find significant differences in intubation rate, except for the large meta-trial implemented by Ehrmann et al.¹¹⁷ In the follow-up meta-analysis published by Li et al in March 2022,¹⁰⁹ 9 out of 10 RCTs^{106,237-244} were included, together with another RCT that had not yet been published,²⁴⁵ they found that APP reduced the need for intubation, particularly among patients who required advanced respiratory support (HFNC or CPAP/NIV).¹⁰⁹ No significant differences in

intubation risk were found between APP and standard care for patients receiving conventional oxygen therapy or those treated in general wards.¹⁰⁹ The findings of Li et al¹⁰⁹ agreed with a recently published RCT by Alhazzani et al.²³⁶ In that study, while they did not find significant differences in intubation rate between APP and standard care groups, they reported a lower risk of intubation for patients who received HFNC in their subgroup analyses.²³⁶

Qian et al¹⁰⁸ reported worse clinical outcomes on day 5 among patients receiving APP in their quasi-RCT. In this study, over 2/3 of enrolled patients received conventional low-flow oxygen therapy. With the incorporation of the results from the 2 more recent RCTs,^{108,236} an updated meta-analysis found unchanged results with Li et al (Figure 13),¹⁰⁹ which supports APP for patients with COVID-19 induced AHRF, especially those needing HFNC or CPAP/NIV.¹⁰⁹

The daily duration of APP was associated with treatment success, particularly in patients who were in the prone position for at least 8 hours/day. Awake patients in the prone position for less than 8 h/day were more often intubated.^{106,110} The association of duration and treatment success may explain the non-significant

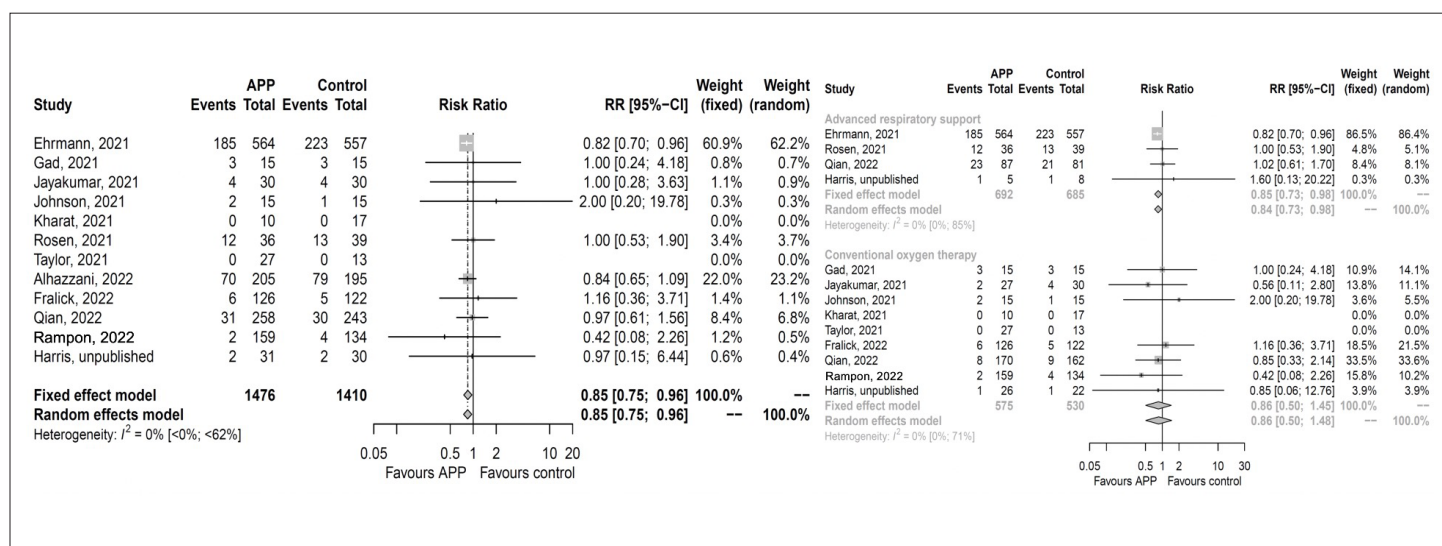


Figure 13. Awake prone position reduced the need for intubation, particularly among patients who required advanced respiratory support (HFNC or CPAP/NIV). Updated analysis from Li J, Luo J, Pavlov I, Perez Y, Tan W, Roca O, et al. Awake prone positioning for non-intubated patients with COVID-19-related acute hypoxaemic respiratory failure: A systematic review and meta-analysis. *Lancet Respir Med* 2022;10(6):573-583

differences in most RCTs,^{109,236,237} as few patients in the APP groups achieved 8 hours/day in the prone position.

Unlike prone positioning for intubated patients, APP duration relies on patient adherence and tolerance, which can be affected by various factors. Future studies investigating influential factors on APP compliance/tolerance and related studies with care bundles to improve patient adherence/tolerance to APP are needed. Besides APP duration, determining when to initiate APP plays a critical role in improving treatment success. Kaur et al reported that early initiation of APP (defined as starting APP within 24 hours of HFNC use) could improve survival for patients with COVID-19 induced AHRF.²⁴⁶

There are concerns that APP might delay intubation due to transient improvement in oxygenation.¹⁰⁸ As such, it is crucial to assess patient response to APP and evaluate the need for an escalation of treatment. In a post-hoc analysis of an RCT comparing APP with standard care for patients receiving HFNC for COVID-19 induced AHRF, Mirza et al²⁴⁷ reported an average improvement in $\text{SpO}_2/\text{FIO}_2$ at day 2 $\geq 11.5\%$ and pre-prone $\text{SpO}_2/\text{FIO}_2 \geq 150$ were possible predictors of APP treatment success. Similarly, Ibarra-Estrada et al¹¹⁰ reported that a lower breathing frequency (< 25 breaths/min), an increase in ROX > 1.25 after the first APP session, APP duration of > 8 hours/day, and a decrease in lung ultrasound score ≥ 2 within the first 3 days were significantly associated with APP treatment success. To confirm these findings, the study investigators conducted a prospective observational study on 74 subjects with COVID-19 induced AHRF.²⁴⁸ In that study, lung ultrasound assessment was more sensitive than ROX or $\text{SpO}_2/\text{FIO}_2$ changes in predicting APP treatment success. A reduction in lung ultrasound score at dorsal lung zones > 1 after the first APP session was associated with decreased risk for intubation.²⁴⁸ Therefore, it appears that a lung ultrasound assessment on patient response to the first APP session, especially in the dorsal lung zones, predicts the need for treatment escalation. If not available, changes in ROX during the first APP session or $\text{SpO}_2/\text{FIO}_2$ changes after APP on the second day might be used to assess the need for treatment escalation.²⁴⁷ Further studies are needed to evaluate the benefits of the early treatment escalation guided by those assessments.

In conclusion, APP should be used for patients with COVID-19 induced AHRF, especially for those patients who are indicated for HFNC or CPAP/NIV therapy. APP should be initiated as soon as the HFNC treatment is indicated and should be applied preferably 8 hours/day until HFNC is discontinued. After the first session of APP, a reduction in lung ultrasound score at dorsal zones > 1 or an increase in ROX index > 1.25 might indicate a lower risk for intubation.

Prone position in intubated patients

Since the PROSEVA trial was published,²⁴⁹ prone positioning has been recommended for intubated patients with ARDS and $\text{PaO}_2/\text{FIO}_2$ less than 150 mm Hg.²⁵⁰ During the COVID-19 pandemic, prone positioning was used to treat nearly 70% of intubated patients with COVID-19.^{241,251,252} Unlike APP, no RCTs have been published comparing the effects of prone positioning versus standard care for intubated patients with COVID-19.²⁵³ While it is unclear why RCTs were not conducted, it probably indicates that prone positioning for intubated patients with COVID-19 was generally accepted and adopted in clinical practice due to previous non-COVID-19 related research. Instead, published studies have focused on exploring the mechanisms of prone positioning in improving oxygenation and avoiding ventilator-induced lung injury, as well as influential factors on mortality.

Using a $\text{PaO}_2/\text{FIO}_2$ improvement of 20 mm Hg after prone positioning as an indicator of oxygenation response, the proportion of oxygenation responders to prone positioning varied from 72%-79% in 3 multi-center retrospective studies among intubated ARDS patients with COVID-19.²⁵⁴⁻²⁵⁶ This response rate was similar in patients with non-COVID-19 ARDS,²⁵⁴ and responders were found to have lower mortality than non-responders.^{254,256} Notably, these 3 studies defined the oxygenation responses based on the first prone positioning session.²⁵⁴⁻²⁵⁶ Weiss et al²⁵⁷ observed no significant differences in oxygenation improvement in the first prone positioning session between subjects who survived and those who died or were placed on ECMO. They found that, during the second and third prone positioning sessions, subjects who survived continued to respond to prone positioning while those who died or were placed on ECMO had no longer responded.²⁵⁷ This finding suggests that clinicians should not only evaluate patient response to prone positioning in the first session but also in the next 2 consecutive sessions, in order to decide if treatment escalation is needed.

