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Effectiveness and Harms of High-Flow Nasal Oxygen (HFNO) for Acute Respiratory Failure: An Evidence Report for a Clinical Guideline by the American College of Physicians

Arianne K. Baldomero, MD, MS[1,2], **Anne C. Melzer, MD, MS**[1,2], **Nancy Greer, PhD**[3], **Brittany N. Majeski, BA**[3], **Roderick MacDonald, MS**[3], **Eric J. Linskens, BS**[3], **Timothy J. Wilt, MD, MPH**[3,4]

[1]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, Minneapolis Veterans Affairs Health Care System, Minneapolis, MN, USA

[2]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN, USA

[3]Center for Care Delivery and Outcomes Research, Minneapolis Veterans Affairs Health Care System, Minneapolis, MN, USA

[4]Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Abstract

Background: High-flow nasal oxygen (HFNO) for treatment of adults with acute respiratory failure (ARF) has increased.

Corresponding author: Arianne K. Baldomero, MD, MS, 1 Veterans Drive, Pulmonary 111-N, Minneapolis, MN, USA, baldo004@umn.edu.

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DISCLOSURE
The materials presented here solely represent the views of the authors and do not represent the view of the U.S. Department of Veterans Affairs, the United States Government or the National Institutes of Health's National Center for Advancing Translational Sciences.

Current mailing address for AKB, ACM:
1 Veterans Drive, Pulmonary 111-N
Minneapolis, MN, USA

Current mailing address for all other authors:
One Veterans Drive (111–0)
Minneapolis, MN 55417

Purpose: Assess HFNO versus noninvasive ventilation (NIV) or conventional oxygen therapy (COT) for ARF in hospitalized adults.

Data Sources: English language searches of MEDLINE®, Embase, CINAHL, and Cochrane Library from January 2000 to July 2020; systematic review reference lists.

Study Selection: Twenty-nine randomized controlled trials (RCTs) evaluated HFNO versus NIV (k=11) or COT (k=21).

Data Extraction: Data extraction by single investigator verified by a second; dual-investigator assessment of risk of bias; consensus determination of evidence certainty.

Data Synthesis: We reported results separately for HFNO versus NIV and HFNO versus COT and by initial or post-extubation management. Compared to NIV, HFNO may reduce all-cause mortality, intubation, and hospital-acquired pneumonia and improve patient comfort in initial ARF management (low evidence certainty), but not as post-extubation management. Compared to COT, HFNO may reduce reintubation and improve patient comfort in post-extubation ARF management (low evidence certainty).

Limitations: Trials varied in populations enrolled, ARF etiologies, and treatment protocols. Trial design, sample size, treatment/follow-up duration, and results reporting were often inadequate to adequately assess many outcomes. Protocols, clinician/health system training, cost and resource use were poorly characterized.

Conclusion: Compared to NIV, HFNO as initial ARF management may improve several clinical outcomes. Compared to COT, HFNO as post-extubation management may reduce reintubations and improve patient comfort. HFNO resulted in fewer harms than NIV or COT. Broad applicability, including required clinician and health system experience and resource use, is not well known.

INTRODUCTION

Acute respiratory failure (ARF) is generally defined as the new onset of clinically important hypoxia, hypercapnia, or both. Noninvasive respiratory treatment options for ARF vary by etiology and severity, and include “conventional oxygenation therapy” (COT)–oxygen delivered through nasal cannula, simple face mask, air-entrainment mask, partial rebreathing mask, or non-rebreather mask, with maximum flow rate of approximately 15 L/min–and more advanced support modalities such as noninvasive ventilation (NIV). NIV encompasses continuous or bilevel positive airway pressure ventilation and requires specialized training and equipment to deliver. High-flow nasal oxygen (HFNO), a newer mode of noninvasive oxygen support, has been increasingly used, in part due to perceived benefits in comparison to COT and NIV. COT, NIV, and HFNO have unique characteristics related to user interface, inspired oxygen concentration and flow rate, heat/humidification, use of positive pressure and ventilatory support(1) (Appendix Table 1).

Compared to COT, HFNO is purported to provide additional support through washout of anatomic dead space(2), higher oxygen flow rates (up to 60 L/min)(3,4), generation of low level positive-end expiratory pressure (PEEP)(5–9), and higher concentrations of heated humidified oxygen (up to 100% FiO_2). Compared to NIV, which is typically delivered by

full face mask, HFNO is delivered through a small, pliable nasal cannula, potentially improving clearance of secretions, patient comfort, and resource utilization. HFNO is considered to offer a number of physiologic advantages, such as improved oxygenation and ventilation(10,11). However, comparative benefits and harms of HFNO on clinical outcomes including mortality, intubation, hospital length of stay, patient comfort(12–14), clearance of airway secretions(15,16), and reduced work of breathing(13,17,18) are not well known.

The Minnesota Evidence Synthesis and Dissemination Center was commissioned by the American College of Physicians (ACP) to review the evidence regarding the comparative effectiveness and harms of HFNO compared to NIV or COT for ARF in hospitalized adults. This review was used by the ACP-Clinical Guidelines Committee (ACP-CGC) to develop a clinical guideline for the use of HFNO in hospitalized adults with ARF.

METHODS

Our protocol was developed with input from the ACP-CGC as well as an independent technical expert panel and registered in PROSPERO (CRD42019146691). Our protocol underwent additional peer review and was published(19). A summary is presented in Appendix Table 2.

Data Sources and Study Selection

We searched multiple databases (January 2000-July 2020) for peer reviewed, English language, randomized controlled trials (RCTs) (Appendix Table 3). Abstracts and potentially eligible full text articles were independently reviewed by 2 investigators. We included parallel group and crossover studies of hospitalized adults (age ≥18 years) with ARF randomized to receive HFNO or either COT or NIV. We defined HFNO as delivery of humidified oxygen via nasal cannula at a flow rate ≥20 L/min. We excluded studies evaluating HFNO for oxygenation support before and during intubation and studies of pre-hospital HFNO. We included studies if ≥75% of enrollees met at least one ARF criterion: SpO_2<90%, PaO_2:FIO_2 ratio≤300, PaO_2≤60 mmHg, or $PaCO_2$≥45 mmHg.

Outcome Measures

Critical outcomes defined by the ACP-CGC were: all-cause mortality (in-hospital and the longest available through 90 days), hospital-acquired pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU) admission/transfers, patient comfort, and hospital length of stay. Important and intermediate outcomes are described in Appendix Table 2.

Data Extraction and Quality Assessment

Data extraction was completed by one investigator and verified by a second. We assessed risk of bias using a modification of the Cochrane guidance for randomized trials(20). Individual elements were rated low, unclear, or high risk of bias. A study with unclear elements was considered moderate risk of bias.

Data Synthesis and Analysis

We examined clinical and methodological heterogeneity to determine appropriateness of quantitative synthesis. Heterogeneity was assessed using the I^2 statistic, Chi-squared test, and visual inspection of the forest plots. An I^2 statistic of 75% or greater may indicate substantial heterogeneity. We pooled outcomes from clinically homogeneous studies using Comprehensive Meta Analysis V.3 or R. We calculated risk ratios (RR) or Peto odds ratios (OR) and corresponding 95% confidence intervals for categorical outcomes. The Peto method was applied when events were rare, particularly when trials reported zero events in one of the treatment arms(21). Mean and standardized mean differences (MD, SMD) were calculated for continuous outcomes. If there were at least 5 trials for pooled analysis, the Hartung–Knapp–Sidik–Jonkman method for random-effects models was applied to calculate SMD for continuous outcomes and relative measures of effect for categorical outcomes with corresponding 95% CI(22). If there were fewer than 5 trials and no between-study variance (tau^2 at or near 0) data were meta-analyzed with a fixed-effects model(23). When there were no events in a treatment arm, we used the treatment arm continuity correction. Anticipated absolute event rates and corresponding risk differences were generated in GRADEpro software(24,25). In addition, we calculated pooled absolute event rates and 95% CIs for the primary harm outcomes for each study group using the Freeman-Tukey double arcsine transformation(26).

