# Initial Noninvasive Oxygenation Strategies in Subjects With De Novo Acute Hypoxemic Respiratory Failure

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**BACKGROUND: De novo hypoxemic respiratory failure is defined as significant hypoxemia in the absence of chronic lung disease such as COPD, and excluding respiratory failure occurring in the immediate postoperative or postextubation period. We aimed to evaluate the efficacy of various oxygenation strategies including noninvasive ventilation (NIV), high-flow nasal cannula (HFNC), and conventional oxygen therapy in patients with de novo hypoxemic respiratory failure. METHODS: We performed electronic database searches of PubMed, Cochrane Library, and Embase from inception to December 2018 to include randomized controlled trials that compared various oxygenation strategies in cases of de novo hypoxemic respiratory failure occurring in adult subjects without a preexisting chronic lung disease and excluding respiratory failure in the immediate postoperative or postextubation periods. We performed a Bayesian network meta-analysis to calculate odds ratio (OR) and Bayesian 95% credible intervals (CrI). RESULTS: 16 studies were included, involving 2,180 subjects with a mean age of 61 ± 17 y (66% were male; 46% of the included subjects were treated with conventional oxygen, 27.8% were treated with NIV, and 25.8% were treated with HFNC). Compared to conventional oxygen, NIV was associated with reduced intubation rates (OR 0.42, 95% CrI 0.26–0.62) but no significant reduction in short-term (OR 0.73, 95% CrI 0.47–1.02) or long-term mortality (OR 0.60, 95% CrI 0.29–1.06). There was no significant difference between NIV and HFNC or between HFNC and conventional oxygen regarding all outcomes. In a sensitivity analysis, the results remained consistent after exclusion of studies that included subjects with respiratory failure secondary to cardiogenic pulmonary edema. CONCLUSION: Among subjects with hypoxemic respiratory failure, NIV was associated with a significant reduction in intubation rates but not short- or long-term mortality when compared to conventional oxygen therapy. There was no significant difference between NIV and HFNC or between HFNC and conventional oxygen regarding all outcomes.** *Key words: high-flow nasal cannula; noninvasive ventilation; de novo respiratory failure; meta-analysis; network; hypoxemic respiratory failure; conventional oxygen.* [Respir Care 2019;64(11):1433–1444. © 2019 Daedalus Enterprises]

## Introduction

De novo hypoxemic respiratory failure is defined as significant hypoxemia ($P_{aO_2}/F_{IO_2} \leq 300$ mm Hg) with tachypnea and other signs of respiratory distress in the absence of chronic lung disease such as COPD and excluding respiratory failure occurring in the immediate postoperative or postextubation period.[1] The use of noninvasive venti-

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lation (NIV) has been associated with a reduction in intubation rates for patients with exacerbations of COPD and cardiogenic pulmonary edema.[2-4] Additionally, NIV has been recommended by the current European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines in patients with COPD and cardiogenic pulmonary edema.[1] However, the use of NIV in patients with postoperative respiratory failure, trauma patients, and as prophylaxis for respiratory failure in high-risk populations after extubation are conditional and are largely dependent on the overall context.[1]

Nevertheless, in patients with de novo hypoxemic respiratory failure, ERS/ATS has no clear recommendation regarding use of NIV.[1] Results of previous randomized controlled trials (RCTs) concerning NIV in non-hypercapnic acute hypoxemic respiratory failure have been conflicting.[5-8] Several meta-analyses showed significant reduction in rates of intubation and mortality with NIV usage.[9,10]

Recently, high-flow nasal cannula (HFNC) therapy has been used more frequently in the treatment of acute hypoxemic respiratory failure.[11] In a large RCT, Frat et al[5] reported that HFNC was associated with a reduction in 90-d mortality when compared to NIV and conventional oxygen therapy in subjects with acute hypoxemic respiratory failure. However, further subsequent trials and meta-analyses showed no difference between HFNC and conventional oxygen therapy[12-17] or NIV.[18,19]

In light of these controversies and the lack of head-to-head studies comparing HFNC and NIV, we conducted a network meta-analysis comparing the 3 initial oxygenation strategies (NIV vs HFNC vs conventional oxygen therapy) in subjects with de novo acute hypoxemic respiratory failure.