Three prospective studies utilized computed tomography (CT) to assess the lung morphological changes during prone positioning for intubated subjects with COVID-19,²⁵⁸⁻²⁶⁰ with the aim to explain the oxygenation responses to prone positioning. In all 3 studies, it was observed that recruitment occurred in the dorsal lung zones and de-recruitment occurred in the ventral lung zones.²⁵⁸⁻²⁶⁰ Rossi et al²⁶⁰ pointed out that the oxygenation response was correlated with the balance of the 2 changes. More recruitment in dorsal lungs than de-recruitment in ventral lungs not only improves oxygenation,²⁶⁰ but also reduces atelectrauma.²⁵⁸ Additionally, they found a reduction in over-aerated lung zones during prone positioning.^{258,259} Overall, the dead space/shunt ratio decreased significantly after

prone positioning, indicating an improved ventilation-perfusion matching.²⁵⁸ Notably, prone positioning in all the 3 studies were conducted in the computed tomography (CT) room, with a short interval between prone positioning and the CT scan (about 5 minutes). As such, the changes in CT scans only reflect short-term patient responses to prone positioning, while lung morphological changes under prone positioning over time remain unclear.

A retrospective study was conducted to report the results of the prolonged use of prone positioning for 61 intubated subjects with COVID-19 with a mean $\text{PaO}_2/\text{FIO}_2$ of 95 mm Hg.²⁶¹ Prone positioning was applied without daily supine positioning and 42 (69%) survived. However, there were no significant differences in the duration of the first prone positioning session between survivors and non-survivors (3.0 versus 3.3 days).²⁶¹ Notably, there were many serious adverse events during the prolonged prone positioning that included 64% of subjects requiring endotracheal tube repositioning and 71% having ventral surface wounds.²⁶¹ Recently, an RCT was implemented to compare the use of 24-hour prolonged prone positioning with traditional prone positioning for 16 hours.²⁶² Compared to the 16-hour prone duration group, patients in the 24-hour prone duration group had similar total prone duration (in terms of days prone) and adverse events but fewer sessions.²⁶² Moreover, the incidence of adverse events was lower than that in the retrospective study which had an average prone duration of 3 days. Thus, the 24-hour prolonged prone positioning seems promising. However, more studies with cautious evaluation, especially over 24 hours, are still warranted.

Key points

- Current evidence supports the use of APP for non-intubated patients with COVID-19 induced acute hypoxemic respiratory failure to reduce the need for intubation.
- APP is indicated for patients who require advanced respiratory support including HFNC and CPAP/NIV.
- APP should be initiated as soon as patients require HFNC.
- A duration of 8 hours/day of APP is recommended. Efforts should be made to improve patient compliance/tolerance to APP.
- After the first session of APP, a reduction in lung ultrasound score at dorsal zones > 1 or an increase in ROX index > 1.25 might indicate a lower risk for intubation.
- Oxygenation improvement after prone positioning for intubated patients with COVID-19, especially continuum of oxygenation response in the consecutive prone positioning sessions, may indicate a better outcome.
- After prone positioning for intubated patients with COVID-19, the balance of the recruitment in dorsal lung zones and the de-recruitment in ventral zones decides the oxygenation response.
- Prolonged prone positioning for 24 hours rather than 16 hours might help reduce the frequency of repositioning, but its safety and effectiveness needs additional studies to confirm the benefit.

HUMIDIFICATION

Humidification of inspired gases via active or passive humidification is a standard of care during invasive ventilation, HFNC, and NIV for acute respiratory failure.²⁶³⁻²⁶⁵ During mechanical ventilation, heated humidification (HH) with a heated wire circuit (HWC) is commonly used during the acute phase of respiratory failure, particularly with lung protective ventilation. Heat and moisture exchangers (HME), without or with a filter (HMEF) are more commonly used in the operating room and for short-term ventilation.²⁶³⁻²⁶⁶

The use of HMEs in critical care has been associated with progressive narrowing of the artificial airway with secretions, with significant increases in airway resistance commonly occurring on day 3 of mechanical ventilation.^{267,268} This occurs because the HME is a passive humidifier, returning a portion of the heat and humidity exhaled by the patient. Even the best HMEs result in a net loss of moisture from the respiratory tract over time. In the presence of increased airway secretions, high minute ventilation, and elevated body temperatures, this moisture loss has consequences.

Additionally, the use of an HME adds to the mechanical dead space of the ventilator circuit.²⁶⁹⁻²⁷² When HMEs were first introduced, tidal volumes during mechanical ventilation were routinely at 10-15 mL/kg. At these volumes, an HME of 60-100 mL internal volume represented only 10-15% of the V_T . With current lung protective approaches and V_T of 350-500 mL, the addition of an HME and the catheter mount contributes significantly to the volume of gas rebreathed. Lellouche and colleagues²⁷⁰⁻²⁷² have contributed a number of papers demonstrating the untoward effects of passive humidifiers on CO_2 elimination.

During COVID-19, using of a passive humidifier with a filter poses some theoretical advantages related to reduced environmental contamination of exhaled gases in patients with a febrile respiratory illness spread via respirable particles. While this potential advantage has not been studied, the placement of an HMEF or a circuit filter may offer the staff some additional comfort related to safety. Of course, this is no substitute for properly worn personal protective equipment.

At least in one instance early in the pandemic, concerns over condensate in the ventilator circuit prompted one group to turn off heated humidifiers.²⁷³ Not unexpectedly, this was followed by occluded endotracheal tubes with thick airway secretions. Further concerns for staff safety prevented use of bronchoscopy and other airway clearance techniques compounding the problem. The story of COVID-19 includes several unintended consequences of well-intentioned actions.

Risk of ETT occlusion

COVID-19 is characterized by severe hypoxemic respiratory failure and ARDS that requires prolonged mechanical ventilation. However, COVID-19 is also severe viral sepsis and pneumonia often complicated by hypotension and the need for vasopressors. Alterations in lung mechanics associated with COVID-19 pneumonia include increased V_D/V_T and as with any febrile illness, minute ventilation requirements are elevated.^{15,274} In this context, the risk for ETT occlusion in COVID-19 may be elevated.²⁷⁵ Use of an HME appears to increase the risk of retained secretions and ETT obstruction in COVID-19.²⁷⁶

Wiles and colleagues reported a cases series of endotracheal tube obstruction in invasively ventilated patients with COVID-19.²⁷⁵ They described 19 patients with COVID-19 experiencing partial or complete ETT obstruction over a period of 2 months. During this same timeframe, no ETT obstructions were identified in non-COVID patients. Half of patients exhibited hypercoagulability and the average duration of ventilation at the time of ETT obstruction was 14 days. Examination of airway secretions revealed mucin mixed with necrotic cell debris, degenerated inflammatory cells, oral contaminants, and red blood cells. Another group described sloughing of airway epithelium as a possible cause of ETT obstruction in COVID-19. In a series of 110 patients, they reported ETT obstruction in 28 patients requiring emergent endotracheal tube change.²⁷⁷ In this case series, all patients were ventilated with heated humidification and heated wire systems. Another potential cause is that, secondary to reduced staffing, patient

surge, and concern for infection, suctioning frequency was reduced compared to normal ICU care. These rates of airway obstruction far exceed rates under normal conditions. COVID-19 pneumonia and possibly secondary bacterial infection appear to increase the risk of ETT obstruction and requires attention to maintain adequate humidification and secretion removal.

Environmental Conditions

Nearly 20 years ago, Lellouche and colleagues demonstrated that high gas temperatures generated by turbine-based ventilators and environmental temperatures can impact delivered humidity with both HH and HME.²⁷⁸ More recently, this group reported a number of endotracheal tube occlusions associated with HH, but not HME, in patients with COVID-19.²⁷⁹ They attributed this finding to changes in environmental conditions.

During the pandemic, conversion of ICU rooms to negative pressure rooms often involved homemade systems including the use of large fans and heating and air conditioning conduits. The report by Lavoie-Berard et al²⁷⁹ from Quebec City, a city at a northern latitude where air conditioning is rarely required is noteworthy. The authors found that during the summer months, increased air temperatures in the hospital were associated with decreased humidity output by HH. They monitored heater plate temperatures and increased the maximum heater plate setting, effectively eliminating further incidences of ETT obstruction. They also restored ambient temperatures. This represents another case of unintended consequences during COVID-19.²⁸⁰

There is clearly a signal for increased secretions and greater risk of ETT obstruction during COVID-19. Prolonged mechanical ventilation, airway debris, minute ventilation requirements and elevated body temperatures all conspire to conflate this complication. Attention of humidification is critical during care of the COVID-19 patient.²⁸¹

Key Points

- COVID-19 pneumonia is often associated with thick and copious secretions.
- HMEs provide insufficient humidity over time in COVID-19 patients.
- HME dead space can hinder gas exchange in severe ARDS.
- There is an increased incidence of ETT obstruction in COVID-19 pneumonia.
- Changes in environmental conditions associated with creation of additional ICU space and negative flow rooms can alter humidifier operation.