We analyzed results separately for studies of initial ARF management and studies of post-extubation ARF. We conducted subgroup analyses to explore potential causes of heterogeneity by clinical setting, disease indication, treatment duration, and ARF type. If quantitative synthesis was not appropriate, findings were summarized narratively. We used a modification of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to rate overall certainty of evidence for critical outcomes as high, moderate, low, or insufficient(24,25). At the request of the ACP-CGC, we also assessed certainty of evidence for skin breakdown. The thresholds indicating level of magnitude for our critical outcomes were derived through input by our content experts and technical expert panel (Tables 1 and 2).

Role of Funding Source

This review was funded by a contract with the ACP. An ACP representative provided technical support and served as an ACP-CGC and technical expert panel liaison. The ACP-CGC assisted in the development of key questions, study inclusion criteria, and outcome measures of interest but did not participate in data collection, analysis, or manuscript preparation.

RESULTS

Search results are in Appendix Figure 1. We identified 29 eligible RCTs (in 32 articles)(27–58). An overview of included trials is presented in Appendix Table 4 and patient characteristics in Appendix Table 5. Patients typically had at least moderate ARF according to baseline PaO_2/FIO_2 ratio (<200) or SPO_2 (≤88%). In the NIV parallel group studies, the baseline SpO_2 weighted mean in the initial management trials was 76% while the baseline

PaO_2/FIO_2 ratio weighted mean in the post-extubation trials was 198. In the COT parallel group studies, the baseline SpO_2 weighted mean in the initial management trials was 88% while the baseline PaO_2/FIO_2 ratio weighted mean in the post-extubation trials was 227. Studies did not require patients to have failed initial oxygen therapy prior to randomization though information was sparse on pre-randomization oxygen treatments. Detailed study and treatment characteristics, individual study risk of bias, and outcomes data are reported in Supplementary Tables 1-10. We report results separately for studies comparing HFNO versus NIV and HFNO versus COT and by whether treatment was for initial or post-intubation ARF management. Treatment protocols varied by study based mostly on physiologic parameters, with most studies targeting SpO_2 levels ≥92% (range 88–95%). Information from crossover studies was limited to comfort and dyspnea outcomes in initial management. Pooled absolute event rates within each study arm calculated by the Freeman-Tukey method are provided in Supplementary Table 11. Subgroup analyses for both NIV and COT controls are presented in Supplementary Tables 12-15. The effect of treatments did not differ significantly by clinical setting, disease indication, treatment duration, or type of ARF, although for most outcomes there were few or no studies available for these comparisons. Data on physiologic outcomes were inadequate to derive conclusions due to variable types and timing of physiologic data reported (Supplementary Tables 16-19). The greatest difference in physiologic outcomes was in PaO_2/FiO_2 ratio, particularly in post-extubation management, where post-treatment values were generally higher in NIV compared to HFNO (Supplementary Table 17) and in HFNO compared to COT (Supplementary Table 19).

HFNO versus NIV

Initial Management of Acute Respiratory Failure—Eight studies (4 parallel design and 4 crossover studies) compared HFNO to NIV for initial management of ARF among patients with multiple diagnoses(32,34,35,49,54), chronic obstructive pulmonary disease (COPD) (29), cystic fibrosis(50), and during bronchoscopy(48) (Appendix Tables 4 and 5). One of these studies reported outcomes on subgroups of acute decompensated heart failure (36) and COPD exacerbation or acute hypercapnic respiratory failure (57). Two were rated low risk of bias while 6 were rated moderate (Supplementary Table 2).

Critical Outcomes

Intubation: Pooled results from 2 RCTs (n=420) indicate that HFNO may reduce intubations by a moderate amount (23.0% vs. 32.4%; absolute risk difference [ARD] −9.4%, [−15.2, −1.6]) compared with NIV (RR 0.71 [0.53, 0.95]; I^2=0%; low evidence certainty) (Figures 1 and 2/Table 1)(32,34).

All-cause Mortality: Results from 1 RCT (n=216) indicate that HFNO may reduce all-cause mortality by a large amount (12.4% vs. 28.2%; ARD −15.8% [−21.4, −5.9]) compared with NIV (RR 0.44 [0.24, 0.79]; low evidence certainty) (Figures 1 and 2/Table 1)(34). The trial included patients with hypoxic ARF from multiple etiologies.

Hospital-acquired Pneumonia: One RCT (n=216) among adults with hypoxic ARF due to multiple etiologies evaluated hospital-acquired pneumonia (34). HFNO may reduce hospital-

acquired pneumonia by a moderate amount (3.8% vs. 8.2%; ARD −4.4% [−7.0%, 3.7%]) compared to NIV (RR 0.46 [0.15, 1.45]; low evidence certainty) (Figure 1/Table 1).

ICU Admissions and ICU Length of Stay: Few trials reported ICU admissions(32) or length of stay(32,34) (Supplementary Figure 1). Study protocol, rather than clinical outcomes, primarily determined ICU admission and length of stay. It is uncertain whether HFNO reduces ICU admissions or ICU length of stay (insufficient evidence) (Figure 1/Table 1).

Hospital Length of Stay: Two RCTs (n=372) including patients with hypoxic and/or hypercapnic ARF reported hospital length of stay (Supplementary Figure 2)(39,32). HFNO may make little or no difference in hospital length of stay compared to NIV (MD 0.45 days [−0.69, 1.59]; I^2=0%; low evidence certainty) (Figure 1/Table 1).

Patient Comfort and Dyspnea: Seven RCTs (n=644) reported comfort measures(28,32,34,35,49,50,54) and 7 RCTs (n=464) provided dyspnea measures(32,34,35,48–50,54); none could be pooled. HFNO may improve patient comfort but may make little or no difference in dyspnea compared to NIV (low evidence certainty) (Figure 1/Table 1).

Important Outcomes—No trials comparing HFNO with NIV reported barotrauma, skin breakdown, discharge disposition, hospital readmissions, compromised nutrition, functional independence, or cost/resource utilization.

Intermediate Outcomes—Treatment escalation, defined as switching from HFNO to NIV or from NIV to HFNO, was rarely reported. One trial(32) suggested higher rates of device switching in HFNO to NIV than from NIV to HFNO. Two trials(48,49) reported higher rates of device intolerance in NIV versus HFNO.

Post-extubation Management of Acute Respiratory Failure—Three RCTs compared HFNO to NIV in post-extubation management of ARF(37,39,53). All were ICU trials in patients with multiple diagnoses, COPD exacerbation, or post-cardiothoracic surgery (Appendix Tables 4 and 5). Two trials were rated low risk of bias; 1 moderate (Supplementary Table 2).

Reintubation: Three RCTs (n=1476) evaluated reintubation(37,39,53). HFNO may increase reintubations by a small amount (17.3% vs. 15.3%; ARD 2.0% [−1.5, 6.6]) compared with NIV (RR 1.13 [0.90, 1.43]; I^2=0%; low evidence certainty) (Figures 1 and 2/Table 1).

All-cause Mortality: We pooled 3 RCTs (n=1476) that reported all-cause mortality(37,39,53). HFNO may increase all-cause mortality by a small amount (12.9% vs. 11.2%; ARD 1.7% [−1.3, 5.7]) compared to NIV (RR 1.15 [0.88, 1.51]; I^2=0%; low evidence certainty) (Figures 1 and 2/Table 1).