## Methods

### Study Design and Data Source

Our study was a systematic review and network meta-analysis of RCTs conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2015 Statement.[20] An electronic database search was performed utilizing the PubMed, Embase, and the Cochrane Library databases from inception until December 2018 without language restrictions. Two reviewers (BK, MB) independently and separately performed literature searches, and any discrepancy was resolved with consensus with a third reviewer (YZ). Articles were first screened by abstract and title, and the full text of eligible articles were reviewed before exclusion. The following MeSH terms were used: hypoxemic respiratory failure, hypoxemic respiratory failure, de novo respiratory failure, respiratory failure, acute respiratory failure, noninvasive ventilation, high-flow nasal cannula, NIV, HFNC, and oxygen. In addition, we reviewed the references of relevant articles and performed a manual internet search for possible inclusion.

### Study Selection

Our study included only RCTs that compared HFNC, NIV, and conventional oxygen therapy in subjects with hypoxemic respiratory failure, defined by having at least one of the following criteria: $P_{aO_2}/F_{IO_2} \leq 300$, $P_{aO_2} \leq 65$ mm Hg, $S_{pO_2} \leq 92\%$ with signs and symptoms of respiratory distress. Patients with chronic lung diseases or who developed respiratory failure in the immediate postoperative or postextubation period were excluded. We excluded RCTs that exclusively enrolled subjects with COPD, cardiogenic pulmonary edema, or postextubation respiratory failure. In studies that included different patient populations and provided results for outcomes of interest based on the reason of acute respiratory failure, we extracted outcomes for subjects with de novo hypoxemic respiratory failure that met our inclusion criteria. In studies that included a proportion of subjects with pulmonary edema as a cause for hypoxemic respiratory failure without reporting data for specific patient populations, we opted to include these studies in the primary analysis; however, they were removed in a sensitivity analysis.

Data were extracted by two reviewers (LR, HD) into a predesigned table, and any discrepancies was solved by a consensus with a third reviewer (YZ).

### Outcomes

The primary outcome was intubation rates and the need for invasive mechanical ventilation. Secondary outcomes included short-term mortality (ie, during ICU length of stay or $\leq$ 28 d) and long-term mortality (defined as hospital mortality or mortality at the longest follow-up period provided by each study).

### Quality Assessment

Quality assessment was performed independently and separately by two reviewers (BK, MB) using the Cochrane collaboration tool to evaluate risk of bias for random sequence generation, allocation concealment, blindness of participants and health care personnel, blindness of outcome assessment, incomplete outcome data, selective reporting, and other biases in each of included studies in each of the included studies. Any discrepancy was resolved with consensus with a third reviewer (YZ).

### Statistical Analysis

A Bayesian framework for the network meta-analysis was performed using the Markov Chain Monte Carlo simulation to derive the posterior distribution of the parameter estimates. We used the Brooks-Gelman-Rubin method to assess convergence. A random effects model for consistency was utilized to account for the population heterogeneity. Data were reported as odds ratios (ORs) and Bayesian 95% credible intervals (CrIs). Inconsistency was assessed using the deviance residuals and deviance information criteria statistics.

In an exploratory analysis, we performed a meta-regression analysis to explain any significant heterogeneity for direct meta-analysis. Moderators included study-level covariates: age, Simplified Acute Physiology Score II, breathing frequency, $P_{aO_2}/F_{IO_2}$ ratio, and $P_{aCO_2}$. Furthermore, a sensitivity analysis was performed for all outcomes by excluding studies that included subjects with respiratory failure secondary to pulmonary edema.

## Results

### Included Studies and Study Population

After reviewing 5,081 studies, 16 studies met our inclusion criteria and were included in the final analysis. Our search process is illustrated in Figure 1. Two trials compared HFNC versus conventional oxygen therapy,[12,17] 12 trials compared NIV versus conventional oxygen therapy,[6-8,21-30] 1 trial compared HFNC versus NIV,[19] and 1 trial compared HFNC versus NIV versus conventional oxygen therapy.[5] The network geometry showed that most studies compared NIV to conventional oxygen therapy; the next most frequent comparison was between HFNC and conventional oxygen therapy, and the least frequent comparison was HFNC versus NIV. Overall, conventional oxygen therapy was the most studied intervention, followed by NIV and then HFNC. Performance bias was noted in the included studies given the inherent difficulty in blinding a study to personnel and participants due to the nature of the intervention. Quality assessment results of the included studies, based on our judgment for each risk of bias, is illustrated in Figure 2. The characteristics of the included studies are shown in Table 1.