POST-EXTUBATION STRIDOR FOLLOWING COVID-19

Post-extubation stridor is relatively uncommon in adults. When found, it is associated with prolonged intubation, excessive airway cuff pressures, agitation, multiple intubations, and a large ETT diameter relative to the native airway.²⁸² Post-extubation stridor following mechanical ventilation for COVID-19 has been reported at a much greater rate by several groups.²⁸³⁻²⁸⁵

It has been suggested that tracheobronchial sloughing associated with ETT tube occlusion in patients COVID-19 might also be related to post-extubation stridor.²⁷⁷ Others have attributed the increase in post-extubation stridor to active shedding of SARS-CoV-2.²⁸³ Like other issues, the findings in COVID-19 can be related to traditional pathophysiology. That is, patients with COVID-19 are more likely to have been emergently intubated, more likely to have received prolonged mechanical ventilation, and more likely to have had shock, and more likely to be nursed in the prone position.²⁸⁶ Together, these factors may explain the increase in post-extubation stridor beyond any specific COVID-19 pathophysiology.

Key points

- There appears to be an increased risk of post-extubation stridor in patients with COVID-19.
- Post-extubation stridor is likely related to prolonged ventilation, increased use of prone position and risk factors associated with airway injury in non-COVID disease.

SHARED VENTILATION

Shared ventilation or multiplex ventilation is a technique wherein a single ventilator is modified to allow ventilation of more than 1 patient.²⁸⁷ Prior to COVID-19 there were 6 publications regarding shared ventilation²⁸⁸, 3 of these²⁸⁹⁻²⁹¹ cautioning authors of the other 2^{292, 293}, that this technique was far more complicated and fraught with complications than these naïve publications claimed. By the Spring of 2022, there were over 50 published papers on shared ventilation.

Ethics

While most shared ventilation publications focus on how to modify a ventilator and or ventilator circuit to provide shared ventilation, the ethics of shared ventilation were awakened by the COVID-19 pandemic. To be clear, there are no FDA-cleared devices that allow shared ventilation. Early in the pandemic, FDA allowed Emergency Use Authorization (EUA) of some molded or 3-D printed splitters or Y-pieces which were hailed by the manufacturers as a solution for a predicted ventilator shortage. They were not.²⁸⁷

Ethical issues surrounding shared ventilation pit 2 extremes. If there are insufficient numbers of ventilators and 1 patient receives a ventilator and the other does not, death is likely certain for the patient denied ventilatory support. However, if the 2 patients share a single ventilator, the outcome is less clear. In ideal circumstances, both patients might survive. It is also possible that the complexity of the technique, lack of specific monitoring and alarms, and inability to meet each individual patient's needs, may result in harm to one

or both. It is possible that with the limitations of shared ventilation coupled with patient severity of illness, both patients might die. This has led to the frequent suggestion that shared ventilation should be a technique of last resort.²⁹⁴⁻³⁰²

Of note, discussions of ethics during shared ventilation have been among the most thoughtful and well-written literature surrounding ventilation and COVID-19. Publication titles include references to Last Resorts²⁹⁸, Siren's Song³⁰², The Good The Bad and The Ugly²⁹⁵ and Desperate Times Call for Desperate Measures^{297,299}. Analogies for shared ventilation include lifeboats - do we use the lifeboat for the number of people intended, leaving some behind? Or do we overload the lifeboat and risk losing all passengers?³⁰¹ At its simplest, the choice of providing or denying shared ventilation is a decision of delivering the standard of care to some patients or a lower standard of care to a larger group of patients.

Answering the technical, how-to, question of shared ventilation is simply the tip of the iceberg. Even if the technical issues are solved, there remain substantial concerns related to training staff, monitoring patient response and clinical decision-making that must consider the impact on both patients, not just one. Cook³⁰⁰ provides the most scientific approach to this problem, finding a cut point for justification of shared ventilation based on the relationship of mortality during standard of care ventilation to shared ventilation (Figure 14). This model assumes that all patients denied mechanical ventilation will die and that the mortality rate of shared ventilation is not less than standard ventilation.

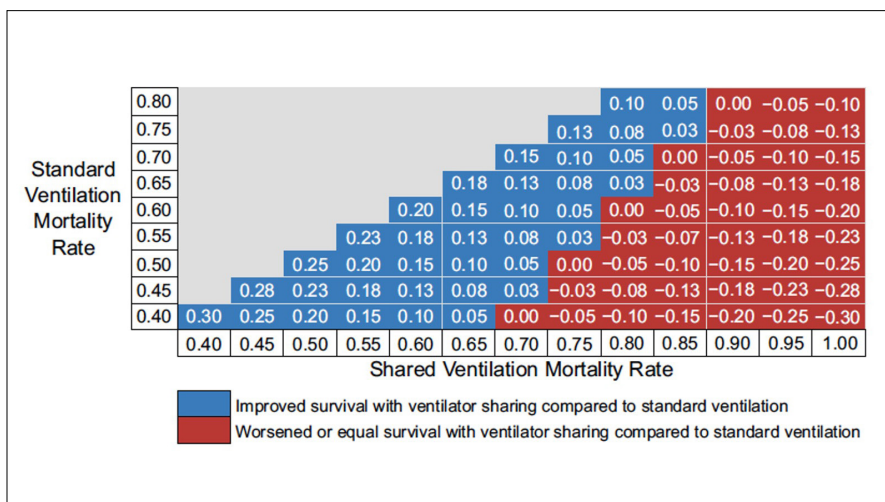


Figure 14. Comparing survival differences with shared or standard ventilation by their hypothetical mortality rates. The numbers within each cell represent the proportional change in survival with shared ventilation for a population of patients comparing the shown mortality rates. Four key assumptions are made in this analysis: (1) the shared ventilation strategy doubles treatment capacity (a condition that is unlikely to be met in practice), (2) all patients receive either shared ventilation or standard ventilation, (3) all patients not receiving ventilator treatment will die, and (4) the mortality rate of shared ventilation will not be less than standard ventilation. From Cook DC. Implementing shared ventilation must be scientific and ethical, or it risks harm. Br J Anaesth. 2020;125(1):e181-e3.

Principles of Shared Ventilation

Technologic modifications to circuits and ventilators aim to reduce the known risks of shared ventilation using a splitter to deliver gas to 2 patients. These modifications are minimal and are termed naïve systems.³⁰³ Distribution of ventilation and changes in end-expiratory lung volume with PEEP are primarily determined by individual lung mechanics resulting in an uneven distribution of delivered V_T . Monitoring and alarms have to be set for the system as a whole, not individual patients, creating safety concerns. A list of the risks of naïve shared ventilation are detailed in Table 10.

Proposed solutions

Moving beyond simply splitting the circuit between two patients, more sophisticated solutions employ several techniques to allow individual V_T and PEEP, independent monitoring of airway pressure and volume and preventing gas sharing between patients. Importantly, none of the proposed solutions for shared ventilation have overcome the requirement to prevent spontaneous breathing. Allowing spontaneous breathing increases the risk of cross-contamination and allows one patient to select the respiratory rate for both, leading to hyperventilation, hypotension, air-trapping and other untoward events. Providing separate FIO_2 for each patient has been described, but the modifications result in additional equipment and even greater concerns for safety.^{288,304}

Most shared ventilation systems include a splitter or Y-piece

to separate gas flow to the individual patients. One-way valves are placed in line with the inspiratory and/or expiratory limbs to reduce the chance of cross-contamination. In the inspiratory limb, a pressure relief valve, pressure regulator or pinch valve is used to modulate V_T between patients. This can take the form of a PEEP valve or a flow control valve such as a flexible tube compressed by a screw (much like a needle valve). The expiratory limb of the circuit includes separate PEEP valves or one PEEP valve. In the latter case, the ventilator controls PEEP in one patient and the PEEP valve controls PEEP in the other patient. In most cases, authors agree that shared ventilation requires the ventilator be set in pressure control. In volume control, sudden deterioration in one patient (pneumothorax, plugged endotracheal tube) results in all the V_T being delivered to the other patient (until the high-pressure alarm threshold is reached). These techniques have been described in detail elsewhere and further description is available in those publications.^{298,303-327}

Sorg et al³²⁸ have described a unique system that combines the splitter and flow control into a single component, using PEEP valves to provide differential PEEP and include a separate device (2 variable orifice flow transducers) to monitor V_T and pressure to each patient. Figure 15 depicts the system as a whole. Figure 16 demonstrates the adjustable flow diverter. The flow diverter acts as a splitter and the method for partitioning V_T . As the valve is rotated, the gas flow to one patient is reduced while the other is increased.