Hospital-acquired Pneumonia: Two RCTs (n=1434) evaluated hospital-acquired pneumonia(37,53). HFNO may make little to no difference in hospital-acquired pneumonia

(13.2% vs. 14.7%; ARD −1.5% [−4.4, 2.3%]) compared to NIV (RR 0.90 [0.70, 1.16]; I^2=0%; low evidence certainty) (Figure 1/Supplementary Figure 3/Table 1).

ICU Admissions: Not applicable.

ICU Length of Stay: Three RCTs (n=1476) reported ICU length of stay(37,39,53). In pooled results from 2 RCTs in medical patients (n=646), HFNO made little or no difference in ICU mean length of stay compared with NIV (MD −0.98 days [−1.99, 0.03]) (Supplementary Figure 1)(37,39). A third trial of post-cardiothoracic surgery patients(53) (n=830) only reported median length of stay and showed a similar effect. HFNO may make little to no difference in ICU length of stay compared with NIV (low evidence certainty) (Figure 1/Table 1).

Hospital Length of Stay: Two RCTs (n=1434) reporting hospital length of stay(37,63) were not pooled (data reported as means and medians). It is uncertain whether HFNO reduces hospital length of stay compared to NIV (insufficient evidence) (Figure 1/Table 1).

Patient Comfort and Dyspnea: Two RCTs (n=872) provided patient comfort measures (39,53) but could not be pooled, and 1 trial reported dyspnea measures(53) (post-cardiothoracic surgery, n=752). One trial found slight improvement in comfort with HFNO(39) and 1 showed no difference(53). HFNO may make little or no difference in patient comfort compared to NIV (low evidence certainty) (Table 1). HFNO may make little or no difference in dyspnea compared to NIV (58.0% vs. 60.4%; ARD −2.4% [−8.5 to 4.8]; low evidence certainty) (Figure 1/Table 1).

Important Outcomes—Three trials (n=1454) comparing HFNO versus NIV reported nasal/facial skin breakdown(37,39,53). All 3 trials consistently showed significantly higher event rates in the NIV group; 2 trials reported no events in the HFNO groups(37,39) but 1 of the trials (n=604) reported that 42.9% of patients, all from the NIV group, had “nasal septum and skin trauma” resulting in discontinuation of NIV(37). The pooled skin breakdown event rate was 24.3% in NIV compared to 4.6% in HFNO (Peto OR 0.15 [0.02, 1.13]; I^2=88%) (Supplementary Figure 4). HFNO may reduce nasal/facial skin breakdown by a large amount (low evidence certainty). Reported findings for barotrauma, gastric dysfunction, and cost/resource utilization were inadequate to derive conclusions.

Intermediate Outcomes—Three trials (n=1150) reported “treatment” or “respiratory” failure but did not report specific numbers of patients that were escalated to a different treatment. Results were mixed(37,39,53). As noted above, one trial reported intolerance due to skin trauma(37).

HFNO versus COT

Initial Management of Acute Respiratory Failure—We included 14 trials comparing HFNO to COT for initial ARF management among patients with multiple diseases(28,31,34,40,44,46,49,52,54), cardiogenic pulmonary edema(43), COPD exacerbation(45), those who were immunocompromised(27,41), and in palliative care(47). Nine were parallel design RCTs and 5 were crossover studies. Eight studies enrolled fewer

than 100 participants (Appendix Tables 4 and 5). Risk of bias was rated low for 6 studies and moderate for 8 (Supplementary Table 2).

Intubation: We pooled 8 parallel design RCTs (n=1694) that evaluated intubation(27,28,34,40,41,43,46,52). HFNO may make little or no difference in intubation (26.1% vs. 26.5%; ARD −0.4% [−15.6, 23.9]) compared with COT (Peto OR 0.98 [0.34, 2.82]; I^2=12%; low evidence certainty) (Figures 1 and 3/Table 2).

All-cause Mortality: We pooled 4 RCTs of hypoxic ARF (n=1407) that reported all-cause mortality(27,34,40,43). HFNO may make little or no difference in all-cause mortality (26.3% vs. 27.2%; ARD −0.8% [−4.9, 3.8]) compared with COT (RR 0.97 [0.82, 1.14]; I^2=42%; low evidence certainty) (Figures 1 and 3/Table 2).

Hospital-acquired Pneumonia: One RCT (n=200) evaluated hospital-acquired pneumonia in ICU patients with hypoxic ARF from multiple etiologies(34). HFNO may result in a moderate reduction in hospital-acquired pneumonia (3.8% vs. 8.5%; ARD −4.7% [−7.3%, 3.7%]) compared with COT (RR 0.44 [0.14, 1.43]; low evidence certainty) (Figure 1/Table 2).

ICU Admissions: Two RCTs (n=403) reported ICU admissions(28,40). It is uncertain whether HFNO reduces ICU admissions compared to COT (insufficient evidence) (Figure 1/ Supplementary Figure 5/Table 2).

ICU Length of Stay: Three RCTs (n=1036) reported ICU length of stay(27,34,44) of which 2 trials of hypoxic ARF (n=976) were pooled(27,34). It is uncertain if HFNO reduces ICU length of stay (insufficient evidence) (Figure 1/Supplementary Figure 6/Table 2).

Hospital Length of Stay: Four RCTs (n=1267) reported hospital length of stay(27,40,43,44) which could not be pooled. HFNO may make little or no difference in hospital length of stay compared to COT (medians ranged from 1 to 24 vs. 1 to 27 days; low evidence certainty) (Figure 1/Table 2).

Patient Comfort and Dyspnea: Twelve RCTs (n=1611) provided patient comfort measures(27,28,31,34,40,41,43,45,46,49,52,54). Four trials (n=415) provided data that permitted pooling. HFNO improved patient comfort based on visual analog scale scores (SMD −0.61 [−0.81, −0.41]; I^2=45%)(34,43,46,52) (Supplementary Figure 7). Results from the other 8 RCTs were mixed. Overall, HFNO may improve patient comfort compared with COT (low evidence certainty) (Table 2). Thirteen RCTs (n=1799), including 4 crossover studies, provided dyspnea measures(27,28,31,34,40,41,43,45–47,49,52,54); 4 trials (n=258) could be pooled. HFNO provided moderate improvement in dyspnea compared to COT (SMD −0.56 [−1.35 to 0.24]; I^2=67%) (Supplementary Figure 8)(43,46,47,52). HFNO increased the percentage of individuals with improved dyspnea based on results from 3 trials that used different threshold criteria for defining improvement(28,34,40). Based on all 9 studies that included data that could not be pooled results were mixed reported(27,28,31,34,40,41,45,49,54). Overall, HFNO may improve dyspnea compared with COT (low evidence certainty) (Figure 1/Table 2).

Important Outcomes—Two trials (n=431) comparing HFNO versus COT reported skin breakdown (facial pressure sore or nasal ulceration)(40,43). Both trials reported no cases of skin breakdown in the HFNO group. One trial reported no events in the COT group(40) while the other trial did not report skin breakdown in the COT group (insufficient evidence) (43). Other outcomes were rarely or not reported.

Intermediate Outcomes—Seven trials (n=1,503) comparing HFNO versus COT reported treatment escalation from COT to either HFNO or NIV (4 studies) and from HFNO to NIV(27,28,40,41,43,44,46). Studies generally reported higher treatment escalation for COT than for HFNO (Supplementary Figure 9). Six trials reported device intolerance to the assigned treatment(27,40,43,46,47,49). We were unable to derive conclusions due to limited reporting.

Post-extubation Management of Acute Respiratory Failure—Seven parallel group RCTs (n=1,065) compared HFNO with COT for post-extubation ARF. All were ICU trials in medical (mixed diagnoses)(38,42,51,56,58) and post-cardiothoracic surgery patients(30,55) (Appendix Tables 4 and 5). Three studies were rated low risk of bias and 4 moderate (Supplementary Table 2).