A total of 2,180 subjects were included in our analysis with a mean age of 61 ± 17 y (66% were male); 46% of the included subjects were treated with conventional oxygen therapy, 27.8% were treated with NIV, and 25.8% were treated with HFNC. The baseline subject characteristics are explained in Table 2.

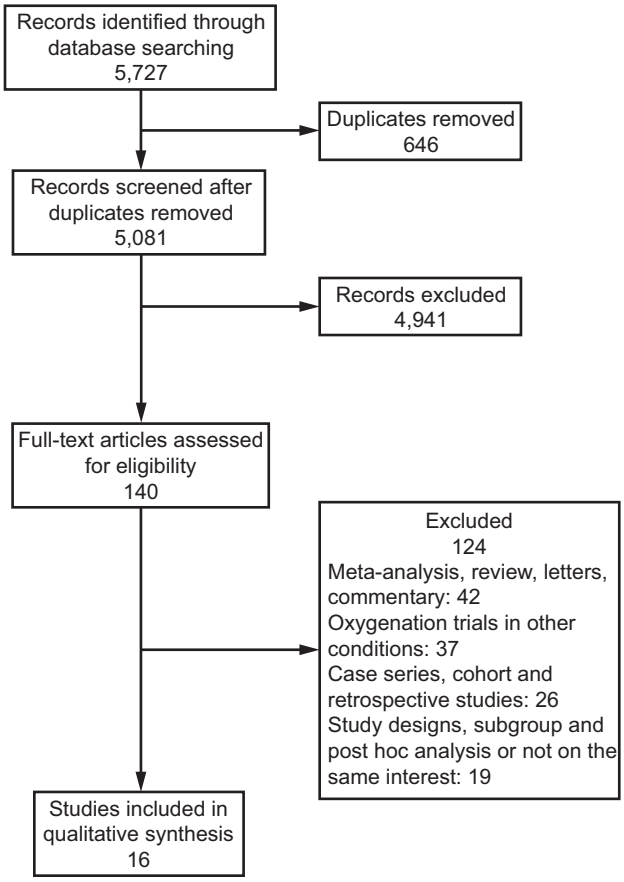


Fig. 1. Flow chart.

### Primary Outcome

The rate of intubation and requirement for invasive mechanical ventilation was 39.4% in the total subject population (34% in NIV, 36% in HFNC, and 44% in the conventional oxygen therapy group). NIV was associated with a significant reduction in requirement for intubation and mechanical ventilation in comparison to conventional oxygen therapy (OR 0.42, 95% CrI 0.26–0.62). There were no significant differences between NIV and HFNC (OR 0.63, 95% CrI 0.29–1.19) or HFNC and conventional oxygen therapy (OR 0.68, 95% CrI 0.36–1.26) (Fig. 3). In a subset analysis performed by excluding studies that included subjects with pulmonary edema, the results remained consistent (see the supplementary materials at http://www.rcjournal.com). In an exploratory meta-regression analysis, there were no significant modifier effects of NIV on intubation rates based on trial-level covariates ($P > .05$).

### Secondary Outcomes

The incidence of short-term mortality in the total patient population included was 28.6%. Although short-term mor-