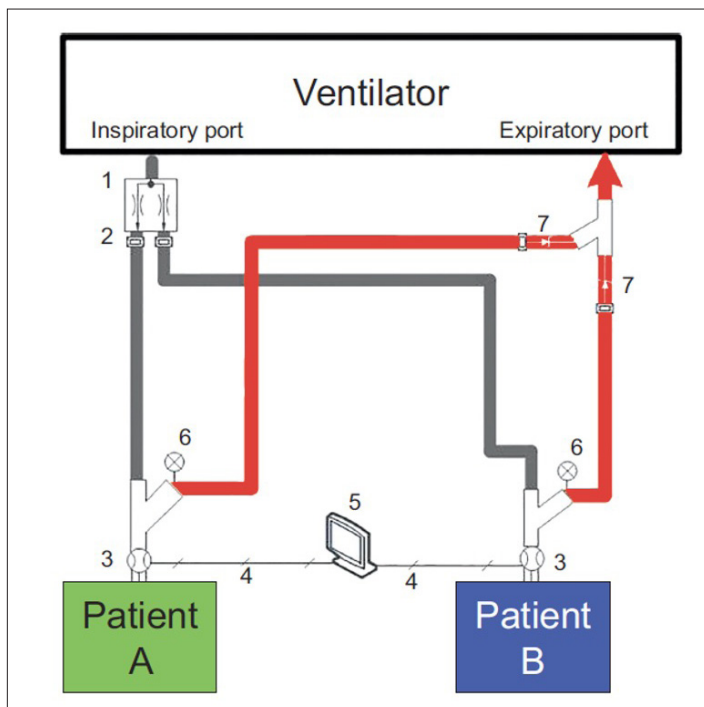


Figure 15. Modified multiplex ventilation circuit, (1) adjustable flow diverter valve, (2) one-way valves, (3) flow sensor, (4) flow signal from flow sensor, (5) dual volume display, (6) disposable PEEP display, (7) PEEP valve with internal one-way valve. From Sorg M, Branson RD, Hatipoglu U, Chatburn RL. Multiplex ventilation: Solutions for four main safety problems. *Respir Care* 2021;66(7):1074-1086.

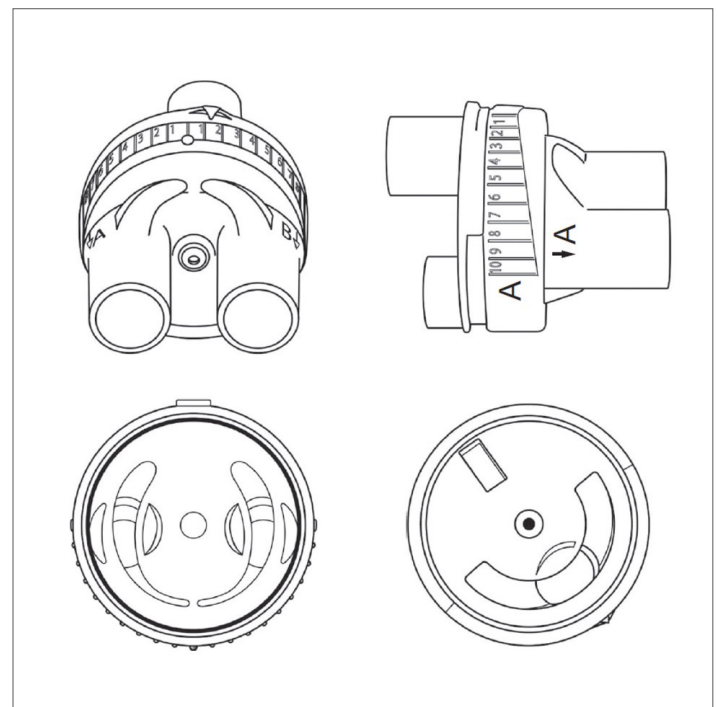


Figure 16. Adjustable flow diverter valve. Bottom images show exploded view. From Sorg M, Branson RD, Hatipoglu U, Chatburn RL. Multiplex ventilation: Solutions for four main safety problems. *Respir Care* 2021;66(7):1074-1086.

Table 10. Shared ventilations limitations in the absence of circuit modifications. From Branson RD, Rodriguez D, Jr. 2020 Year in Review: Shared Ventilation for COVID-19. *Respir Care*. 2021;66(7):1173-83.

- Uneven distribution of tidal volume between patients resulting in both hyperventilation and lung injury or hypoventilation.
- Uneven response to PEEP resulting in variable EELV, further uneven distribution of VT, atelectrauma or overdistension and hemodynamic compromise in the healthiest lung.
- Sharing of exhaled gases between patients at end inspiration as gas equilibrates resulting in cross infection.
- Spontaneous breathing has to be suppressed (paralysis) or one patient controls the respiratory frequency and exhaled gases can move from one patient to the other resulting in cross infection.
- Inability to monitor airway pressures and volumes for each individual patient.
- Alarms can only be set for the system as a whole, precluding identification of the clinical problem.
- Requirement for increased attention by the medical team to assure safety, taking away attention from other patients in a situation where staff is already short.
- Even if patients are matched for respiratory mechanics and ventilator requirements, it is highly unlikely for both patients to improve or decline in the same trajectory over a given timeframe.
- Sudden deterioration in one patient (pneumothorax, occluded endotracheal tube) can result in deterioration in the other patient (over ventilation, loss of ventilation).
- Requirement for a 'back-up' ventilator to treat one subject in a catastrophic situation.

The design of the valve is such that the cross-sectional area remains the same, allowing the pressure waveform to be unaltered. This system was tested in a simulator but was not used on patients.

Clinical experience

Raredon and colleagues described a system for shared ventilation, which used modified PEEP valves in the inspiratory and expiratory limbs of each circuit to control airway pressures. They describe ventilation of a pair of patients with respiratory failure due to COVID-19. Pulmonary compliance was 22 mL/cm H₂O and 26 mL/cm H₂O, respectively. The ventilator was set in pressure control. They observed the development of 2-3 cm H₂O of auto-PEEP and a slight rise in PaCO₂ in each subject. The latter was attributed to the added compressible volume of the circuit. Over 4 hours, gas exchange was maintained and no adverse events were identified.³²⁶

Levin et al³²⁷ described the ventilation of 2 pairs of subjects with COVID-19 for 1 hour each. Patients were matched for PEEP, FIO₂, and breathing frequency. Arterial blood gases were measured every 30 min, and V_T was adjusted independently using flow control valves during pressure control ventilation. Despite disparate lung mechanics between the patients, gas exchange was maintained.

The largest published trial of shared ventilation was described by Beitler and colleagues.³²⁹ They ventilated 3 pairs of individuals with ARDS due to COVID-19 for 48 hours each. Following informed

consent, subjects were matched by driving pressures measured during standard ventilation. No circuit modifications beyond a Y-piece to allow 2 circuits were made. However, a stand-alone respiratory monitor was used for each subject to continuously monitor airway pressure, volume, flow, and end-tidal PCO₂. All subjects were ventilated in pressure control ventilation, and all received neuromuscular blockade. One set of subjects was ventilated with an anesthesia ventilator. This caused several complications including excess humidity and resultant increased resistance of heat and moisture exchangers (HMEs) as well as frequent exhaustion of the CO₂ absorbent. When HMEs collected moisture, resistance increased with a resultant fall in V_T and rise in PaCO₂. The remaining pairs were ventilated with ICU ventilators without incident, although increased HME resistance and the attendant consequences were seen due to secretions. The investigators concluded that shared ventilation was feasible but that the additional attention and monitoring were counterproductive in a mass respiratory failure situation with a surge of patients and too few caregivers. They emphasized that institutional approval of a rigorous clinical protocol, informed consent from the patients' surrogates carefully matching of patient pairs and the use of continuous use of neuromuscular blockade were critical to success. Data for the 3 pairs of subjects ventilated with shared ventilation for 48 hours are shown in Figure 17.

