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# Noninvasive respiratory support following extubation in critically ill adults: a systematic review and network meta-analysis

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## Abstract

**Purpose:** Systematic review and network meta-analysis to investigate the efficacy of noninvasive respiratory strategies, including noninvasive positive pressure ventilation (NIPPV) and high-flow nasal cannula (HFNC), in reducing extubation failure among critically ill adults.

**Methods:** We searched databases from inception through October 2021 for randomized controlled trials (RCTs) evaluating noninvasive respiratory support therapies (NIPPV, HFNC, conventional oxygen therapy, or a combination of these) following extubation in critically ill adults. Two reviewers performed screening, full text review, and extraction independently. The primary outcome of interest was reintubation. We used GRADE to rate the certainty of our findings.

**Results:** We included 36 RCTs (6806 patients). Compared to conventional oxygen therapy, NIPPV (OR 0.65 [95% CI 0.52–0.82]) and HFNC (OR 0.63 [95% CI 0.45–0.87]) reduced reintubation (both moderate certainty). Sensitivity analyses showed that the magnitude of the effect was highest in patients with increased baseline risk of reintubation. As compared to HFNC, no difference in incidence of reintubation was seen with NIPPV (OR 1.04 [95% CI 0.78–1.38], low certainty). Compared to conventional oxygen therapy, neither NIPPV (OR 0.8 [95% CI 0.61–1.04], moderate certainty) or HFNC (OR 0.9 [95% CI 0.66–1.24], low certainty) reduced short-term mortality. Consistent findings were demonstrated across multiple subgroups, including high- and low-risk patients. These results were replicated when evaluating noninvasive strategies for prevention (prophylaxis), but not in rescue (application only after evidence of deterioration) situations.

**Conclusions:** Our findings suggest that both NIPPV and HFNC reduced reintubation in critically ill adults, compared to conventional oxygen therapy. NIPPV did not reduce incidence of reintubation when compared to HFNC. These findings support the preventative application of noninvasive respiratory support strategies to mitigate extubation failure in critically ill adults, but not in rescue conditions.

**Keywords:** Critical care medicine, Mechanical ventilation, Extubation failure, High-flow nasal cannula

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## Introduction

Invasive mechanical ventilation is a widely used life-saving therapy for many critically ill patients [1, 2], but is also associated with important complications, including ventilator-induced lung injury, nosocomial infections [e.g., ventilator-associated pneumonia (VAP)], neuromuscular weakness, and delirium [3–5]. Furthermore, invasive mechanical ventilation requires substantial resource utilization, and is one of the most costly therapies provided in the intensive care unit (ICU) [6]. For all these reasons, providers seek timely and safe liberation of patients from mechanical ventilation [7].

Extubation failure is associated with important harms [8], including increased mortality [9, 10], and occurs in approximately 10–15% of extubated patients. Incidence is even higher (25–40%) in certain patient populations (e.g., patients with heart failure or chronic obstructive pulmonary disease) [7, 11]. To mitigate the risk of extubation failure, clinicians have used noninvasive respiratory support interventions in the post-extubation period to optimize gas exchange and decrease patients' oxygen cost of breathing [12]. These interventions [noninvasive positive pressure ventilation (NIPPV) and high-flow nasal cannula (HFNC)] have been shown to be efficacious in preventing initial intubation in patients with hypoxemic respiratory failure [13], but their efficacy in preventing post-extubation respiratory failure and reintubation is less clear. These support strategies may also be associated with increased patient discomfort and healthcare resource utilization [14]. Further to this, survey studies have demonstrated provider skepticism regarding the efficacy of these interventions [15]. As such, there is substantial practice variation worldwide in the application of such strategies, with overall limited use [16, 17].

We conducted a systematic review and network meta-analysis of randomized controlled trials (RCTs) to evaluate the relative efficacy of conventional oxygen therapy, NIPPV, HFNC, and the strategy of alternating NIPPV and HFNC during the post-extubation period in reducing extubation failure and short-term mortality among critically ill adults. We hypothesized that NIPPV, HFNC, and alternating NIPPV and HFNC would reduce extubation failure, as compared to conventional oxygen therapy.