Reintubation: Based on pooled results from 7 RCTs (n=1065), HFNO may reduce reintubations by a small amount (6.5% vs. 10.4%; ARD −3.9% [−7.8%, 5.3%]) compared to COT (Peto OR 0.60 [0.23, 1.61]; I^2=40%; low evidence certainty) (Figures 1 and 3/Table 2) (30,38,42,51,55,56,58).

All-cause Mortality: We pooled 4 RCTs of ICU patients with hypoxic ARF (n=782) that reported all-cause mortality(38,42,55,56). HFNO may make little or no difference in all-cause mortality (6.3% vs. 6.2%; ARD 0.1% [−2.5%, 4.5%]) compared with COT (RR 1.01 [0.60, 1.72]; I^2=0%; low evidence certainty) (Figures 1 and 3/Table 2)

Hospital-acquired Pneumonia: One RCT (n=527) evaluated hospital-acquired pneumonia in the ICU in medical patients with post-extubation hypoxic (non-hypercapnic) ARF from multiple etiologies(38). HFNO may make little or no difference (1.1% vs. 2.3%; ARD −1.1% [−2.0%, 2.2%]) in hospital-acquired pneumonia compared with COT (RR 0.50 [0.13, 1.97]; low evidence certainty) (Figure 1/Table 2).

ICU Length of Stay: Six RCTs (n=1006) reported ICU length of stay(30,38,42,55,56,58) of which 5 (n=479) were pooled. Compared to COT, HFNO probably makes little or no difference in ICU length of stay (approximately 6 days in each group; MD 0.19 [−0.19, 0.57]; moderate evidence certainty) (Figure 1/Supplementary Figure 6/Table 2) (30,42,55,56,58).

Hospital Length of Stay: Two RCTs reported hospital length of stay; results could not be pooled as one reported medians and one reported means(38,56). It is uncertain whether HFNO reduces hospital length of stay compared to COT (insufficient evidence) (Figure 1/ Table 2).

Patient Comfort and Dyspnea: Four parallel design RCTs (n=324) provided patient comfort measures(42,51,55,58) which could not be pooled due to variation in measures reported. Three trials showed that HFNO resulted in improved patient comfort compared to COT and one reported little or no difference(58). HFNO may improve patient comfort compared with COT (low evidence certainty) (Table 2). Only 1 parallel design RCT (n=155) reported dyspnea with little or no difference in median values(30). It is uncertain whether HFNO improves dyspnea compared to COT (insufficient evidence) (Figure 1/Table 2).

Important outcomes: One trial reported no incidences of skin breakdown were observed with HFNO but this outcome was not reported for the COT arm (insufficient evidence)(38). No trials reported gastric dysfunction, hospital readmissions, compromised nutrition, or functional independence. Only 1 trial reported a measure of cost/resource utilization(42).

Intermediate outcomes: Five RCTs (n=479) reported treatment escalation from COT to either HFNO or NIV and HFNO to NIV(30,42,51,55,58). All trials reported lower treatment escalation in the HFNO versus COT groups [8.1% vs. 18.9%; RR 0.43 [0.27, 0.70]) (Supplementary Figure 9). Two additional trials reported a higher rate of “treatment” or “respiratory” failure in the COT versus HFNO group but ensuing treatment was not clearly defined(38,51). No RCTs comparing HFNO with COT reported device intolerance outcomes.

DISCUSSION

Our review of HFNO versus NIV or COT found that compared to NIV, HFNO may reduce intubation, all-cause mortality, and hospital-acquired pneumonia, and improve patient comfort in initial ARF management. However, compared to NIV, HFNO may increase reintubations and mortality in post-extubation ARF management. Compared to COT, HFNO may reduce reintubation and improve patient comfort in post-extubation ARF management. Benefits of HFNO were less clear compared to COT in initial ARF management. HFNO may reduce facial skin breakdown compared to NIV and decrease treatment escalation. We analyzed results separately for initial or post-extubation ARF management. Such patients are clinically distinct and may have different ARF etiologies and severities. For example, post-extubation ARF frequently results in reintubation, resulting in prolonged intubation duration and higher ICU mortality(59). Our results are generally consistent with past systematic reviews(1,60–76). However, we limited our inclusion criteria to hospitalized adults meeting ARF criteria, included a broader scope of clinical conditions and settings, assessed HFNO against both NIV and COT, evaluated a more comprehensive list of key clinical outcomes, and updated our search through July 2020. We prioritized patient-centered outcomes such as intubation, mortality, pneumonia, length of hospitalization or length of ICU stay, rather than physiologic outcomes.

As respiratory treatment options vary by ARF etiology and severity, we analyzed results separately for NIV and COT. The baseline physiologic parameters of patients enrolled in NIV trials were worse than those enrolled in COT trials. For example, the baseline mean SpO_2 of patients in initial management NIV parallel group trials was 76% compared to 88% in COT trials. Additionally, 5 of 21 (24%) COT trials versus 4 of 11 (36%) NIV trials

included patients with hypercapnic ARF. Intubation rates in NIV trials were higher compared to COT trials in both initial and post-extubation ARF management, likely reflecting the higher ARF severity in the NIV versus COT trials. European Respiratory Society and American Thoracic Society Guidelines(77) identify specific indications for NIV, such as hypercapnia with COPD exacerbation and cardiogenic pulmonary edema. However, many patients are treated with NIV for indications beyond these recommendations(78,79) and in trials included in this review. Because populations were combined, it is not possible to determine if HFNO was equally beneficial over NIV in cases where NIV is recommended versus areas where it is not(77).

Subanalyses were conducted to assess the effect of different study designs and recently published studies. Removing a study that used a broader escalation strategy than only the initial management strategy by allowing crossover(32) did not change the strength of findings. An updated bridge search through February 2021 identified 10 additional eligible RCTs that provided critical or important outcomes(80–89). Three were considered large ($n \geq 100$) and reported on mortality and intubation(80–82). Of these three, one was in individuals with hematologic malignancies(80) and not further assessed. The second was a moderate risk of bias study that evaluated HFNO vs. NIV in post-extubation patients with ARF (n=140)(81). When adding this trial (81) the absolute risk difference of HFNO vs. NIV on reintubation decreased from 2.0% to 1.8%, but did not change the overall certainty of evidence. The third was a low risk of bias study that evaluated HFNO vs. COT as initial management of COPD exacerbation and acute hypoxic respiratory failure with compensated hypercapnea (n=320)(82). Adding this trial(82) did not alter the effect magnitude estimates for either outcome. Findings from these studies were consistent with our overall findings and inclusion of results made little to no difference in effect estimates.

We identified gaps in the existing literature that limited our conclusions and for which future research is needed. Trials varied in populations enrolled, ARF etiology, and protocols used. When numerous causes of ARF were included in a single trial, results were often not stratified or sample sizes were too small to adequately evaluate outcomes across disease states or clinical settings. We were unable to distinguish relative effectiveness of therapies in specific populations. Studies often excluded patients with life-threatening comorbidities or at imminent risk of mechanical ventilation. No studies reported outcomes in patients with SARS CoV-2 infection. Many studies used surrogate endpoints, such as physiologic outcomes, rather than patient-centered outcomes such as mortality. Trial design, sample size, treatment/follow-up duration, and results reporting were often inadequate to accurately assess our pre-specified outcomes. No RCTs evaluated delirium, compromised nutrition, functional independence at discharge, or discharge disposition. Finally, treatment protocols, clinician/health system training, and cost and resource use were poorly characterized. These represent a key part of HFNO utility for a health system.