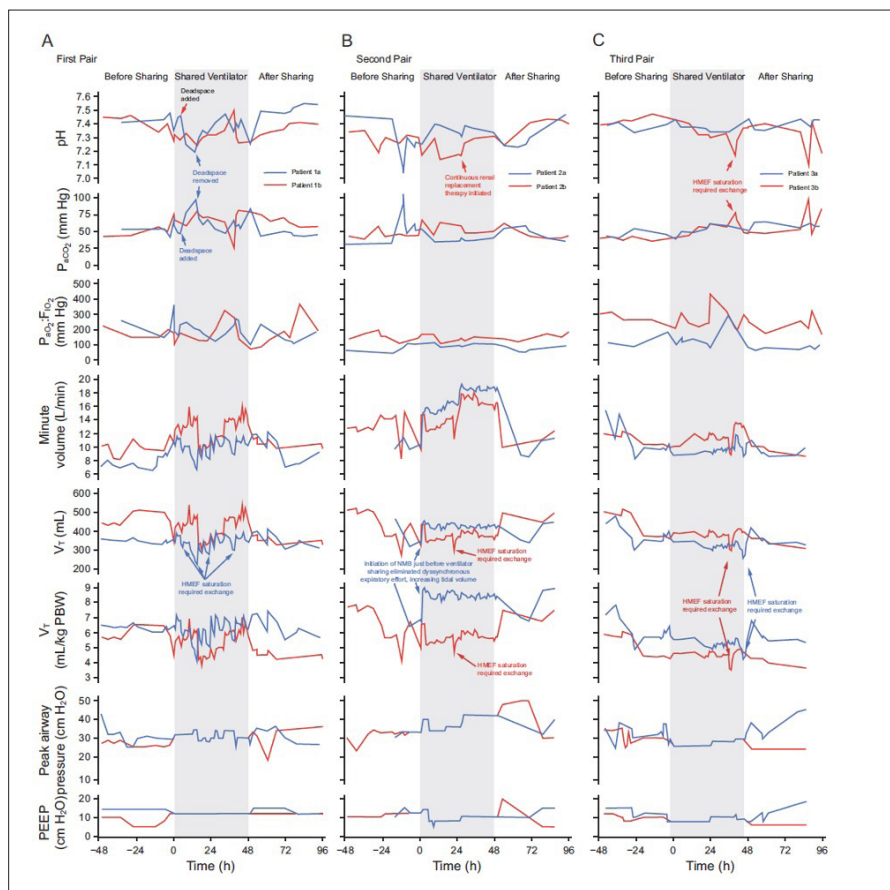


Figure 17. Clinical course of patients during ventilator sharing and for 48 h preceding and afterward. A: The first pair of subjects shared a repurposed anesthesia machine. Approximately 4.5 h after initiating ventilator sharing, Patient 1a became alkalemic (pH 7.46), whereas Patient 1b remained acidemic (pH 7.28). To treat alkalemia, dead space tubing was added to the circuit of Patient 1a, but the resulting pH was lower than intended; with removal of this dead space tubing, acidemia promptly improved. The HMEF had to be changed frequently for both patient circuits as CO₂ absorbent-related moisture buildup increased resistance, an effect most pronounced in Patient 1a. B: The second pair of subjects shared a full-feature ICU ventilator. Patient 2a's course illustrated the importance of ensuring steady-state ventilator requirements and reconfirming compatibility on neuromuscular blockade before initiating sharing. Patient 2a was intubated for 16 h prior to ventilator sharing. During compatibility assessment, ventilator settings were matched and well tolerated but compatibility was not reconfirmed after starting neuromuscular blockade in Patient 2a; the patient exhibited overt, dyssynchronous expiratory effort before paralysis, and eliminating respiratory muscle activity substantially increased V_T for a given driving pressure. Patient 2b was initiated on renal replacement therapy at 28 h for renal failure, which promptly increased pH. The patient's renal failure and plan for renal replacement predated ventilator sharing. C: The third pair of subjects shared a full-feature ICU ventilator. V_T and acid-base balance were well controlled during ventilator sharing, reflecting cumulative experience and protocol refinement with incorporation of lessons learned. Patient 3b experienced a transient decrease in V_T and pH and an increase in PaCO₂ around 36 h due to HMEF oversaturation, which promptly resolved with its exchange. HMEF heat and moisture exchanging filter; NMB neuromuscular blockade; V_T tidal volume. From Beitler JR, Mittel AM, Kallet R, Kacmarek R, Hess D, Branson R, et al. Ventilator Sharing during an Acute Shortage Caused by the COVID-19 Pandemic. *Am J Respir Crit Care Med*. 2020;202(4):600-6044.

Key Points

- Shared ventilation describes a technique where two patients are attached to 1 ventilator.
- Shared ventilation without modifications of the circuit to control V_T and PEEP allows mismatch of gas delivery with the patient with the best lung compliance receiving most of the V_T .
- Shared ventilation remains experimental and there are no FDA-approved devices to perform ventilation of more than one patient at a time.
- Reports of systems built with the intention of ventilating greater than 2 subjects at any one time have never been tested and should be avoided.
- Prior to consideration of how to perform shared ventilation, the ethics of shared ventilation must be explored. This includes mandatory informed consent from the patient's surrogate and institutional approval.
- The primary ethical question of shared ventilation is balancing the risk of standard of care for one patient while denying care to the other vs providing less than standard of care for both.
- The sum of reported applications of shared ventilation total less than a week.
- Shared ventilation should be avoided if possible and only used as a last resort.

THE STRATEGIC NATIONAL STOCKPILE VENTILATORS

At the beginning of the COVID-19 pandemic, the Strategic National Stockpile (SNS) included approximately 18,000 ventilators. This included 14,000 LTV-1200s from the most recent ventilator purchase and about 2000 each of the Impact 754 portable ventilators and Medtronic LP-10 home care ventilators.³³⁰ Early in the pandemic a number of LTV 1200s were sent to New York, Washington State, New Jersey and California. To our knowledge, none of the nearly 20-year-old caches of 754s or LP-10s were ever distributed.

Experience with the LTV-1200

The LTV-1200 was designed for home care, long-term care, and transport. The ventilator was packaged with a circuit, oxygen hose, HME and other disposable adapters. Figure 18 demonstrates the LTV-1200s delivered to a New York City hospital and the push pack with ventilators and ancillary supplies. Keeping track of the boxes with additional circuits was important. The yellow pelican case contained only 2 circuits. One area of concern was that the high-pressure hose was too short. The thought was that the ventilator would be connected to an oxygen cylinder in close proximity. In the ICU, the hoses for ventilators are typically 6 feet long or longer and the short hoses caused positioning problems. Longer oxygen hoses were actively sought for replacements.

All ventilators had an internal and external battery to allow patient movement. If batteries had not been charged and the ventilators had not been maintained, devices were delivered with dead batteries. This allowed the ventilator to operate on AC power, but some depleted batteries failed to charge. This led to concerns as patients from the emergency department were transported to the ICU and the battery only operated the ventilator for a few minutes before shutting down (<https://www.nytimes.com/2020/04/01/us/politics/coronavirus-ventilators.html>, accessed June 13, 2022).^{6,331}

The choice of the LTV-1200 included its ability to provide volume and pressure control breaths, pressure support, CPAP, and support for pediatric patients. The LTV-1200 also allowed measurement of inspired and expired V_T and adjustments for rise time, flow termination and adjustable bias flow. During early use, several shortcomings were revealed. Most ICU ventilators provide



Figure 18. Top. Ventilators delivered to respiratory therapy in New York City 2020. Bottom. Ventilators in the yellow boxes, cardboard boxes include 60 circuits, 120 HMEFs, metered dose inhaler adapters, 60 Suction catheters. Photos courtesy of Felix Kushid.

a set V_T with compensation for compressible volume. The LTV-1200 does not include this feature. The result was that, for the same set V_T , the V_T delivered to the patient was reduced. Most ICU ventilators have an attached heated humidifier. No heated humidifiers were

provided by SNS; all devices came equipped with HMEs. The addition of 60 mL of HME dead space reduced the effective V_T , resulting in an increase in PaCO_2 . Table 11 describes these changes. Finally, the LTV-1200 did not display pressure, volume, and flow waveforms. An optional waveform monitor (the LTM) had not been manufactured in over a decade. Clinicians viewed this as a major limitation when caring for patients with COVID-19 pneumonia and severe hypoxemic respiratory failure.⁶ In the absence of waveforms, asynchrony was difficult to assess for a generation of caregivers accustomed to waveform monitoring.

Finally, despite multiple education efforts by CDC, SNS and AARC, many clinicians had never used the LTV-1200 in their practice and found its use difficult. This is no surprise; ventilators are complicated devices and training on a new device commonly requires multiple in-services. The ventilators arrived with manuals, quick start guides and video instructions. There were also videos hosted online by AARC. During a patient surge, staff found it difficult to take the time to watch or read any training materials. Table 12 describes these challenges.

The rush to buy more and more ventilators was based on prediction that multiple cities would experience surges similarly to New York City. Fortunately, while large cities and rural communities suffered surges and shortages, these were in series not in parallel. The federal government set a target of 200,000 ventilators (<https://www.nytimes.com/2020/03/13/us/coronavirus-deaths-estimate.html?searchResultPosition=1>, accessed June 13, 2022). States, counties and municipalities all purchased devices as well. In retrospect, too many devices and devices lacking the capabilities to support patients with COVID-19 were procured. Many worried that these devices would be insufficient.²⁴

New Ventilators

A list of new ventilators purchased by SNS is shown in Table 13. Ventilators included one ICU ventilator (GE CareStation), several portable ventilators with ICU capabilities, transport ventilators and at least 1 ventilator intended to support ambulatory COPD patients who were not intubated (Hill-Rom). In 2 cases, the Federal Government invoked the Defense Production Act, encouraging automotive manufacturers to partner with ventilator manufacturers to speed production. The US government initially set a goal of purchasing 200,000 ventilators, which was reduced by about 25% as the pandemic progressed.⁸ The range of operation of the devices is quite stunning and comparison of features across the spectrum, demonstrates the nature of the purchases. A focus on quantity over quality resulted in purchases that were likely unnecessary and in

some cases likely to be of little value for patients with ARDS.³³² A few of these devices could be used for non-ARDS patients, but those patients were few during this pandemic.

