UPDATE ALERTS

Update Alert 3: Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19

This is the third update of the living systematic review addressing ventilation techniques and risk for transmission of COVID-19 (1). We previously found that noninvasive ventilation (NIV) may have similar effects to invasive mechanical ventilation (IMV) on mortality in patients with COVID-19 and acute hypoxemic respiratory failure and that high-flow oxygen by nasal cannula (HFNC) may reduce mortality compared with no HFNC. In this update, which encompassed handsearching the bibliographies and searching ClinicalTrials.gov, we included only comparative studies published between 11 July 2020, the search date of our second update, and 21 June 2021.

Supplement Figure 1 displays the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram for living systematic reviews (2). We included 10 new COVID-19 observational studies addressing NIV (3–12) and 1 randomized controlled trial comparing HFNC with no HFNC (13) (**Supplement Tables 1** and **2**). Most observational studies failed to provide adjusted effect estimates for the outcomes of interest.

For continuous positive airway pressure (CPAP) versus oxygen alone, there was 1 new study with only 10 participants (4) that did not alter the conclusions for this comparison that CPAP may reduce mortality but that the effect is very uncertain (**Supplement Table 2**). This latter study and 1 new study by Khalil and colleagues (8) also added very little evidence to the comparison of CPAP with IMV, suggesting similar effects on mortality with these methods, with very low-certainty evidence. Three studies (4, 9, 10) provided new information about the comparison of CPAP with HFNC without a clear difference in the effects, although the study by Franco and colleagues (10) showed higher unadjusted mortality in patients receiving CPAP. For CPAP compared with other NIV, we saw no clear difference in unadjusted effects on mortality in 2 studies (8, 10) and no clear difference on the need for IMV or length of hospital stay. For HFNC versus oxygen alone, only 1 new study was identified, but it contributed no events, and there is still too little data to identify an effect in favor of one or the methods (4). Since our last update, 2 new studies compared HFNC with other NIV (10, 13), and the only adjusted estimate for any of the critical outcomes suggested an increase in need for IMV with HFNC compared with other NIV (13). Two new studies (4, 12) compared HFNC with IMV, but there were no adjusted estimates that would allow for strong conclusions to be made. The better outcomes with HFNC in the study by Patel and colleagues (12) may be due to more favorable baseline characteristics in the group of patients receiving HFNC.

For the comparison of NIV versus IMV, there are now a total of 13 studies, of which 6 were added since our last update (3, 5, 6, 8, 11, 14). A total of 4 studies in this living systematic review provided adjusted effect estimates for mortality (11, 14–16), with a pooled hazard ratio of 0.74 (95% CI, 0.46 to 1.18), but in the presence of high, unexplained heterogeneity (very low certainty of evidence) (**Supplement Table 3** and **Supplement Figure 2**). The largest study by Grasselli and colleagues (14) of critically ill patients (n = 3988, Pa_{O_2} ranging from <76 to >127 mm Hg), found that NIV may have similar effects to IMV on mortality (hazard ratio, 0.81 [CI, 0.65 to 1]; high risk of bias). This study also contributed information to the new evidence base of 4 cohort studies comparing NIV with supplemental oxygen alone (3, 5, 11, 14). The adjusted estimates from the 2 studies reporting an effect estimate suggested no clear difference in mortality (hazard ratio, 1.07 [CI, 0.34 to 3.34]; very low-certainty evidence) (**Supplement Table 4** and **Supplement Figure 3**).

The included randomized controlled trial comparing NIV delivered via helmet interface with the use of HFNC in 109 patients with moderate to severe hypoxemia due to COVID-19 (Pa_{O_2}–FI_{O_2} ≤200 mm Hg) suggested no difference between the groups in mortality (24% for helmet NIV vs. 25% for HFNC) or days free of respirator support at 28 days (20 days [interquartile range {IQR}, 0 to 25 days] for helmet NIV vs. 18 days [IQR, 0 to 22 days] for HFNC), with a lower intubation rate in those receiving HFNC (30% vs. 51%; difference, −21 percentage points [CI, −38 to −3 percentage points]) (13). Furthermore, patients receiving helmet NIV had a higher number of IMV-free days at 28 days than those in the HFNC group (28 days [IQR, 13 to 28 days] vs. 25 days [IQR, 4 to 28 days]; P = 0.04). Nonetheless, the trial had few events and participants and was at high risk of bias because of imbalances of baseline covariates and crossover.

In conclusion, this new evidence does not change our initial conclusions that NIV may have at least similar effects as IMV, and HFNC may reduce mortality. The low-certainty evidence suggests the need for high-quality studies. In addition, we have identified at least 6 ongoing trials on NIV (HiFlo-COVID [High-Flow Nasal Cannula in Severe COVID-19 With Acute Hypoxemic Respiratory Failure], COVID-NIV [Noninvasive Ventilation in Moderate-to-severe COVID-19-associated Acute Respiratory Distress-syndrome], Helmet-COVID [Helmet Non-Invasive Ventilation for COVID-19 Patients], PAP-COVID [Early CPAP in COVID-19 Confirmed or Suspected Patients], COVID HELMET [Helmet CPAP Versus HFNC in COVID-19], and COVID-HIGH [HFNT vs. COT in COVID-19]), which are registered, and their results should be monitored because they will build on the current evidence. Future reviews should focus on these randomized controlled trials to provide conclusions with more certainty. As originally reported, we will retire this living review after 1 year because of lack of dedicated funding for this work.

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This article was published at Annals.org on 14 December 2021.

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Disclaimer: The systematic review was commissioned and in part paid for by the World Health Organization. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the World Health Organization.

Acknowledgment: The authors wish to thank Lara Kahale for her assistance in preparing the living PRISMA flow diagram.

Financial Support: The World Health Organization partially funded the first version of this systematic review but has not been funding further updates.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L21-0424.

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doi:10.7326/L21-0424

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