In conclusion, compared to NIV, HFNO used as initial ARF management may improve several clinical outcomes. Compared to COT, HFNO used as post-extubation management may reduce reintubations and improve patient comfort. HFNO resulted in fewer harms than either NIV or COT. Broad applicability, including required clinician and health system experience and resource use, remain unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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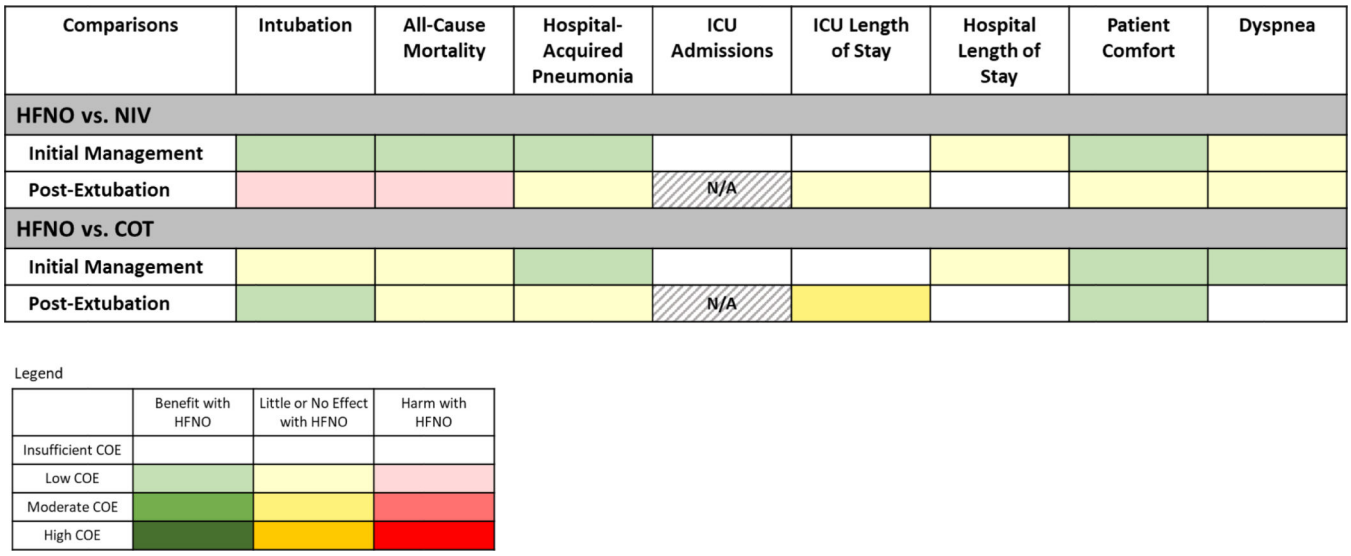
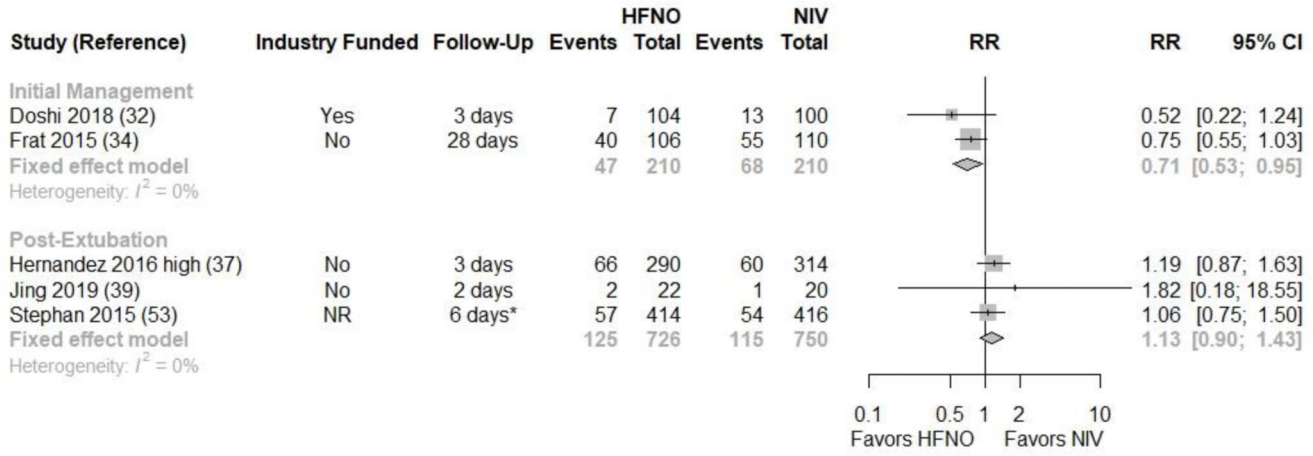


