to some of these approaches. According to a 2019 survey\(^1\) of 4030 US adults residing in households with firearms, 76% to 89% reported that clinicians should “sometimes” or “always” discuss firearm safety with patients as part of routine care in certain clinical scenarios (such as if the patient or family member is at risk for suicide, has mental health or behavioral problems, has alcohol or substance use disorders, has been affected by domestic violence, or has dementia). Other approaches for health care professionals\(^2\) may include involvement in community, state, or national initiatives and activities that support violence prevention from a public health perspective and—depending on the individual physician’s values, perspectives, and beliefs about firearms—consideration of supporting regulatory and legislative measures that limit the availability of firearms.

Without deliberate action, firearm-related violence will not abate. As the articles in this issue of *JAMA* highlight, addressing the challenges, devastation, and complexity of firearm violence will require comprehensive, evidence-based, adequately funded, multidisciplinary approaches involving physicians and other health care professionals, public health leaders, researchers, criminal justice experts, and social scientists partnering with legislators, policy makers, and community leaders. The devastating and unrelenting epidemic of firearm-related violence merits urgent attention and action.

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Respiratory Support in the Time of COVID-19

Alistair D. Nichol, PhD; Cecilia O’Kane, PhD; Daniel F. McAuley, MD

**COVID-19 infection commonly causes pneumonitis**, which can result in acute hypoxemic respiratory failure (AHRF).\(^1\) While many hospitalized patients recover after only requiring conventional oxygen therapy (typically nasal cannula or face mask oxygen), a number of patients require additional noninvasive respiratory support, such as high-flow nasal oxygen (HFNO), continuous positive airway pressure (CPAP), and noninvasive ventilation (NIV). Despite this support, however, a significant proportion of patients experience clinical deterioration necessitating invasive mechanical ventilation and these patients are at high risk of death and significant morbidity.\(^1\)

The optimal initial method to provide noninvasive respiratory support to patients with COVID-19–related AHRF is subject of significant controversy. Early in the pandemic, there was marked variability in guideline recommendations on the use of noninvasive respiratory support,\(^2\) particularly HFNO. The decision to use noninvasive respiratory support was also constrained by resource capacity and concerns regarding aerosol generation and the perceived risk of nosocomial infection, although emerging evidence did not indicate higher risk of environmental contamination.\(^3\) As a result, the use of all forms of noninvasive respiratory support became widespread.

**RESOURCES**

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**Conflict of Interest Disclosures:** None reported.

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Several studies subsequently assessed the effect of different noninvasive respiratory support therapies to reduce intubation rates and mortality in patients with COVID-19–associated AHRF. The HENIOTV trial4 randomized 110 patients with COVID-19–related AHRF in 4 Italian hospitals to receive either helmet NIV or HFNO alone. Although there was no significant difference in the primary outcome of median days free of respiratory support within 28 days after randomization (20 days vs 18 days) or rate of in-hospital mortality (24% vs 25%) in the helmet NIV group vs the HFNO group, the rate of endotracheal intubation was significantly lower in the helmet NIV group than in the HFNO group (30% vs 51%; \( P = .03 \)).

The HiFiLo–Covid trial5 randomized 220 patients with COVID-19–related AHRF in 3 Colombian hospitals to receive either HFNO therapy vs conventional oxygen therapy (low-flow nasal prongs or face mask). The co–primary outcomes of rate of intubation/mechanical ventilation (34.3% vs 51.0%) and the median time to clinical recovery (11 days vs 14 days) were significantly reduced among patients treated with HFNO vs conventional oxygen therapy. However, there was no significant difference in day 28 mortality (hazard ratio, 0.49 [95% CI, 0.21–1.16]; \( P = .11 \)) in the HFNO group vs the conventional oxygen therapy group.

In a single-center trial, Nair et al6 randomized 109 patients with COVID-19–related AHRF to receive either face mask NIV or HFNO. The primary outcome of intubation rate by 48 hours did not differ between the groups. However, intubation rate by day 7 was lower in the HFNO group (27% vs 46%; relative risk, 0.59 [95% CI, 0.35–0.99]; \( P = .045 \)). Mortality at day 28 was 29% in the HFNO group and 46% in the NIV group (at \( P = .06 \)). This study was small, and the mortality rate was high in the NIV group, which may limit the interpretation of these findings.6

The RECOVERY-RS trial7 randomized 1273 patients with COVID-19–related AHRF at 75 centers using a design that separately compared CPAP (\( n = 380 \)) and HFNO (\( n = 418 \)) with a common shared control group of conventional oxygen therapy (\( n = 475 \)). There was a statistically significant reduction in the number of patients who met the composite primary outcome of tracheal intubation or mortality within 30 days, occurring in 36% of the patients in the CPAP group vs 44% in the conventional oxygen therapy group, a difference driven by a reduction in intubation. There was no statistically significant difference in the primary outcome between the HFNO group and the conventional oxygen therapy group. The rates of adverse events were highest in the CPAP group (34.2%) vs the HFNO (20.6%) and standard oxygen therapy (13.9%) groups. This trial was halted prematurely for logistical considerations and was subject to high rates of crossover, particularly in the conventional oxygen group and, therefore, may have been underpowered to detect an effect in the HFNO group.