## Methods

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement extension for network meta-analysis [18, 19], and registered our protocol with the Open Science Framework (<https://www.osf.io/49xgd>).

In this network meta-analysis of 36 randomized trials and 6806 patients, we found that both NIPPV and HFNC reduced reintubation in the post-extubation period, compared to conventional oxygen therapy. Magnitude of benefit was increased among patients at highest risk of reintubation. The results supported the preventative or prophylactic application of noninvasive ventilation, but not use of these interventions for rescue.

## Data sources and search strategy

We searched six databases (Medline, PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Database of Systematic Reviews) from inception to October 11, 2021. An experienced health sciences librarian helped develop the search strategy (Supplemental Fig. 1). We conducted further surveillance searches using the 'related articles' feature [20], and performed a grey literature search, including screening the reference lists of all included studies, and subsequent guidelines on non-invasive ventilation.

## Study selection

Two reviewers (SMF and AT) independently screened titles and abstracts identified through the searches using Covidence (Melbourne, Australia), and then independently assessed full texts of the selected articles from phase one. Reviewers resolved disagreements by discussion. We included English-language RCTs (parallel, cluster, or cross-over) meeting the following criteria: (1) enrolled adult patients ( $\geq 16$  years of age); (2) conducted primarily ( $\geq 70\%$  of patients) in an ICU setting; (3) randomized patients to receive NIPPV, HFNC, conventional oxygen therapy, or a combination of the above; (4) conducted in the post-extubation period, and evaluated these treatments for prevention (i.e. prophylactic application immediately post-extubation) or rescue (i.e. application only in patients developing symptoms and signs of respiratory failure post-extubation); and (5) reported at least one of the outcomes of interest. We excluded trials that: (1) were conducted in the emergency department, operating room, or post-anesthetic care unit; (2) evaluated the effect of these interventions on "weaning" (e.g. passing a spontaneous breathing trial) but did not provide data on extubation failure; (3) exclusively evaluated patients with self-extubation; (4) evaluated these interventions for transitioning to palliative care; and (5) randomized patients to liberation or post-extubation protocols, rather than treatments [21].

The primary outcome of interest was extubation failure, defined as reintubation using an endotracheal tube and recurrent invasive mechanical ventilation. In the absence of a widely accepted time-based definition of

“extubation failure” [11], we included trials that evaluated this outcome at any point during the index ICU admission. Other important outcomes included short-term mortality (28-day, 30-day, or in-hospital), incidence of VAP, patient discomfort (described as a binary outcome in the included trials), incidence of tracheostomy, time to re-intubation, ICU length of stay, and total hospital length of stay. For studies reporting length of stay as a median (with interquartile range), this was converted to a mean (with standard deviation), using appropriate methods [22].

### Data extraction

One investigator (SMF) used a pre-designed data extraction form to collect the following variables: author information, publication year, eligibility criteria, and number of patients (Supplemental Table 1). Two investigators (SMF and AT) independently collected data related to descriptions of interventions and outcomes. Disagreements were resolved through discussion.

### Risk of bias assessment

Two reviewers (SMF and AT) independently assessed the risk of bias of the studies, using a modified Cochrane Collaboration tool [23], that included sequence generation, allocation sequence concealment, blinding, missing outcome data, and other biases. Reviewers resolved disagreement through discussion.

### Data synthesis and analysis

For each outcome and each pair of interventions, we calculated odds ratios (OR) and corresponding 95% confidence intervals (CIs). Initially, we performed conventional pairwise meta-analysis using a DerSimonian and Laird random-effects model for all comparisons with two RCTs or more [24]. We assessed heterogeneity for each direct comparison using visual inspection of forest plots, the  $I^2$  statistic and the Chi-squared test. We evaluated the feasibility of conducting network meta-analysis by evaluating the: (1) availability of evidence (e.g. number of trials, number of interventions); (2) homogeneity of study designs, patients, and characteristics of interventions across the body of evidence (transitivity assumption); (3) structural properties of the network of evidence (e.g. connectivity); and (4) coherence in network (using the ‘design-by-treatment’ model), and in each closed loop of the network.