Figure 1.
Map of Certainty of Evidence

HFNO versus NIV: Intubation



HFNO versus NIV: Mortality

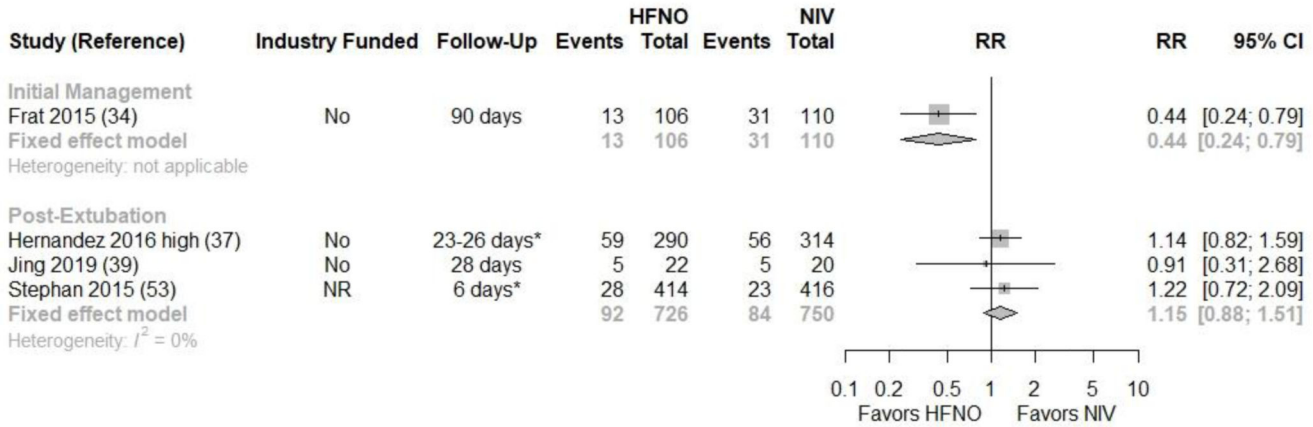


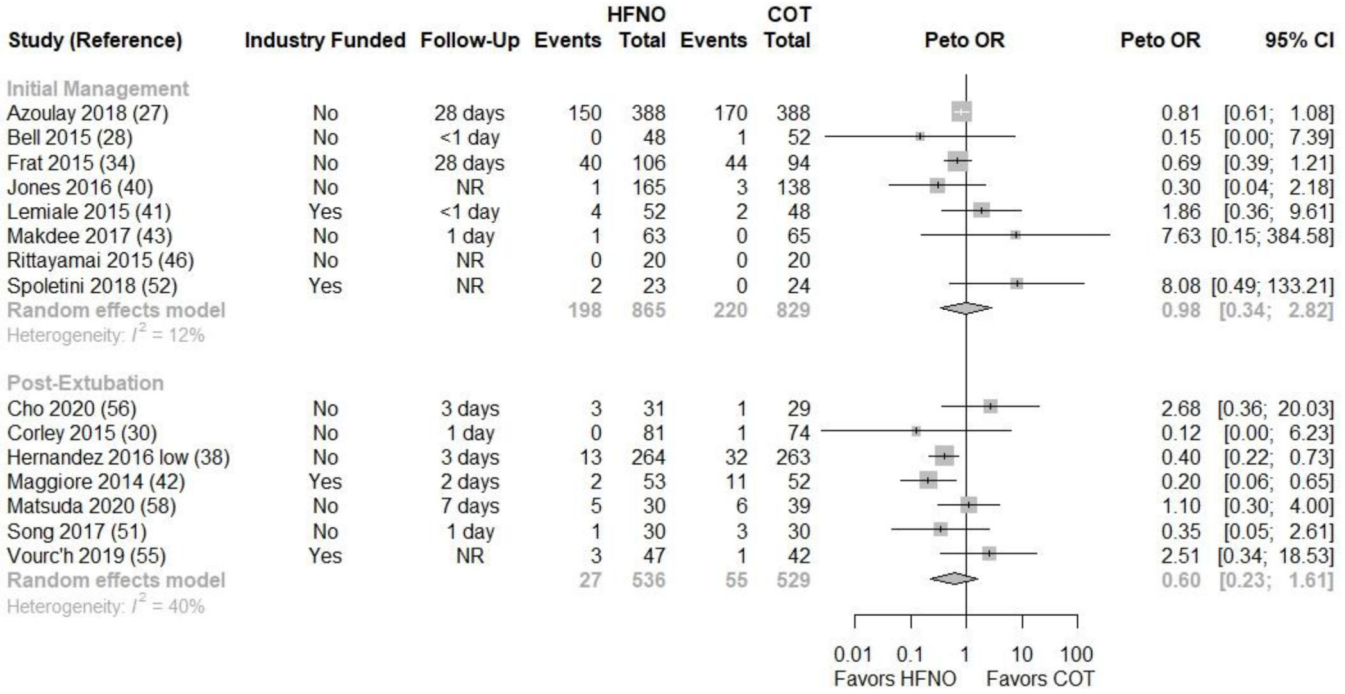
Figure 2. Intubation and Mortality Plots for HFNO versus NIV

CI=confidence interval; HFNO=high-flow nasal oxygen; ICU=intensive care unit; NIV=non-invasive ventilation; RR=risk ratio

*This is an estimated follow-up time based on the reported median ICU length of stay.

CI=confidence interval; HFNO=high-flow nasal oxygen; ICU=intensive care unit; NIV=non-invasive ventilation; RR=risk ratio*These are estimated follow-up times based on the reported median hospital or ICU length of stay.

HFNO versus COT: Intubation



HFNO versus COT: Mortality

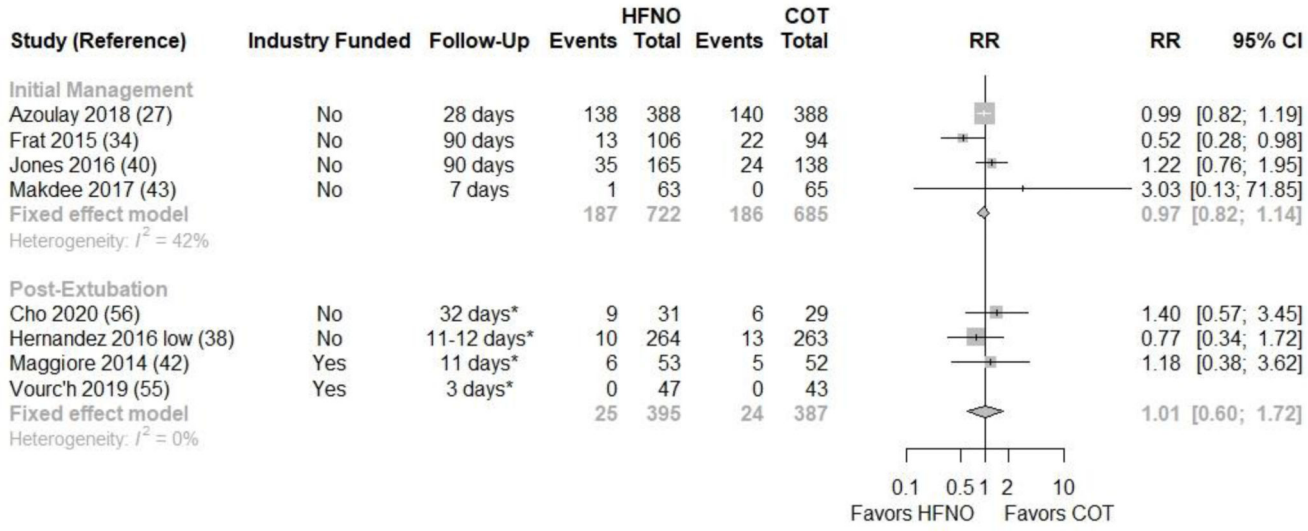


Figure 3. Intubation and Mortality Plots for HFNO versus COT

CI=confidence interval; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; OR=odds ratio; NR=not reported

CI=confidence interval; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; ICU=intensive care unit; RR=risk ratio

*These are estimated follow-up times based on the reported mean/median hospital or ICU length of stay.

Table 1.

Certainty of Evidence for HFNO versus NIV

Outcome: Population № of participants (studies) References	Relative effect or Standardized mean difference (95% CI)	Anticipated absolute event rates* HFNO	Anticipated absolute event rates* NIV	Absolute risk difference (95% CI)	Certainty	What happens
Initial management of acute respiratory failure population trials						
Intubation: 420 (2 RCTs) (32,34)	RR 0.71 (0.53 to 0.95)	**23.0%**	32.4%	−9.4% (−15.2 to −1.6)	Low†‡	HFNO may reduce intubations by a moderate amount
All-cause Mortality: 216 (1 RCT) (34)	RR 0.44 (0.24 to 0.79)	**12.4%**	28.2%	−15.8% (−21.4 to −5.9)	Low§	HFNO may reduce all-cause mortality by a large amount
Hospital-acquired Pneumonia: 216 (1 RCT) (34)	RR 0.46 (0.15 to 1.45)	**3.8%**	8.2%	−4.4% (−7.0 to 3.7)	Low‖	HFNO may reduce hospital-acquired pneumonia by a moderate amount.
ICU Admissions (yes/no): 204 (1 RCT) (32)	RR 0.98 (0.73 to 1.32)	**46.1%**	47.0%	−0.9% (−12.2 to 15.0)	Insufficient†‡¶	It is uncertain if HFNO reduces ICU admissions.
Length of stay, ICU: 420 (2 RCTs) (32,34)		**Mean (days) 7.7**	Mean (days) 8.3	MD −0.64 days (−1.67 to 0.39)	Insufficient†‡¶	It is uncertain if HFNO reduces ICU length of stay.
Length of stay, hospital: 372 (2 RCTs) (29,32)		**Mean (days) 11.6**	Mean (days) 11.1	MD 0.45 days (−0.69 to 1.59)	Low†‡	HFNO may make little or no difference in hospital length of stay.
Patient comfort, including related to dryness, based on VAS or % improved: 644 (7 RCTs) (29,32,34,35,49,50,54)	One trial (n=216) (34) reported HFNO improved comfort (SMD −0.51 [−0.78 to −0.24]) based on an unmarked 100 mm VAS and 1 (n=168) (29) reported higher percentage of patients feeling comfort with HFNO (88.2% vs. 67.9%; ARD 21.4% [9.4 to 33.4]). One trial (n=204) (32) reported little to no difference in patient comfort based on a 5-point VAS (medians 2 vs. 2 on scale, 5=most discomfort). Among 4 crossover trials (n=56), 3 reported little to no difference (35,50,54) and 1 reported improvement with HFNO in short-term patient comfort based on a 10-point numeric rating scale (49).				Low**††	HFNO may improve patient comfort.
Dyspnea, based on VAS or Borg scale scores or % improved: 464 (7 RCTs) (32,34,35,48–50,54)	One trial (n=177) (34) reported greater improvement in dyspnea short-term in patients allocated to HFNO compared with NIV (75.6% vs. 58.2%; ARD 17.3% [3.7 to 30.9]). One trial (n=180) (32) reported little to no difference in longer-term (SMD 0.21 [−0.12 to 0.54] dyspnea based on Borg. One trial (n=51) (48) reported little to no difference in short-term dyspnea based on 10-point VAS scale (mean change from baseline −0.1 vs. −0.9). Among 4 crossover trials (n=56), 2 reported little to no difference based on VAS, (50,54) 1 reported worsening based on VAS,(35) and 1 reported improvement in short-term dyspnea based on Borg with HFNO.(49)				Low**††	HFNO may make little or no difference in dyspnea.
Skin breakdown (facial pressure sore or nasal ulceration):	**Not reported**					
Post-extubation acute respiratory failure population trials						