To date there have been no published reports regarding the use of the new SNS ventilators in hospitals. There are reports of ventilator deliveries to US hospitals, but that is the limit of our knowledge (<https://www.freep.com/story/money/cars/general-motors/2020/04/17/gm-ventilators-ventec-coronavirus/5151821002/>, accessed June 13, 2022; <https://www.detroitnews.com/story/business/autos/general-motors/2020/04/17/first-ventilators-built-general-motors-arrive-chicago-hospitals/5152035002/>, accessed June 20, 2022). The ongoing stockpiling and maintenance of the ventilator stockpile will become a new challenge for the government. The expense of preventative maintenance and charging of batteries will be tens of millions of dollars. Just as important, education regarding device operation will be paramount. The possibility of training users on the 14 possible devices that might be delivered seems daunting. It might be wise for the SNS to decide to maintain the devices most likely to be useful in the next pandemic.

Respiratory therapists have been at the tip of the spear concerning the COVID-19 pandemic. From oxygen therapy, intubation, and prolonged mechanical ventilation, the therapist has literally been face-to-face with the SARS-CoV-2 virus. If the SNS ventilators are deployed in a future pandemic, it will be the role of the respiratory therapist to choose the device which best matches the patient's needs. In the case of ARDS, that will be less than half the ventilators currently housed in the stockpile.

Key points

- Delivery of ventilators from the SNS to several states in the Spring of 2020 prevented the need for rationing ventilators.
- During the COVID-19 pandemic, predictions for ventilator needs suggested numbers as high as 1 million ventilators; thankfully, these estimates were wrong.
- The federal government invoked the defense production act to have automobile manufacturers build ventilators in partnership with medical device manufacturers.
- There were 14 different ventilators purchased by the SNS ranging from ICU devices to devices with minimal functionality.
- Understanding the limitations of these devices and matching device to the patient requirements will be the purview of the respiratory therapist.

Table 11. Comparison between full feature ICU ventilator compared to a portable ventilator with regards to potential sources of decreased tidal volume (VT) which may help explain the differences in ventilation seen when switching between devices. Modified from Branson R, Dichter JR, Feldman H, Devereaux A, Dries D, Benditt J, et al. The US Strategic National Stockpile Ventilators in Coronavirus Disease 2019: A Comparison of Functionality and Analysis Regarding the Emergency Purchase of 200,000 Devices. Chest 2021;159(2):634-652.

	ICU Full Feature Ventilator	Portable Ventilator
Humidification	ICU ventilators typically have a heated humidifier	Switching to a portable ventilator using a heat and moisture exchanger (HME) adds dead space to the circuit. The dead space of an HME is typically 20-60 ml. At tidal volumes typically used for ARDS, this decreases the effective tidal volume (V_T) by 10-20%. SOLUTION – increase V_T upon transition to portable ventilator, and verify new set tidal volume is indeed equivalent to ICU ventilator V_T . Caveat – increased airway pressures with larger V_T .
Compressible volume compensation	ICU ventilators typically compensate for the loss of volume in the circuit secondary to tubing compliance. As an example, if set V_T is 400 mL and the peak pressure is 30 cm H ₂ O and with normal circuit compliance is 2-3 mL/cm H ₂ O, then 90 mL could potentially be lost in the circuit reducing V_T to 310 mL. The ICU ventilator would increase the V_T by 90 mL (490 mL) to assure the patient receives the full 400 ml V_T .	The transport ventilator does not compensate for compressible volume loss in the circuit due to tubing compliance. In the example, the effective V_T on the portable ventilator is then 90 mL less than on the ICU ventilator. At a respiratory frequency of 20 breaths/min this is a decrease in the minute ventilation of almost 2 L.
Pressure ventilation	ICU ventilators deliver pressures relative to (above) PEEP. As an example, if PEEP is 10 cm H ₂ O and the set pressure during pressure support or pressure control is 20 cm H ₂ O, then peak pressure would be 30 cm H ₂ O.	In bilevel devices and some portable ventilators, the pressure is absolute, and not set above PEEP. In the example, with settings of peak pressure of 20, this includes added PEEP and would therefore be only 10 cm H ₂ O above PEEP or expiratory pressure – a pressure difference of 10 cm H ₂ O vs 20 cm H ₂ O compared to the ICU ventilator.
Cumulative effect	Set V_T on the ICU ventilator and a portable ventilator result in different delivered V_T . If V_T is reduced by 90 ml due to compressible volume and HME dead space is 60 mL, the cumulative effect is a reduction in effective V_T by 150 mL or 38%.	The combination of the three factors above, which may each individually be only slight, can make a large difference in the delivered minute ventilation, reducing carbon dioxide elimination.

Table 12. Technologic, logistic, and educational challenges encountered with current SNS ventilators, and potential next generation SNS ventilator solutions. Modified from Branson R, Dichter JR, Feldman H, Devereaux A, Dries D, Benditt J, et al. The US Strategic National Stockpile Ventilators in Coronavirus Disease 2019: A Comparison of Functionality and Analysis Regarding the Emergency Purchase of 200,000 Devices. Chest 2021;159(2):634-652.

Challenges encountered with current SNS ventilators	Potential design solutions for next generation SNS ventilators
COVID-19 patients develop severe ARDS and were at times not able to be fully supported by an SNS ventilator – reduced monitoring capabilities and function not equivalent to ICU ventilators	SNS ventilators should have a full suite of features and compatible to treat severe ARDS
Logistic difficulties with SNS ventilators included short or absent gas hoses, insufficient amount of compatible disposable supplies, and some ventilators arrived damaged and/or requiring maintenance before they could be used.	SNS ventilators should include power cords and gas hoses long enough for use in most environments, standardized size, sufficient disposable components, and easy maintainability; and standard reliable maintenance in the SNS.
Health care professionals were not familiar with SNS ventilators, had difficulty setting them up, and did not have time to utilize the training materials.	Ventilator design should ensure that end-users are able to quickly and easily understand its use, with accompanying rapid-training materials for just in time education Healthcare organizations should consider maintaining a small inventory of SNS designated ventilators to provide their professionals ongoing device experience.
SNS ventilators were more difficult to use as they did not have graphics display information, could not connect to medical records, and were difficult to hear alarms	SNS ventilators should incorporate: • an intuitive touchscreen interface • Graphic displays of pressure, volume, and flow • Functionality to connect to varied electronic health records, easily audible alarm systems, and operable remotely from outside a patient room.
New SNS ventilators aren't all able to be used with pediatric patients	All future SNS ventilators must be designed to support pediatric patients
When sharing ventilators with international partners, compatibility with their current infrastructure is not always taken into account	The US should publish manuals and educational materials in the language of each international partner, with assured compatibility with their existing supplies and capacity for maintenance and repairs

Table 13. Ventilators acquired by the SNS during the COVID-19 pandemic.

Manufacturer/Ventilator	Intended use	Critical Care Ventilator*	Limitations
Airon GE-Ford/pNeuton AE	pNeuton is a pneumatic ventilator. Electrical power is not required for patient ventilation. pNeuton has been specifically designed for patient support during transport and non-critical care unit mechanical ventilation. It may be used during intra and inter-hospital transport, in aircraft, on ambulances, in emergency rooms, MRI and other radiology suites.	No	Minimum V_T – 360 mL No pressure control SIMV or CPAP only Fixed inspiratory flow of 36 L/min $FIO_2 = 0.65$ or 1.0 only Cannot operate on a low flow O_2 source Does not measure flow or volume Only analog pressure manometer Excess gas consumption Limited alarms
Hamilton /C1	The Hamilton-C1 ventilator is intended to provide positive-pressure ventilatory support to adults and pediatrics, and optionally infants and neonates. Intended areas of use: In the intensive care unit, intermediate care ward, emergency ward, long term acute care hospital, or in the recovery room and during transfer of ventilated patients within the hospital	Yes	Does not provide volume control ventilation (adaptive pressure ventilation when V_T is selected.)
Hamilton/ T1	The Hamilton-T1 ventilator is intended to provide positive-pressure ventilatory support to adults and pediatrics, and optionally infants and neonates. Intended areas of use: • In the intensive care unit, intermediate care ward, emergency ward, long term acute care hospital or in the recovery room • For emergency medical care • During transport within and outside the hospital • During transfer by rescue vehicles, fixed wing aircraft, helicopter or ship	Yes	Does not provide volume control ventilation (adaptive pressure ventilation when V_T is selected.)
Hamilton /C3	The Hamilton-C3 ventilator is intended to provide positive-pressure ventilatory support to adults and pediatrics and optionally infants and neonates. Intended areas of use: • In the intensive care unit, intermediate care ward, emergency ward, long term acute care hospital or in the recovery room • During transfer of ventilated patients within the hospital	Yes	Does not provide volume control ventilation (adaptive pressure ventilation when V_T is selected.)