We performed frequentist random-effects network meta-analysis using multivariate meta-analysis assuming a common heterogeneity parameter [25, 26]. We confirmed the coherence assumption in the entire network using ‘design-by-treatment’ model (global test), as described by Higgins et al. [27]. We also used the side

splitting method to assess the presence of incoherence between direct and indirect estimates of the effect [28, 29]. For each outcome, we estimated ranking probabilities, the Surface Under the Cumulative Ranking Curve (SUCRA), and generated mean treatment rankings. For all direct comparisons, we assessed the small-study effect using Harbord’s test for binary outcomes and Egger’s test for continuous outcomes when 10 or more RCTs were available [30]. We conducted all analyses using STATA 16 (StataCorp, College Station, TX, USA).

### Subgroups and sensitivity analyses

While most trials included mixed populations of critically ill patients, we expected that some trials had exclusively recruited particular patient populations. To explore these between-trial comparisons, we performed network meta-regression among pre-specified subgroups (mixed ICU patients, surgical patients, patients at “high risk” for extubation failure, patients with hypercapnic respiratory failure, and study continent) to assess for effect modification by subgroup. For any subgroup effect that was found to be statistically significant, we used the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) to evaluate credibility [31]. Finally, to further assess these therapies across various conditions, we performed network meta-regression to adjust for baseline risk of reintubation among the included trials. The baseline risk for reintubation was generated using the incidence of reintubation among patients receiving conventional oxygen therapy in the included trials. Additionally, we performed a sensitivity analysis using a possible range of baseline risks for reintubation (range from 5 to 40%, supported by evidence and confirmed by our clinical experts) to estimate absolute risk reductions and number need to treat (NNT) for the outcome of reintubation.

Trials may also differ in timing of patient recruitment and application of noninvasive ventilation. Although we expected that most trials would test the efficacy of prophylactic or preventative noninvasive ventilation in the immediate post-extubation period, some trials may exclusively recruit patients with evidence of clinical deterioration prior to rescue application of noninvasive ventilation. Consequently, we performed sensitivity analyses only including trials evaluating the efficacy of noninvasive ventilation for prevention of reintubation following extubation. We additionally performed conventional meta-analysis among the trials that used noninvasive ventilation for rescue in patients with evidence of respiratory distress prior to application.

### Assessment of certainty of evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence for each comparison [32]. The certainty assessment addresses the domains of risk of bias, imprecision, inconsistency, indirectness, intransitivity, publication bias, and incoherence [32]. Imprecision for each comparison was assessed at the network level, and not at the level of the direct or indirect estimate. Given our presumption that blinding clinicians to noninvasive treatments would not be possible in the included trials, and that a lack of blinding might lead to potential differences in adjunctive therapies (e.g., suctioning, positioning) that might affect the outcome, we decided to rate down our GRADE certainty for subjective outcomes (e.g., extubation failure), but not objective outcomes (e.g., mortality). We applied a minimally contextualized approach to evaluate certainty in effect estimates and draw conclusions from network meta-analyses [33].

## Results

### Search results, study characteristics, and risk-of-bias

Of 6899 citations (Supplemental Fig. 2) identified in the search, we screened 6605 following removal of duplicates, and 58 underwent full-text review. We included 36 RCTs [34–69], examining 6806 patients (all ICU patients). Characteristics of the included trials are shown in Table 1, and detailed characteristics are shown in Supplemental Table 2. Of these, 29 studies (2129 patients, 31.3% of patients) investigated conventional oxygenation therapy (delivered via nasal prongs or facemask) [34–43, 45–47, 49–58, 60, 62, 63, 67–69], 24 studies (2149 patients, 31.3%) investigated NIPPV (using facemask interface) [34, 38, 40, 41, 43, 44, 46–51, 54–56, 59–61, 63, 64, 66–69], 18 studies (2189 patients, 32.2%) investigated HFNC [35–37, 39, 42, 44, 45, 48, 52, 53, 57–59, 61, 62, 64–66], and 1 study (339 patients, 5.0%) evaluated the combination of alternating NIPPV and HFNC [65]. Risk-of-bias assessments are shown in Supplemental Table 3. While the majority of trials were considered low risk-of-bias in most domains, all trials were considered to have probable high risk-of-bias with regard to blinding, given the practical inability to blind treating providers to non-invasive respiratory strategies.