In the COVID-High study,8 364 patients with COVID-19–related pneumonia and mild hypoxemia at 27 centers were randomized to receive HFNO or conventional oxygen therapy. There was no significant difference in the rate of escalation of respiratory support, intensive care unit (ICU) admission, rate of recovery, or length of hospital stay between the 2 groups.8

In the COVIDICUS study,9 a multicenter randomized clinical trial in 19 ICUs, 333 patients with COVID-19–related AHRF were randomized to receive conventional oxygen (\( n = 109 \)), CPAP (\( n = 109 \)), or HFNO (\( n = 115 \)). There was no significant difference in the cumulative incidence of invasive mechanical ventilation assessed at day 28, nor in survival or length of ICU or hospital stay.

Prior to the COVID-19 pandemic, except for conditions for which the use of NIV has demonstrated benefit (eg, in chronic obstructive pulmonary disease, heart failure, and postoperatively), the use of noninvasive respiratory support as a strategy for AHRF was also controversial. A 2020 systematic review and network meta-analysis10 of 25 studies with 3804 patients with AHRF conducted prior to the COVID-19 pandemic demonstrated that, compared with conventional oxygen therapy, helmet or face mask NIV and HFNO were associated with a lower risk of endotracheal intubation. In addition, helmet and face mask NIV were also associated with a lower risk of death. However, some of these benefits were no longer evident in sensitivity analyses and when subgroups with known benefit were removed.

In this issue of JAMA, Frat and colleagues11 report the results of the multicenter SOHO-COVID trial, which randomized 711 patients with severe COVID-19 treated in 34 ICUs in France to receive either HFNO (\( n = 357 \)) or conventional oxygen therapy (\( n = 354 \)). The interpretation of the trial is somewhat limited by the change of inclusion criteria during the trial; patients randomized with bacterial community-acquired pneumonia were excluded and the actual mortality rate was substantially lower than that used to estimate the sample size. Nonetheless, the investigators pivoted their trial to address an important question during the COVID-19 pandemic.

There was no statistically significant difference in the primary outcome of 28-day mortality in the HFNO group vs the conventional oxygen group, with mortality rates of 10% vs 11%, respectively (absolute difference, −1.2%; [95% CI, −5.8% to 3.4%]; \( P = .60 \)). However, the rate of intubation (1 of 13 secondary outcomes) was significantly lower in the HFNO group vs the standard oxygen care group (45% vs 53%; absolute difference, −7.7% [95% CI, −14.9% to −0.4%]; \( P = .04 \)). To reduce bias in this open-label trial, the SOHO-COVID investigators used criteria to define the need for intubation. However, many of the criteria used still required subjective assessments by bedside clinicians (eg, work of breathing).

Taken together these studies suggest that initial use of conventional oxygen therapy vs noninvasive respiratory support strategies does not reduce mortality rates. However, the effect of these strategies on rates of intubation and requirement of invasive mechanical ventilation are more complex. It would appear that CPAP or helmet NIV may be more effective than HFNO and conventional oxygen therapy in the larger studies4,7, although a smaller single-center study gave opposing results.6 The effects of HFNO vs conventional oxygen therapy are contradictory with regard to the rates of intubation with the SOHO-COVID trial,11 which showed a lower intubation reduced rate in contrast to the RECOVERY-RS trial,7 which found no difference. However, the interpretation of these findings is somewhat guarded by study limitations, potential biases with end point assessment in an open-label study design, and interpretation of secondary outcomes. While the crossover seen in some of these studies6 is inconvenient from a trialist perspective, it may reflect clinical practice in a patient with a deteriorating condition.12
There is a need to synthesize the available data from the various recently completed clinical trials, and an individual patient data network meta-analysis would assist clinicians to determine which noninvasive respiratory support strategy, if any, is most effective. Furthermore, it is increasingly recognized that the definition of AHRF is broad and captures many different groups of patients. While COVID-19 represents a single disease process, there is increasing evidence that genotypes13,14 and phenotypes15 exist and can affect outcome. There is a clear need to incorporate these phenotypes in AHRF and COVID-19–induced AHRF into future trial designs, to determine which subgroups of patients are most likely to derive benefit (or harm) from these therapies.

The available evidence suggests that the initial choice of supplemental oxygen therapy for patients with COVID-19–related AHRF does not influence mortality. This will provide some reassurance for clinicians in times of reduced availability of certain noninvasive respiratory support strategies during surges in COVID-19 hospitalizations. Particular attention should be given to the potential for complications with each approach, as well as patient preference and tolerance of the selected therapy.

ARTICLE INFORMATION
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Serplulimab With Chemotherapy in Extensive-Stage SCLC

Small cell lung cancer (SCLC) is difficult to control with available treatments, particularly for patients with extensive-stage disease. For decades, there were no improvements in standard platinum-based chemotherapy for initial management of disease that cannot be treated within a single radiation field. Although SCLC is highly responsive to initial platinum chemotherapy in most cases, disease recurrence is nearly universal and has a median survival of less than 1 year from diagnosis.1

In this issue of JAMA, Cheng and colleagues2 report findings from the ASTRUM-005 randomized clinical trial (RCT) in which 585 patients with extensive-stage SCLC received standard chemotherapy with etoposide and carboplatin, with or without the addition of the programmed cell death 1 (PD-1) inhibitor serplulimab. After a median follow-up of 12.3 months, the addition of serplulimab was associated with a significant improvement in the primary outcome of overall survival (15.4 months vs 10.9 months; hazard ratio, 0.63 [95% CI, 0.49-0.82]), as well as the secondary outcome of progression-free...