Critical Review Form
Therapy

RENOVATE Investigators and the BRICNet Authors; Maia IS, Kawano-Dourado L, Tramujas L, et al. High-Flow Nasal Oxygen vs Noninvasive Ventilation in Patients With Acute Respiratory Failure: The RENOVATE Randomized Clinical Trial. JAMA. 2025 Mar 11;333(10):875-890.

Objective: **"to evaluate the noninferiority of high-flow nasal oxygen [HFNO] compared with noninvasive ventilation [NIV] and assess potential superiority in reducing the rates of endotracheal intubation or death across 5 patient groups hospitalized with acute respiratory failure (nonimmunocompromised with hypoxemia, immunocompromised with hypoxemia, COPD exacerbation with respiratory acidosis, acute cardiogenic pulmonary edema, or hypoxemic COVID-19)." (p. 876)**

Methods: **This multicenter, adaptive, non-inferiority randomized controlled trial was conducted at 33 hospitals in Brazil between November 2019 and April 2021. Adult patients (≥18 years) in the ICU, ED, or medical ward with acute respiratory failure, defined by hypoxemia (SpO2 < 90% or PaO2 < 60 mmHg) and either increased respiratory effort or tachypnea (respiratory rate > 25 breaths/min) were eligible. Patients were categorized into four mutually exclusive groups: non-immunocompromised with hypoxemia, immunocompromised with hypoxemia, COPD exacerbation with respiratory acidosis, or acute cardiogenic pulmonary edema. Exclusions included need for urgent intubation, hemodynamic instability, and contraindications to NIV. After March 2020, patients with COVID-19 entered the trial within the defined groups. An amendment in June 2023 separated COVID-19 patients for analysis due to evolving clinical practices and differential intubation rates.**

Patients were randomly assigned to high-flow nasal oxygen via Airvo-2 or NIV via facemask in a 1:1 ratio. The primary outcome was endotracheal intubation or death within 7 days. Predefined criteria for intubation included respiratory or cardiac arrest, hemodynamic instability, cognitive impairment, low SpO2 despite high FiO2, progressive PaCO2 increase, and other critical conditions. Secondary outcomes included 28-day mortality, 90-day mortality, mechanical ventilation-free days at 28 days, and ICU-free days at 28 days. Tertiary outcomes included hospital and ICU length of stay, vasopressor-free days, do-not-intubate orders, and patient comfort scores. Non-inferiority was defined by a non-inferiority posterior probability higher than 0.992 for an OR less than 1.

A total of 2731 patients screened and 1800 were randomized. Following interim analyses, enrollment was halted for futility or when predetermined non-inferiority thresholds were met. The final cohort included 1766 patients (mean age 63.7 years; 40% women). Informed

consent was not obtained from 49 patients who died before their surrogates could provide it; however, data from 15 of these patients were included with ethics committee approval.