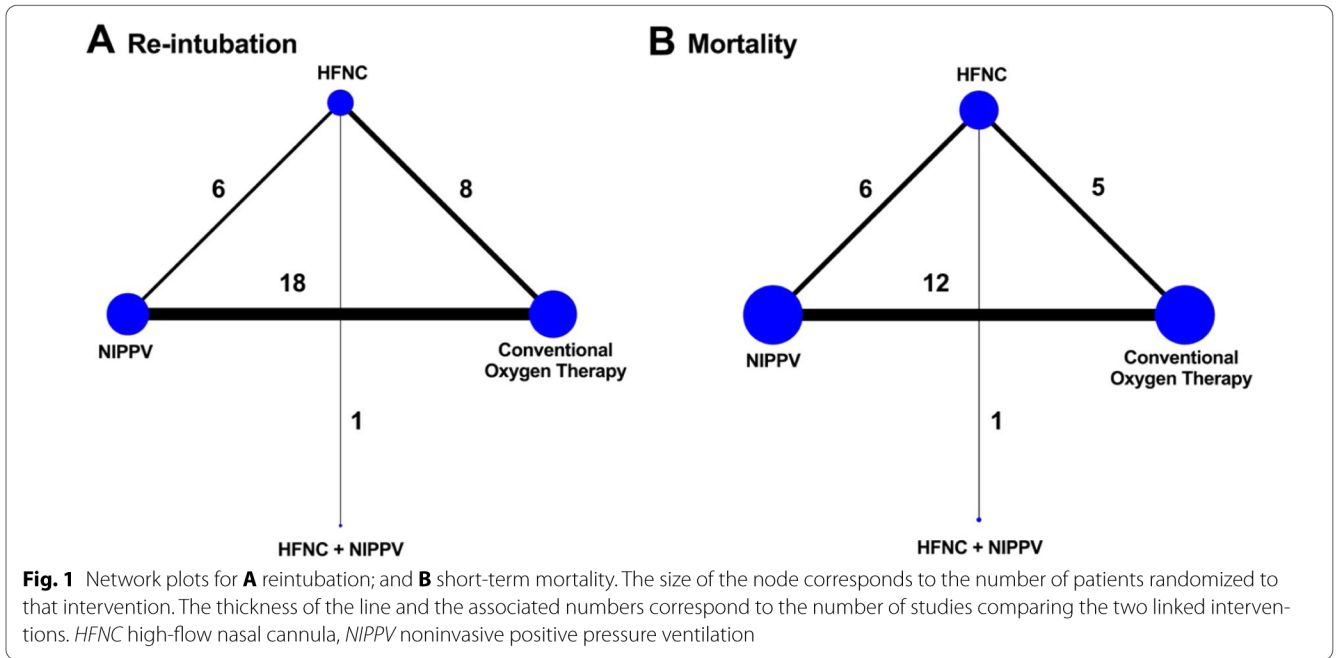
### Reintubation

The network plot for reintubation is displayed in Fig. 1, and the summary of findings, including network estimates, is shown in Table 2. We found that, compared to conventional oxygen therapy, both NIPPV (OR 0.65 [95% CI 0.52–0.82]; absolute risk difference – 5.18 [95% CI

**Table 1 Characteristics of the 36 randomized clinical trials**

Description	Overall (36 studies, n = 6806)	
	Number of studies (%)	Number of patients (%)
<b>Continent of study</b>		
Europe	14 (38.9)	4062 (59.7)
Asia	14 (38.9)	1596 (23.4)
North America	3 (8.3)	163 (2.4)
Australia	2 (5.6)	495 (7.3)
Multicontinental	3 (8.3)	490 (7.3)
<b>Year of publication</b>		
1995–1999	1 (2.8)	93 (1.4)
2000–2004	2 (5.6)	302 (4.4)
2005–2009	4 (11.1)	415 (6.1)
2010–2014	8 (22.2)	1317 (19.4)
2015–2021	21 (58.3)	4679 (68.7)
<b>Sites</b>		
Single center	19 (52.8)	1941 (28.5)
Multicenter	17 (47.2)	4865 (71.5)
<b>Intensive care unit population</b>		
Medical/mixed	14 (38.9)	2273 (33.4)
Surgical	10 (27.8)	2259 (33.2)
High-risk patients	7 (19.4)	1859 (27.3)
Hypercapnic respiratory failure	5 (13.9)	415 (6.1)
<b>Interventions studied</b>		
Conventional oxygen therapy	29 (80.6)	2129 (31.3)
Noninvasive positive pressure ventilation	24 (66.7)	2149 (31.6)
High-flow nasal cannula	18 (50)	2189 (32.2)
Combined noninvasive positive pressure ventilation and high-flow nasal cannula	1 (2.8)	339 (5)
<b>Indication for noninvasive ventilation</b>		
Prevention/prophylaxis	31 (86.1)	6092 (89.5)
Rescue	5 (13.9)	714 (10.5)