General Electric/ Carescape R860	The CARESCAPE R860 ventilator is designed to provide mechanical ventilation or support to neonatal, pediatric, and adult patients weighing 0.25 kg and above. The CARESCAPE R860 ventilator is a microprocessor based, electronically controlled, pneumatically driven ventilator that includes integrated monitoring of FIO₂, airway pressure, flow, and volume. The system is designed for facility use, including within-facility transport, and should only be used under the orders of a clinician.	Yes	Does not provide volume control ventilation (adaptive pressure ventilation when V _T is selected.)
Hill-Rom/ Life 2000	The Life2000 Ventilator is intended to provide continuous or intermittent ventilatory support for the care of individuals who require mechanical ventilation. The ventilator is intended for use by qualified, trained personnel under the direction of a physician. Specifically, the ventilator is applicable for adult patients who require the following types of ventilatory support: • positive-pressure Ventilation, delivered invasively (via ET tube) or non-invasively (via mask). • Assist/Control mode of ventilation. • The ventilator is suitable for use in institutional settings.	No	No pressure control Assist Control only FIO₂ = 1 only Cannot operate on a low flow O₂ source Does not measure flow or volume Excess gas consumption Limited alarms PEEP 0 - 10 cm H₂O Tidal volume dependent upon entrainment of room air
Medtronic/ 560	The Puritan Bennett 560 Ventilator is indicated for the continuous or intermittent mechanical ventilatory support of patients weighing at least 11 lb (5 kg) who require mechanical ventilation. The ventilator is a restricted medical device intended for use by qualified, trained personnel under the direction of a doctor. It is essential to read, understand, and follow these instructions before use. The ventilator is suitable for use in institutional, home, and portable settings. It is not intended for use in Emergency Medical Service (EMS), such as an emergency transport.	No	FIO₂ 0.21-0.6 Cannot operate from high pressure O₂ system
ResMed/Astral	The Astral 100/150 provides continuous or intermittent ventilatory support for patients weighing more than 11 lb (5 kg) who require mechanical ventilation. The Astral device is intended to be used in home, institution/hospital and portable applications for both invasive and non-invasive ventilation	No	Cannot operate from high pressure O ₂ system

AutoMedx/SAVe II	The SAVe II series is intended to provide short-term ventilatory support to adults during CPR or when Positive Pressure Ventilation (PPV) is required to manage Acute Respiratory Failure (ARF). The SAVe II series is appropriate for adults that weigh at least 45 kg (approximately 99 lbs.). It is intended to be used in the pre-hospital, field hospitals and transport environments.	No	Minimum V_T – 200 mL No pressure control Volume assist control only Fixed inspiratory flow of 40 L/min I:E fixed at 1:2 – limits rate/V_T combinations FIO₂ = low flow only Cannot operate on a high pressure O₂ source PEEP = 10 cm H₂O Does not measure flow or volume Cannot display waveforms Digital display of PIP Limited alarms
Philips/EVO	The Trilogy Evo ventilator provides continuous or intermittent positive-pressure ventilation for the care of individuals who require mechanical ventilation. Trilogy Evo is intended for pediatric through adult patients weighing at least 2.5 kg. The ventilator can measure, display, record, and alarm SpO₂, FIO₂, CO₂, and Pulse Rate data when integrated with the appropriate accessories. The ventilator is suitable for use in institutional, home, and non-emergency transport settings for example wheelchair, or personal vehicle. It may be used for both invasive and non-invasive ventilation.	No	FIO₂ = low flow only Cannot operate from a high pressure O₂ source
Philips/EVO 300	The Trilogy EV300 ventilator provides continuous or intermittent positive-pressure ventilation for the care of individuals who require mechanical ventilation. Trilogy EV300 is intended for pediatric through adult patients weighing at least 2.5 kg. The ventilator can measure, display, record, and alarm SpO₂, FIO₂, CO₂, and Pulse Rate data when integrated with the appropriate accessories. The ventilator is suitable for use in institutional, home, and non-emergency transport settings for example wheelchair or personal vehicle. It may be used for both invasive and non-invasive ventilation. The Trilogy EV300 ventilator is intended to be used: • In institutional environments. • While attached to a roll stand or sitting on a flat surface such as a table or nightstand. • While transporting patients within and between facilities, such as an automobile or commercial aircraft.	No	Limited visibility of parameters from outside the room.

Vyarie/ LTV-2200	LTV2 Series ventilators are intended to provide continuous or intermittent ventilator support for the care of the patients requiring mechanical ventilation. The ventilator is a restricted medical device intended for use by qualified, trained personnel under the direction of a physician. Specifically, the ventilator is suitable for adult and pediatric patients weighing at least five kilograms (11 pounds) who require the following types of ventilator support: • positive-pressure Ventilation, delivered invasively or non-invasively • Assist/Control, SIMV, CPAP, or NPPV modes of ventilation The ventilator is suitable for use in institutional, home, or transport settings.	No	Cannot display waveforms. Limited visibility of parameters from outside the room.
Vyarie LTV 2150	LTV2 Series ventilators are intended to provide continuous or intermittent ventilator support for the care of the patients requiring mechanical ventilation. The ventilator is a restricted medical device intended for use by qualified, trained personnel under the direction of a physician. Specifically, the ventilator is suitable for adult and pediatric patients weighing at least five kilograms (11 pounds) who require the following types of ventilator support: • positive-pressure Ventilation, delivered invasively or non-invasively • Assist/Control, SIMV, CPAP, or NPPV modes of ventilation The ventilator is suitable for use in institutional, home, or transport settings.	No	FIO₂ = low flow only Cannot operate from a high pressure O₂ source Cannot display waveforms
Ventec GM/ V+ Pro	VOCSN V+ Pro Unified Respiratory System is intended to provide continuous or intermittent ventilatory support for the care of individuals who require mechanical ventilation. It may be used in invasive and non-invasive applications. VOCSN is intended for pediatric through adult patients weighing at least 5 kg. It is intended for use in home, hospital, institutional, and transport settings, including portable applications.	Yes	Limited visibility of parameters from outside the room.
Zoll/ EMV 731	Each model of the ZOLL 731 Series of Ventilators is indicated for use in the management of infant through adult patients weighing greater than or equal to 5 kg with acute or chronic respiratory failure or during resuscitation by providing continuous positive pressure ventilation. ZOLL Ventilators are appropriate for use in hospitals, outside the hospital, during transport and in severe environments where they may be exposed to rain, dust, rough handling, and extremes in temperature and humidity.	No	Does not measure expired flow or volume Does not display flow or volume waveforms (pressure vs time is displayed).

*To be classified as a critical care ventilator, the device must have the ability to set the FIO₂, measure tidal volume and flow, display ventilator waveforms, provide pressure and volume control, deliver inspiratory flow > 60 L/min and PEEP at least 20 cm H₂O.

ANESTHESIA VENTILATORS IN THE ICU

Following the first SARS CoV group of infections in the early 2000s, several authors suggested that anesthesia workstations from the operating theater could provide a source of additional ventilators in the case of a surge of patients with respiratory failure.^{330,333,334} Most current anesthesia workstations have modern ventilators with the capability to perform multiple modes of ventilation and contain a full suite of monitoring equipment. Logically this made perfect sense.

Uniformly, the experience with anesthesia ventilators in the ICU during COVID-19 was fraught with unforeseen problems.³³⁵⁻³⁴¹ This was in part a consequence of device design. Anesthesia ventilators were meant to be used with anesthesia personnel in proximity and for short-term use. Alarm volumes are set low and the device must be checked out much like a pre-use test every 24 hours. For this check, the patient must be disconnected from the ventilator.

The CO₂ absorbent in the anesthesia machine typically is used short-term in the operating room and at nominal minute ventilations. In the ICU, in patients with viral sepsis and ARDS, minute ventilation and CO₂ productions were elevated. The by-product of absorption of CO₂ is heat and water. Reports from the ICU regarding use of anesthesia devices demonstrated excessive rain out in ventilator circuits and multiple issues dealing with water.^{337,338,341,342}

Many other problems were identified. These included the lack of a heated humidifier, the presence of vaporizers on the anesthesia machine, the use of fresh gas flow, and variable methods for setting FIO₂.³³⁵ Tables 14 and 15 describe the differences in anesthesia ventilators and ICU ventilators as well as commonly reported problems and possible mitigations.

Bottiroli et al³³⁸ performed a retrospective review of COVID-19 patients ventilated with traditional ventilators compared to those ventilated with an anesthesia ventilator. This was not a randomized trial; patients were in different care sites and there were far fewer patients on the anesthesia ventilators than ICU ventilators (17 versus 72). Importantly, mortality rate in the group on anesthesia ventilators was 70% versus 37%.³³⁸ At a minimum, this report should give us pause on the use of anesthesia devices in the ICU. More importantly, if this is part of a surge strategy, these problems should be addressed prior to an event with education and practice.