Outcome: Population № of participants (studies) References	Relative effect or Standardized mean difference (95% CI)	Anticipated absolute event rates*		Absolute risk difference (95% CI)	Certainty	What happens
		HFNO	NIV			
Reintubation: 1476 (3 RCTs) (37,39,53)	RR 1.13 (0.90 to 1.43)	**17.3%**	15.3%	2.0% (−1.5 to 6.6)	Low‖	HFNO may increase reintubations by a small amount
All-cause Mortality: 1476 (3 RCTs) (37,39,53)	RR 1.15 (0.88 to 1.51)	**12.9%**	11.2%	1.7% (−1.3 to 5.7)	Low‖	HFNO may increase all-cause mortality by a small amount
Hospital-acquired Pneumonia: 1434 (2 RCTs) (37,53)	RR 0.90 (0.70 to 1.16)	**13.2%**	14.7%	−1.5% (−4.4 to 2.3)	Low‖	HFNO may make little to no difference in hospital-acquired pneumonia
ICU Admissions (yes/no)	**Not applicable**					
Length of stay, ICU: 1476 (3 RCTs) (37,39,53)	Pooled mean differences from 2 trials (37,39) (n=646) found HFNO made little or no difference in ICU length of stay (mean days NA; MD −0.98 days [−1.99 to 0.03]. One trial (n=830) reported little to no difference in ICU length of stay (medians 6 vs. 6 days).(53)				Low‖	HFNO may make little to no difference in ICU length of stay
Length of stay, hospital: 1434 (2 RCTs) (37,53)	One trial (n=604) (37) reported a lower hospital length of stay with HFNO (medians 23 vs. 26 days; MD −3 days [−6.8 to −0.8]). One trial (n=830) (53) reported little to no difference in hospital length of stay (medians 13 vs. 14 days).				Insufficient‖**	It is uncertain if HFNO reduces hospital length of stay.
Patient comfort, based on % improved or VAS: 872 (2 RCTs) (39,53)	One large trial (n=748) (53) reported little to no difference in the percentage of participants reporting good comfort (51.3% vs. 52.9%; ARD −1.6% [−8.7 to 5.6]). One small trial (n=42) (39) found HFNO may improve comfort (SMD −0.75 [−1.38 to −0.12]) based on VAS.				Low**††	HFNO may make little or no difference in patient comfort.
Dyspnea, based on % improved: 752 (1 RCT) (53)	RR 0.96 (0.86 to 1.08)	**58.0%**	60.4%	−2.4% (−8.5 to 4.8)	Low‖	HFNO may make little or no difference in dyspnea.
Skin breakdown (facial pressure sore or nasal ulceration): 1454 (3 RCTs) (37,39,53)	Peto OR 0.15 (0.02 to 1.13)	**4.6%**	24.3%	−19.7% (−23.7 to 2.3)	Low‡**	HFNO may reduce skin breakdowns by a large amount

Abbreviations

ARD=absolute risk difference; CI=confidence interval; HFNO=high flow nasal oxygen; ICU=intensive care unit; MD=mean difference; NA=not available; NIV=noninvasive ventilation; OR=odds ratio; RCT=randomized controlled trial; RR=risk ratio; SMD=standardized mean difference; VAS=visual analog scale

GRADES of certainty of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate

certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Insufficient certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Thresholds for determining magnitude by outcome

Intubation: Little or no effect: <2%; Small effect: 2–3.9%; Moderate effect: 4–9.9%; Large effect ≥10%

All-cause mortality: Little or no effect: <1%; Small effect: 1–1.9%; Moderate effect: 2–4.9%; Large effect: ≥5%

Pneumonia: Little or no effect: <2%; Small effect: 2–3.9%; Moderate effect: 4–9.9%; Large effect: ≥10%

Length of Stay: Little or no effect: <1 day; Small effect: ≥1 day; Moderate effect: NA; Large effect: ≥3 day

Skin breakdown: Little or no effect: <2%; Small effect: 2–3.9%; Moderate effect: 4–9.9%; Large effect: ≥10%

[*] Pooled event rates calculated with Freeman-Tukey double arcsine variance-stabilizing transformation can be found in Supplementary Table 11

Explanations

[†] Downgraded for study limitations, particularly moderate attrition and/or unclear allocation concealment

[‡] Downgraded for imprecision (wide CIs)

[§] Downgraded two levels based on results derived from one trial (n=216) and imprecision, difficult to determine if there is a definitive benefit based on only a single study.

[‖] Downgraded two levels for imprecision (very wide CIs) and/or difficult to interpret based on the variability in the reporting of the effects

[¶] Downgraded for indirectness, ICU stay possibly protocol driven

[**] Downgraded due to inconsistency

[††] Downgraded due to imprecision, difficult to interpret based on the variability in the reporting of the effects

Table 2.

Certainty of Evidence for HFNO versus COT

Outcome: Population № of participants (studies) References	Relative effect or Standardized mean difference (95% CI)	Anticipated absolute event rates* HFNO	COT	Absolute risk difference (95% CI)	Certainty	What happens
Initial management of acute respiratory failure population trials						
Intubation: 1694 (8 RCTs) (27,28,34,40,41,43,46,52)	Peto OR 0.98 (0.34 to 2.82)	**26.1%**	26.5%	−0.4% (−15.6 to 23.9)	Low†‡	HFNO may make little or no difference in intubation
All-cause Mortality: 1407 (4 RCTs) (27,34,40,43)	RR 0.97 (0.82 to 1.14)	**26.3%**	27.2%	−0.8% (−4.9 to 3.8)	Low†‡	HFNO may make little or no difference in all-cause mortality
Hospital-acquired Pneumonia: 200 (1 RCT) (34)	RR 0.44 (0.14 to 1.43)	**3.8%**	8.5%	−4.7% (−7.3 to 3.7)	Low§	HFNO may result in a reduction in hospital-acquired pneumonia by a moderate amount
ICU Admissions (yes/no): 403 (2 RCTs) (28,40)	RR 1.11 (0.58 to 2.12)	**8.8%**	7.9%	0.9% (−3.3 to 8.8)	Insufficient†‡//	It is uncertain if HFNO reduces ICU admissions.
Length of stay, ICU: 1036 (3 RCTs) (27,34,44)	Two trials (n=976) (27,34) found little or no difference in ICU length of stay (mean days NA; MD 0.41 days [−1.08 to 1.90]). One trial (n=60) reported little to no difference in ICU length (P=.20, no data reported).(44)				Insufficient†‡//	It is uncertain if HFNO reduces ICU length of stay
Length of stay, hospital: 1267 (4 RCTs) (27,40,43,44)	Four trials reported little to no difference in hospital length of stay based on medians (medians ranged from 1 to 24 vs. 1 to 27 days) (27,40,43) and/or p-values.(44)				Low§	HFNO may make little or no difference in hospital length of stay
Patient comfort, including comfort related to dryness, based on VAS or % improved: 1611 (12 RCTs total, some trials reported ≥1 measure of comfort) (27,28,31,34,40,41,43,45,46,49,52,54)	Pooled results from 4 trials (n=415) (34,43,46,52) found HFNO improved comfort (SMD −0.61 [−0.81 to −0.41]) based on VAS. Results pertaining to patient comfort based on median or unclear (27) scale scores varied: 1 trial (n=100) (28) reported higher comfort based on a 5 point Likert scale (4 vs. 3 on a 5-point scale, 5=most comfort, P=.04) while 2 trials (n=876) (27,41) reported little to no difference in patient comfort on a 10-point scale (7.9 vs. 6.8, 10=perfect) (27) and medians 3 vs. 3 on a 10-point scale (10=worst).(41) One trial (n=158) (40) reported a lower percentage of participants with discomfort related to dryness (29.8% vs. 45.3%; ARD −15.5% [−30.8 to −0.2]). Four small crossover studies (n=62) (31,45,49,54) reported little to no difference in short-term patient comfort.				Low¶ **	HFNO may improve patient comfort.
Dyspnea, based on VAS and Borg scale scores or % improved: 1799 (13 RCTs) (27,28,31,34,40,41,43,45–47,49,52,54)	Pooled results from 4 trials (n=258) (43,46,47,52) found HFNO improved dyspnea (SMD −0.56 [−1.35 to 0.24]) based on VAS and Borg scales. Two trials (n=876) (27,41) reported little to no difference in short-term dyspnea based on median scale scores (medians 2.3 to 3 vs. 2.6 to 3 on a 10-point scale, 10=most severe). Three trials (n=417) (28,34,40) reported a greater percentage of participants with improvement in dyspnea or improved				Low¶ **	HFNO may improve dyspnea.