– 8.09 to – 2.26]) and HFNC (OR 0.63 [95% CI 0.45–0.87]; absolute risk difference, – 3.84 [95% CI – 6.7 to – 0.98]) reduced the incidence of reintubation (moderate certainty). NIPPV had no effect on reintubation compared to HFNC (OR 1.04 [95% CI 0.78–1.38]; absolute risk difference – 1.34 [95% CI – 4.40 to 1.72], low certainty). The combination of alternating HFNC and NIPPV did not decrease the incidence of reintubation, as compared to NIPPV alone (OR 0.58 [95% CI 0.3–1.11]; absolute risk difference – 5.07 [95% CI – 13.38 to 3.24]), or HFNC alone (OR 0.6 [95% CI 0.33–1.08]; absolute risk difference – 6.41 [95% CI – 14.13 to 1.31]), based on low certainty evidence. Direct estimates, indirect estimates, and SUCRA table are shown in Supplemental Table 4.



**Table 2** Network and absolute estimates evaluating the efficacy of the interventions for prevention of reintubation in critically ill adults

Comparison	Network odds ratio (95% CI)	Absolute risk difference (95% CI)	Number needed to treat	GRADE
NIPPV vs conventional oxygen	0.65 (0.52–0.82)	– 5.18 (– 8.09 to – 2.26)	20 (13 to 45)	Moderate <sup>a</sup>
HFNC vs conventional oxygen	0.63 (0.45–0.87)	– 3.84 (– 6.7 to – 0.98)	26 (15 to 102)	Moderate <sup>a</sup>
NIPPV vs HFNC	1.04 (0.78–1.38)	– 1.34 (– 4.4 to 1.72)	N/A	Low <sup>a,b</sup>
HFNC + NIPPV vs conventional oxygen	0.38 (0.19–0.74)	– 10.25 (– 18.49 to – 2.01)	10 (6 to 50)	Moderate <sup>a</sup>
HFNC + NIPPV vs NIPPV	0.58 (0.3–1.11)	– 5.07 (– 13.38 to 3.24)	N/A	Low <sup>a,b</sup>
HFNC + NIPPV vs HFNC	0.6 (0.33–1.08)	– 6.41 (– 14.13 to 1.31)	N/A	Low <sup>a,b</sup>

*NIPPV* noninvasive positive pressure ventilation, *HFNC* high-flow nasal cannula, *GRADE* grading of recommendations assessment, development, and evaluation, *OR* odds ratio, *CI* confidence interval

<sup>a</sup> Lowered for risk of bias

<sup>b</sup> Lowered one level for imprecision as CIs don't exclude harm

### Mortality

The efficacy of these treatments in preventing short-term all-cause mortality is depicted in the network plot (Fig. 2b), with summary findings displayed in Table 3. Compared to conventional oxygen therapy, neither NIPPV (OR 0.8 [95% CI 0.61–1.04]; absolute risk difference – 1.65 [95% CI – 3.81 to 0.5], moderate certainty), nor HFNC (OR 0.9 [95% CI 0.66–1.24]; absolute risk difference – 0.29 [95% CI – 1.58 to 1.01]), were associated with reduced short-term mortality, based on low certainty evidence. NIPPV did not reduce mortality compared to HFNC (OR 0.89 [95% CI 0.69–1.13]; absolute risk difference – 1.37 [95% CI – 3.47 to 0.72], moderate certainty). Direct estimates, indirect estimates, and SUCRA table are shown in Supplemental Table 4.