Critical Review Form: Therapy

Guide	Comments
Are the results valid?	
Did experimental and control groups being the study with a similar prognosis?	
Were patients randomized?	Yes. Patients were randomly assigned to high-flow nasal oxygen via Airvo-2 or NIV via facemask in a 1:1 ratio.
Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be "randomized" to a particular group?	"The randomization list was generated electronically with permuted block sizes that were unknown to the investigators. The allocation concealment was maintained via an online central automated system available 24 hours daily, stratified by center and acute respiratory failure patient group." (p.877)
Were patients analyzed in the groups to which they were randomized?	Data was analyzed in an intention-to-treat population. "The allocated intervention was received by 93.3% of patients (824/883) in the high-flow nasal oxygen treatment group and by 91.5% of patients (808/883) in the noninvasive ventilation treatment group." (p. 880)
Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Within subgroups, patients assigned to the two treatments were similar with respect to prognostic factors considered.
Did experimental and control groups retain a similar prognosis after the study started?	
Were patients aware of group allocation?	Yes. Given the nature of the intervention, it would not have been possible to blind patients or clinicians. It is possible that performance bias could have influenced outcomes.
Were clinicians aware of group allocation?	Yes. See above.
Were outcome assessors aware of group allocation?	Uncertain. The authors make no mention of blinding of outcome assessors (observer bias).
Was follow-up complete?	Yes. There were some excluded patients who were randomized, but for whom consent was not obtained, but follow-up was obtained for all enrolled patients.
What are the results?	
How large was the treatment effect?	• The primary outcome (intubation or death within 7 days) occurred in 39.0% of patients in the HFNO group and 38.1% in the noninvasive NIV group, for a risk difference of 0.9% (95% CI -3.2% to 5.0%). o **Nonimmunocompromised patients with hypoxemia**: the primary outcome occurred in 32.5% in the HFNO group versus 33.1% in the NIV group (OR 1.02; 95% CrI 0.81-1.26), with a noninferiority posterior probability of 0.999. o **COPD Exacerbation with Respiratory Acidosis**: the primary outcome occurred in 28.6% in the HFNO group versus 26.2% in the NIV group (OR 1.05; 95% CrI 0.79-1.36), with a noninferiority posterior probability of 0.992. o **Acute Cardiogenic Pulmonary Edema**: the primary outcome occurred in 10.3% in the HFNO group versus 21.3% in the NIV group (OR 0.97; 95% CrI 0.73-1.23), with a noninferiority posterior probability of 0.997. o **Hypoxemic COVID-19**: the primary outcome occurred in 51.3% in the HFNO group versus 47.0% in the NIV group (OR

	1.13; 95% CrI 0.94-1.38), with a noninferiority posterior probability of 0.997. o **Immunocompromised Patients with Hypoxemia**: the primary outcome occurred in 57.1% in the HFNO group versus 36.4% in the NIV group (OR 1.07; 95% CrI 0.81-1.39), meeting the criterion for futility with a noninferiority posterior probability of 0.989. • **Median 28-Day Mortality Rates**: there was no significant difference between the HFNO and NIV groups for any patient subgroup. • HFNO was superior to NIV in terms of patient comfort. **Sensitivity Analysis** • **Posterior Probabilities of Noninferiority**: o Results were consistent with the main analysis for the per-protocol population and post-hoc sensitivity analyses using weakly informative priors. **Adverse Events** • The incidence of serious adverse events was similar between the HFNO group (9.4%) and the NIV group (9.9%).
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	See above.

How can I apply the results to patient care?	
Were the study patients similar to my patient?	No. This study was conducted at 33 hospitals in Brazil. Difference in ethnicity/race, body habitus, and medical comorbidities make it difficult to generalize these results to our patient population (external validity). Additionally, there may be differences in patient management that would influence outcomes.
Were all clinically important outcomes considered?	Mostly yes. The only outcome not measured that would help our understanding of the benefits of the proposed treatment was patient comfort.
Are the likely treatment benefits worth the potential harm and costs?	Likely yes. Use of HFNO met the prespecified criteria for noninferiority compared to NIV for the primary outcome (endotracheal intubation or death within 7 days) in 4 of 5 subgroups of patients with respiratory failure. The only group for which the study could not prove noninferiority was immunocompromised patients with hypoxemia. Assuming improved comfort and tolerability of HFNO compared to NIV with a facemask, this is a reasonable alternative treatment for patients meeting inclusion in these frou subgroups.

Limitations:

1. **Given the nature of the intervention, it would not have been possible to blind patients or clinicians. It is possible that performance bias could have influenced outcomes.**

2. **Difference in ethnicity/race, body habitus, and medical comorbidities make it difficult to generalize these results to our patient population (external validity).**

3. **Enrollment was stopped early in the immunocompromised patients with hypoxemia group for perceived futility (The Dangers of Stopping Trials Early).**

Bottom Line:

This large, multicenter, adaptive, non-inferiority randomized controlled trial conducted at 33 hospitals in Brazil found that the use of HFNO met the prespecified criteria for noninferiority compared to NIV for the primary outcome (endotracheal intubation or death within 7 days) in 4 of 5 subgroups of patients with respiratory failure. The only group for which the study could not prove noninferiority was immunocompromised patients with hypoxemia.