Outcome: Population № of participants (studies) References	Relative effect or Standardized mean difference (95% CI)	Anticipated absolute event rates* HFNO	COT	Absolute risk difference (95% CI)	Certainty	What happens
	breathing (78.0% vs. 55.8%; ARD 22.2% [13.3 to 31.1]). Four small crossover studies (n=62) (31,45,49,54) reported little to no difference in short-term dyspnea.					
Skin breakdown (facial pressure sore or nasal ulceration): 431 (2 RCTs) (40,43)	Both trials reported no incidences of skin breakdown were observed with HFNO. For COT, one trial reported no incidences (40) and the other trial did not report this outcome.(43)				Insufficient††	It is uncertain if HFNO reduces skin breakdown.
Post-extubation acute respiratory failure population trials						
Reintubation: 1065 (7 RCTs) (30,38,42,51,55,56,58)	Peto OR 0.60 (0.23 to 1.61)	**6.5%**	10.4%	−3.9% (−7.8 to 5.3)	Low§	HFNO may reduce reintubations by a small amount
All-cause Mortality: 782 (4 RCTs) (38,42,55,56)	RR 1.01 (0.60 to 1.72)	**6.3%**	6.2%	0.1% (−2.5 to 4.5)	Low§	HFNO may make little or no difference in all-cause mortality
Hospital-acquired Pneumonia: 527 (1 RCT) (38)	RR 0.50 (0.13 to 1.97)	**1.1%**	2.3%	−1.1% (−2.0 to 2.2)	Low§	HFNO may make little or no difference in hospital-acquired pneumonia
ICU Admissions (yes/no)	**Not applicable**					
Length of stay, ICU: 1006 (6 RCTs) (30,38,42,55,56,58)	Pooled results from 5 trials (n=479) (30,42,55,56,58) found HFNO makes little or no difference in ICU length of stay (approximately 6 days in each group; MD 0.19 days [−0.19 to 0.57]. One trial not pooled (n=527) (38) reported little to no difference in ICU length of stay (medians 6 vs. 6 days).				Moderate‡	HFNO probably makes little or no difference in ICU length of stay
Length of stay, hospital: 587 (2 RCTs) (38,56)		**Study 1** Median 11 (IQR 6 to 15) **Study 2 Mean** **37.7**	Study 1 Median 12 (IQR 6 to 16) Study 2 Mean 25.7	Study 1 (38) MD 4 days (−28 to 32) Study 2 (56) MD 12 days (0.15 to 23.85)	Insufficient††	It is uncertain if HFNO improves hospital length of stay.
Patient comfort, including comfort related to dryness and interface, based on VAS or % improved: 324 (4 RCTs total, some trials reported ≥1 measure of comfort) (42,51,55,58)	One trial (n=105) (42) found HFNO improved comfort (SMD −0.70 [−1.10 to −0.31]) based on a 10 point VAS where lower is better. One trial (n=60) (51) reported higher comfort or less dryness with HFNO based on median scale scores. One trial (n=90) (55) reported a lower percentage of participants with discomfort related to dryness with HFNO (38.3% vs. 69.8%; ARD −31.5% [−51.0 to −11.9]). Two trials (n=165) (42,52) reported lower discomfort related to interface with HFNO versus COT (Trial 1 SMD −0.89 [−1.29 to −0.49]) (42) and Trial 2 medians 3 vs. 7 on a 10-point scale, 10=maximal discomfort, P<.001).(51) One trial (n=69) (58) reported little to no difference in any measure of discomfort on a 10-point scale (nasal, oral, or pharynx) based on medians.				Low§	HFNO may improve patient comfort.
Dyspnea, based Borg scale score: 155 (1 RCT) (30)	One trial reported little to no difference in short-term dyspnea (medians 1 vs. 0 on a 10-point scale, 10=maximal dyspnea).				Insufficient††	It is uncertain if HFNO improves dyspnea.

Outcome: Population № of participants (studies) References	Relative effect or Standardized mean difference (95% CI)	Anticipated absolute event rates* HFNO	COT	Absolute risk difference (95% CI)	Certainty	What happens
Skin breakdown (facial pressure sore or nasal ulceration): 527 (1 RCT) (38)	One trial reported no incidences of skin breakdown were observed with HFNO but this outcome was not reported for the COT arm.				Insufficient††	It is uncertain if HFNO reduces skin breakdown.

Abbreviations

ARD=absolute risk difference; CI=confidence interval; COT=conventional oxygen therapy; HFNO=high flow nasal oxygen; ICU=intensive care unit; IQR=interquartile range; MD=mean difference; NA=not available; OR=odds ratio; RCT=randomized controlled trial; RR=risk ratio; SMD=standardized mean difference; VAS=visual analog scale

GRADES of certainty of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Insufficient certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Thresholds for determining magnitude by outcome

Intubation: Little or no effect: <2%; Small effect: 2–3.9%; Moderate effect: 4–9.9%; Large effect ≥10%

All-cause mortality: Little or no effect: <1%; Small effect: 1–1.9%; Moderate effect: 2–4.9%; Large effect: ≥5%

Pneumonia: Little or no effect: <2%; Small effect: 2–3.9%; Moderate effect: 4–9.9%; Large effect: ≥10%

Length of Stay: Little or no effect: <1 day; Small effect: ≥1 day; Moderate effect: NA; Large effect: ≥3 day

Skin breakdown: Little or no effect: <2%; Small effect: 2–3.9%; Moderate effect: 4–9.9%; Large effect: ≥10%

*Pooled event rates calculated with Freeman-Tukey double arcsine variance-stabilizing transformation can be found in Supplementary Table 11.

Explanations

†Downgraded for imprecision (wide CIs)

‡Downgraded for study limitations

§Downgraded two levels for large imprecision (very wide CIs) and/or sparse data and/or difficult to interpret based on the variability in the reporting of the effects

‖Downgraded for indirectness, ICU stay possibly protocol driven

¶Downgraded due to inconsistency

**Downgraded due to imprecision, difficult to interpret based on the variability in the reporting of the effect

††Downgraded to insufficient based on the enormity of the imprecision or difficult to interpret based on the variability in the reporting of the effects