### Ventilator-associated pneumonia, discomfort, and other outcomes

Compared to conventional oxygen therapy, both NIPPV (OR 0.39 [95% CI 0.25–0.61]) and HFNC (OR 0.35 [95% CI 0.21–0.59]) were associated with a reduced incidence of VAP (moderate certainty) (Supplemental Table 5). As documented by clinician ratings or patient-reported experience, NIPPV was associated with increased patient discomfort (OR 30.89 [95% CI 1.48–645.7], low certainty), compared to conventional oxygen therapy (Supplemental Table 6). Finally, comparison between the treatments and outcomes including ICU length of stay (Supplemental Table 7) and incidence of tracheostomy (Supplemental Fig. 3) were uncertain, due to very low certainty of evidence.

**Table 3 Network estimates evaluating the efficacy of the interventions for prevention of short-term all-cause mortality in critically ill adults**

Comparison	Network odds ratio (95% CI)	Absolute risk difference (95% CI)	GRADE
NIPPV vs conventional oxygen	0.8 (0.61–1.04)	– 1.65 (– 3.81 to 0.5)	Moderate <sup>b</sup>
HFNC vs conventional oxygen	0.9 (0.66–1.24)	– 0.29 (– 1.58 to 1.01)	Low <sup>a</sup>
NIPPV vs HFNC	0.89 (0.69–1.13)	– 1.37 (– 3.47 to 0.72)	Moderate <sup>b</sup>
HFNC + NIPPV vs conventional oxygen	0.95 (0.56–1.62)	0.41 (– 5.36 to 6.18)	Low <sup>a</sup>
HFNC + NIPPV vs NIPPV	1.19 (0.73–1.95)	2.07 (– 3.93 to 8.07)	Low <sup>a</sup>
HFNC + NIPPV vs HFNC	1.05 (0.69–1.62)	0.7 (– 4.93 to 6.33)	Low <sup>a</sup>

NIPPV noninvasive positive pressure ventilation, HFNC high-flow nasal cannula, GRADE grading of recommendations assessment, development, and evaluation, OR odds ratio, CI confidence interval

Imprecision only incorporated at network level not at direct or indirect

<sup>a</sup> Lowered two levels for imprecision as wide CIs don't exclude important harm

<sup>b</sup> Lowered one level for imprecision as CIs don't exclude harm

### Subgroup and sensitivity analyses

The results of network meta-regression among the subgroups of interest (proportion of surgical patients, proportion of “high risk” patients, proportion of hypercapnic patients, and by continent) for the outcomes of reintubation and short-term mortality are shown in Supplemental Tables 8–9. We did not find evidence of an effect modification among subgroups of patient populations, but did find evidence for statistically significant effect modification by continent of study publication, with trials conducted in Europe demonstrating greater efficacy of NIPPV and HFNC, as compared to conventional oxygen therapy. However, the credibility of this subgroup finding was judged to be low. Table 4 shows that compared to conventional oxygen, the predicted absolute effect of NIPPV, HFNC, and alternating HFNC and NIPPV for prevention of reintubation are highest in patients at increased baseline risk of reintubation.

The sensitivity analyses that only included studies testing the efficacy of noninvasive respiratory support for prevention or prophylaxis are shown in Supplemental

Tables 10–12, and are consistent with the primary analyses. Conversely, pairwise meta-analyses did not demonstrate benefit of noninvasive ventilation in reducing reintubation or death when provided as rescue therapy (Supplemental Figs. 4–5).

### Discussion

Extubation failure is a critical outcome that is prognostically important (i.e., associated with mortality) and is patient-important [9, 10]. Therefore, treatments that may mitigate the risk of reintubation are of value to a variety of stakeholders [70]. Although noninvasive respiratory support in the post-extubation period has been studied, there is variation in its use in this setting [71], and providers have expressed skepticism in its efficacy [15]. In this context, we found evidence suggesting that both NIPPV and HFNC reduced reintubation in the post-extubation period compared to conventional oxygen therapy, with increased effect size in patients with the highest baseline risk for reintubation. These effects were present when noninvasive respiratory support