Key Points

- Ventilators within anesthesia workstations have been proposed as possible surge capacity for ventilator shortages.
- There are important differences in the intended use and operation of anesthesia ventilators compared to ICU ventilators.
- Monitoring, alarms, humidification and rain-out were all identified as limitations of anesthesia ventilator use in the ICU.

Table 14. Differences in ICU ventilators and anesthesia ventilators. From Austin PN, Branson RD. Anesthesia Machine Ventilators for Use in Critical Care During the COVID-19 Pandemic. *Respir Care* 2021;66(7):1184-1195.

Summary of Important Differences Between an Anesthesia Machine and a Critical Care Ventilator	
Anesthesia Machine	Critical Care Ventilator
Major Differences	
Operates as a non-rebreathing, partial rebreathing, or complete rebreathing system by using a circle breathing system where exhaled gases can be recycled and reintroduced with fresh gas flow	Operates as a non-rebreathing system, does not use a circle system
Equipped with a CO ₂ absorber (if depleted, may result in increased inspiratory CO ₂ and hypercapnia)	No need for a CO ₂ absorber
Can deliver manual or mechanical ventilation	Delivers only mechanical ventilation
FIO ₂ determined by settings on the gas flowmeters or an FIO ₂ control	The operator directly sets the FIO ₂
Equipped with a scavenger system that prevents pollution of room with anesthetics	No need for a scavenger system
Other Differences	
Operated by a continuously present anesthesia provider, maintained by an anesthesia provider or anesthesia technician	Operated and maintained by a respiratory therapist
Delivers O ₂ and other gases such as air and nitrous oxide and volatile (inhaled) anesthetics (such as isoflurane, sevoflurane and desflurane)	Typically delivers only O ₂ and air
Requires an operator in attendance at all times	Not required for the operator to be with the device at all times
Designed for intermittent use during a single day with multiple patients	Designed for continuous use for days with the same patient
Alarm volume may not be loud enough to be heard in the critical care unit	Alarm volume designed to be heard in a critical care unit
Alarms do not interface with the hospital nurse call alarm system	Alarms may generate alerts in the hospital nurse call alarm system
May contain residual amounts of anesthetic agents in the breathing system (remote risk of malignant hyperthermia)	Does not contain residual amounts of anesthetic agents
Often has an integrated gas and anesthetic monitor	May contain or interface with a gas monitor
May have a physiologic monitor	Typically, no integrated physiologic monitor
May interface with an electronic anesthesia record (that ultimately becomes part of the patient record) but not directly with the patient electronic medical record	May interface directly with the patient electronic medical record
Rarely used with a heated humidifier	Commonly used with a heated humidifier

Table 15. Potential Problems When Ventilating a COVID-19 Patient Using an Anesthesia Machine - Possible Causes and Possible Mitigation Steps. From Austin PN, Branson RD. Anesthesia Machine Ventilators for Use in Critical Care During the COVID-19 Pandemic. *Respir Care* 2021;66(7):1184-1195.

Problem	Possible Cause	Steps to Help Mitigate the Problem
Respiratory therapist and critical care physicians unfamiliarity with anesthesia machines	It is not expected for respiratory therapists to be familiar with anesthesia machines	All stakeholders should be involved with the policy and procedure of using the anesthesia machine as a ventilator including their responsibilities and methods of communication
Excess water in the breathing circuit	Water production from CO ₂ removal by the CO ₂ absorber	FGF higher than minute ventilation (may be 1.5 times minute ventilation or more) as this will decrease the need for the absorber to remove CO ₂ and decreasing the resultant water byproduct*; monitor closely
Occlusion of the HMEF located between the endotracheal tube and patient	Patient secretions and water	Monitor the condition of the HMEF Change periodically and as needed keeping in mind the possible need to conserve supplies
Frequent exhaustion of the CO ₂ absorber	Insufficient FGF	FGF should be greater than the minute ventilation (such as 1.5 times minute ventilation) to help decrease the need for the CO ₂ absorbent to remove CO ₂ from the exhaled breath*
Alveolar de-recruitment and possible hypoxemia when changing HMEF; breathing circuit or removing the patient from the anesthesia machine for anesthesia machine check out procedure	Decrease in airway pressure, FIO ₂ , and/or minute ventilation	Plan and rehearse procedures when the patient will be separated from the anesthesia machine
Excessive airway pressure and patient discomfort	Patient-ventilator asynchrony	Adjust the ventilation mode May have to switch to a critical care ventilator as it may not be possible to set the desired inspiratory time in a high minute ventilation scenario
Gas monitoring sample line tubing and/or water trap contamination or occlusion	HMEF not positioned to protect the gas monitoring sample line	Reposition HMEF appropriately, monitor closely
Anesthesia machine flow sensor malfunction	Excess moisture in the patient circuit	Be sure the HMEF is placed between the endotracheal tube and the patient connector on the breathing circuit; Use adequate FGF to help limit the amount of water production from the CO ₂ absorbent
Use with inline nebulizer	Not designed for use with an inline nebulizer	Closely monitor if a nebulizer is used
Leak compensation	Likely no leak compensation	Monitor closely if a breathing circuit leak is suspected, NIV with the anesthesia ventilator is not recommended

Quick emergency activation to deliver FIO ₂ 1.0	Not present on an anesthesia machine	Must adjust the flowmeters to deliver FIO ₂ 1.0
Unwanted activation of the oxygen flush valve with resulting increased airway pressure	Accidental activation of the valve by personnel	Orientation of non-anesthesia providers to the basic components and function of the anesthesia machine
Loss of electrical power to the anesthesia machine	Overloading of circuit breaker dedicated to the patient room	Carefully monitor the demands of the devices in the patient room
Lack of procedures for documentation of anesthesia machine settings and output from machine and physiologic monitors	Current documentation procedures may be problematic, anesthesia machine does not interface directly with the patient electronic medical record	Consult information technology personnel to determine if the anesthesia machine and physiologic monitors can interface directly with the patient record Identify a documentation procedure

*See the manufacturer for guidance on setting the FGF. Reports of using FGF of 10 L/min has been effective in limiting water production from the CO₂ absorbent.

CCV = critical care ventilator

FGF = fresh gas flow (flow per minute of O₂ and other gases such as nitrous oxide)

HMEF = Heat and moisture exchanging filter

LONG COVID

Some patients who have recovered from the acute phase of COVID-19 experience prolonged multiorgan symptoms and complications. Post-COVID-19 syndrome is defined as symptoms continuing more than 12 weeks after the onset of confirmed or probable SARS-CoV-2 infection not explained by an alternative diagnosis. Common symptoms include chronic cough, shortness of breath, chest tightness, cognitive dysfunction, and extreme fatigue.³⁴³ Although commonly called long COVID, it has also been called post-COVID-19 condition, post-acute sequelae of SARS-CoV-2 infection, and post-COVID syndrome (Table 16).³⁴⁴ The precise incidence of long COVID is unknown, but given the large number of individuals that have recovered from COVID-19, this has important public health implications. Because long COVID can be associated with respiratory symptoms, there are clear

implications for respiratory therapists. Pulmonary rehabilitation appears beneficial.³⁴⁵⁻³⁴⁷ However, available evidence does not support a role for bronchodilators, airway clearance therapy, or incentive spirometry for this patient population.

Key points:

- For some patients recovering from COVID-19, symptoms persist beyond 12 weeks; this is called long COVID.
- Pulmonary rehabilitation might have a role in the care of patients with long COVID.

Table 16. Definitions Used to Describe Long COVID. Adapted from Long COVID: aiming for a consensus. Munblit D, O'Hara ME, Akrami A, Perego E, Olliaro P, Needham DM. *Lancet Respir Med* 2022

Name	Developed By:	Definition
Long COVID	Patients and people with lived experience.	Symptoms and sequelae that continue or develop after acute COVID-19 for any period of time; generally multisystemic; might present with a relapsing-remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events.
Post-COVID-19 condition	World Health Organization	Occurs 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis; common symptoms include fatigue, shortness of breath, and cognitive dysfunction, and generally have an impact on everyday functioning; symptoms might be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness; symptoms might also fluctuate or relapse over time.
Ongoing symptomatic COVID-19	National Institute for Health and Care Excellence	Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks
Post-COVID-19 syndrome	National Institute for Health and Care Excellence	Symptoms that develop during or after COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis; usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body; post-COVID-19 syndrome might be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.
Post-COVID conditions	Centers for Disease Control and Prevention	Physical and mental health consequences experienced by some patients that are present 4 or more weeks after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection
Post-acute sequelae of SARS-CoV-2 infection	Centers for Disease Control and Prevention	Persistent or new symptoms after COVID-19 infection.

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DISCLOSURES

Richard D. Branson

Daedalus Enterprises
Engineered Medical Systems
Pfizer
Mallinckrodt
Ventec Life Systems
Vyaire
Lungpacer
Zoll
Department of Defense

Dean R. Hess

Daedalus Enterprises
American Respiratory Care Foundation
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