**Table 4 Predicted absolute network estimates (with 95% confidence intervals) for efficacy of the interventions for prevention of reintubation in critically ill adults, using baseline risk for reintubation**

Comparison	NIPPV (compared to conventional oxygen)		HFNC (compared to conventional oxygen)		HFNC + NIPPV (compared to conventional oxygen)	
	Absolute estimate <sup>a</sup>	NNT	Absolute estimate	NNT	Absolute estimate	NNT
5% risk of reintubation	– 1.69 (– 2.4 to – 0.81)	60 (42 to 124)	– 1.84 (– 2.74 to – 0.57)	55 (37 to 176)	– 3.09 (– 4.06 to – 1.11)	33 (25 to 91)
10% risk of reintubation	– 3.26 (– 4.64 to – 1.56)	31 (22 to 65)	– 3.56 (– 5.34 to – 1.09)	29 (19 to 92)	– 6.05 (– 8.04 to – 2.12)	17 (12 to 48)
20% risk of reintubation	– 6.02 (– 8.69 to – 2.82)	17 (12 to 36)	– 6.58 (– 10.09 to – 1.97)	16 (10 to 51)	– 11.53 (– 15.69 to – 3.86)	9 (7 to 26)
40% risk of reintubation	– 9.77 (– 14.63 to – 4.38)	11 (7 to 23)	– 10.73 (– 17.32 to 3.03)	N/A	– 20.21 (– 29.29 to – 6.08)	5 (4 to 17)

HFNC high-flow nasal cannula, NIPPV noninvasive positive pressure ventilation, NNT number needed to treat

<sup>a</sup> Absolute estimates refer to the risk difference between the interventions (NIPPV, HFNC, and HFNC + NIPPV) and conventional oxygen therapy

was used prophylactically following extubation, but not when it was applied for rescue in patients who were deteriorating post-extubation. Finally, no difference between NIPPV and HFNC was detected in prevention of reintubation. These data have important implications for providers, patients, and clinical practice guidelines.

The most recent iteration of the European Respiratory Society and American Thoracic Society clinical practice guidelines on the use of NIPPV, published in 2017, provided a conditional recommendation (low certainty) for its use in high-risk patients post-extubation, and a conditional recommendation (low certainty) against the use of NIPPV in low-risk patients post-extubation [72]. These recommendations were based on evidence existing at the time of guideline development, which showed benefit of NIPPV only in selected populations. Use of post-extubation HFNC was addressed in the more recent European Society of Intensive Care Medicine guideline, which provided a conditional recommendation (low certainty) for its use in high-risk patients who had received invasive ventilation for more than 24 h [73].

Our work has important implications in this regard. Here, we found evidence suggesting that both NIPPV and HFNC reduced the incidence of extubation failure in heterogeneous cohorts of ICU patients, without effect modification in higher risk patients, as demonstrated in our subgroup analyses. This reduction in reintubation likely contributed to the lower incidence of VAP among patients receiving noninvasive ventilation. Previous work comparing the use of NIPPV during weaning against invasive ventilation has demonstrated its superiority in reducing mortality, while preventing weaning failure and reducing ICU length of stay [74]. Our review builds upon this existing work, and shows that NIPPV is likely superior to conventional oxygen therapy in reducing reintubation in the post-extubation period. Compared to the existing guideline recommendations, our results are aligned with and reinforced by more recent randomized data, supporting more widespread use of noninvasive ventilation in the post-extubation period. In light of these new trials and findings, updated guidelines are warranted.

Further to this, our review evaluated heterogeneity of treatment effect, which has implications for the application of our findings. Of note, the effect size of these interventions was greatest for patients at highest baseline risk of reintubation. For example, as compared to conventional oxygen, NIPPV had a NNT for prevention of reintubation of 60 among patients with a 5% baseline risk of reintubation, but a NNT of 11 in patients with a 40% baseline risk. This is important in evaluating the use of these therapies relative to their resource use and individual costs. That is, routine use of noninvasive ventilation may be considered in high-risk patient populations,

but the purported benefits may not outweigh associated resource use and costs in low-risk populations.

We performed further sensitivity analyses comparing the use of noninvasive respiratory support therapies for prevention/prophylaxis, or rescue of symptomatic patients. Our findings were replicated among trials evaluating use of noninvasive ventilation for prevention or prophylaxis, supporting the efficacy of these therapies in this context. However, we did not find similar efficacy of noninvasive ventilation in the rescue of symptomatic patients post-extubation. We found only one ICU trial demonstrating benefit of NIPPV in the rescue setting [46], and this trial was conducted in post-operative patients where post-extubation hypoxemia is most likely secondary to atelectasis, and where NIPPV has been shown to have some evidence of benefit in ward patients [75, 76]. In mixed ICU populations, rescue use of NIPPV post-extubation was not beneficial, and indeed may be associated with harm [38]. Together, our work importantly differentiates between these two clinical indications, and identifies disparate conclusions favouring use in prophylactic application, but not rescue.

Our findings were less conclusive when examining the differences in effect between NIPPV and HFNC. Although HFNC does have some theoretical benefits compared to NIPPV (e.g., improved patient comfort, and fewer hemodynamic consequences), we found no difference in terms of reintubation or mortality for NIPPV compared to HFNC. HFNC generally consumes fewer healthcare resources and is more suitable for use outside the ICU setting, while NIPPV is typically applied in an ICU or step-down unit [52]. Whether NIPPV is superior to HFNC in this context remains unclear, underscoring the need for further trials. Finally, we evaluated the alternating combination of HFNC and NIPPV, and found that it did not reduce the incidence of reintubation, compared to either alone (low certainty evidence). For now, the use of this combination could be considered efficacious in patients at high risk of extubation failure (as shown in the HIGH-WEAN trial [65]), and if tolerated, could be considered over either NIPPV or HFNC alone.

This review has several strengths, including a broad search, and a pre-registered protocol. We included 36 RCTs with over 6800 patients. We conducted rigorous subgroup and sensitivity analyses to test the robustness of our findings across populations and indications, and applied GRADE to rate the certainty of estimates. There are also important limitations. First, all included trials were judged to be at potentially high risk-of-bias for blinding, as blinding of treating clinicians to treatment allocation among noninvasive respiratory support interventions is difficult. However, we accounted



for this through GRADE ratings, downrating confidence for subjective outcomes (e.g., reintubation). The results of network meta-analyses may potentially be influenced by indirect evidence, which may have issues related to transitivity. However, in this review, we did not find issues with intransitivity, and the network estimates were largely driven by direct data, with coherent indirect data. Second, the included trials enrolled heterogeneous subgroups, as well as combined studies evaluating various indications for noninvasive ventilation (prevention vs. rescue). However, we mitigated concerns related to this through important subgroup and sensitivity analyses, which indicate the scenarios where noninvasive respiratory support may be of greatest benefit. Unfortunately, there were some sources of heterogeneity (such as definition of “extubation failure”, definition of “VAP”, or proportion of patients with obesity) that could not be accounted for by secondary analyses, and must be taken into consideration. Third, we included only English-language RCTs. Finally, trials did not report costs such as consumables, clinician time, and other aspects of resource utilization, which may influence practice or policy decisions.

## Conclusion

Our results suggest that both NIPPV and HFNC are efficacious in reducing the incidence of reintubation, compared to conventional oxygen therapy. The magnitude of treatment effect of these interventions is highest in patients at increased baseline risk of reintubation. Finally, these therapies appear efficacious in prophylactic application, but not for rescue in symptomatic patients following extubation. Taken together, our study has important implications for clinicians caring for mechanically ventilated adults, and should prompt re-evaluation of guidelines for the use of noninvasive respiratory support for the treatment of critically ill patients post-extubation.

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## Author contributions

SMF, AJES, and BR conceived the study idea. SMF and BR coordinated the systematic review. SMF and AT designed the search strategy. SMF and AT screened abstracts and full texts. SMF and AT acquired the data and judged risk of bias in the studies. BS verified the data and performed the analyses. BR created the GRADE evidence profiles. All authors interpreted the data analyses. All authors co-wrote and revised the manuscript for intellectual content. All authors provided their final approval for manuscript submission. AJES and BR contributed equally as co-senior authors. All authors agree to be accountable for all aspects of the work. SMF is guarantor.

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## Declarations

### Conflicts of interest

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## Ethics approval

Not required.

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