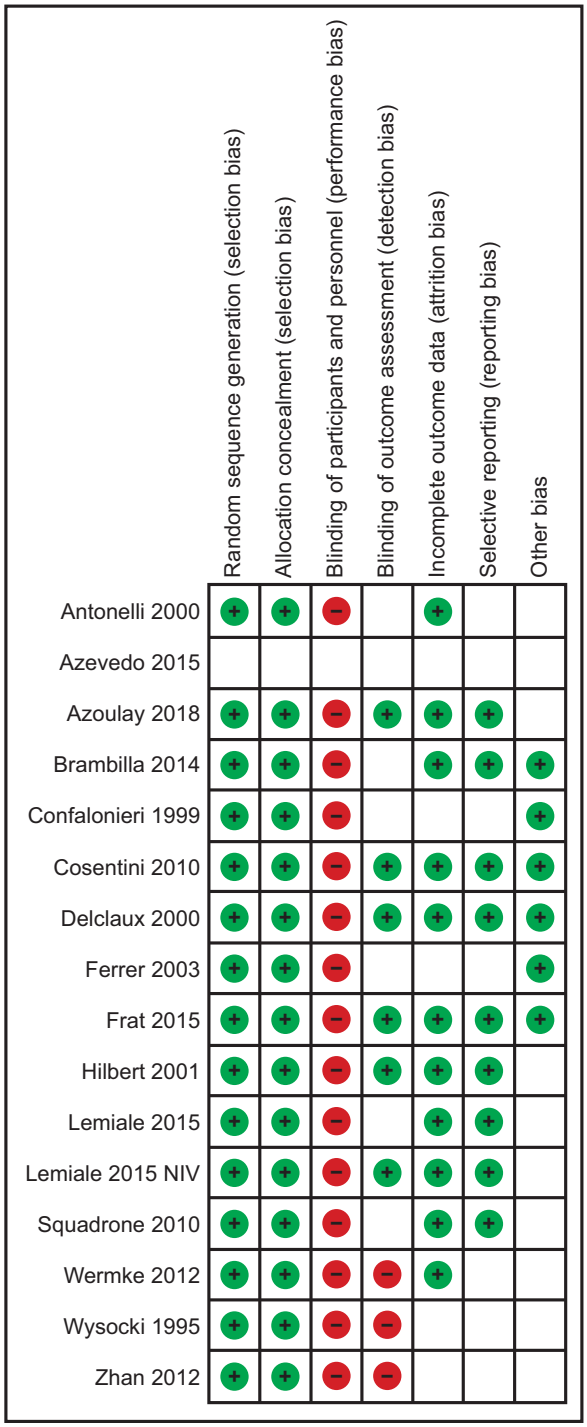


Fig. 2. Summary of risk of bias in the included studies based on the authors' judgments. Blank squares indicate unclear risk of bias.

tality rates were lower in NIV in comparison to conventional oxygen therapy (22% vs 31%), the difference didn't reach statistical significance (OR 0.73, 95% CrI 0.47–1.02). Furthermore, there were no significant differences between NIV versus HFNC (OR 1.00, 95% CrI 0.57–1.1.84) or HFNC versus conventional oxygen therapy (OR 0.73, 95% CrI 0.39–1.15) (Fig. 4). Meta-regression analysis of the NIV effects on short-term mortality showed no modifier effects based on trial-level covariates ($P > .05$).

With regard to long-term mortality, the incidence was 36%. There was no significant reduction in long-term mortality between NIV and conventional oxygen therapy (OR 0.60, 95% CrI 0.29–1.06), NIV versus HFNC (OR 1.02, 95% CrI 0.39–2.63) or HFNC versus conventional oxygen therapy (OR 0.59, 95% CrI 0.23–1.25) (Fig. 5). Additionally, by performing a meta-regression analysis, we found an increased long-term mortality with advanced ages among NIV-treated patients compared with patients treated with conventional oxygen therapy ($R^2 = 42\%$; $b = 0.08$; standard error = 0.04, $P = .04$) (see the supplementary materials at http://www.rcjournal.com). In a sensitivity analysis, results remained consistent for short-term and long-term mortality after excluding studies that included subjects with pulmonary edema (see the supplementary materials at http://www.rcjournal.com).

## Discussion

In this first network meta-analysis evaluating the role of initial oxygenation strategies among patients with de novo respiratory failure, we observed that NIV was associated with decreased intubation rates in comparison to conventional oxygen therapy. Although rates of short- and long-term mortality were lower in the NIV group, the difference didn't reach statistical significance. However, there were no significant differences in the requirement for intubation, short- or long-term mortality between NIV and HFNC, or between HFNC and conventional oxygen therapy.

ERS/ATS guidelines have no clear recommendations regarding the use of NIV in patients with de novo respiratory failure, and the use of HFNC is not addressed in these guidelines.[1] The physiological effects of NIV are largely attributed to improvements in gas exchange and reduction in work of breathing.[1] NIV is often used in patients with de novo hypoxemic respiratory failure, which is often caused by community-acquired pneumonia and ARDS, to relieve respiratory distress and work of breathing and to avoid intubation and mechanical ventilation.[1] However, the use of NIV has several limitations in these patients because it is less efficacious in relieving work load, such as in patients with COPD or cardiogenic pulmonary edema. Furthermore, increased tidal volume delivered with NIV increases transpulmonary pressure and can lead to further lung injury.[31,32] HFNC is a new oxygenation strategy that delivers $F_{IO_2}$ 1.0 at flows up to 60 L/min, which can overcome the high peak inspiratory flow during acute hypoxemic respiratory failure by generating a positive pressure.[33,34] Furthermore, HFNC can deliver a

Table 1. Characteristics of Included Studies

| Study | Number of Subjects, Total and by Group | Study Design | Inclusion Criteria | Flow of $O_2$ in HFNC and NIV Setting With Goal of Tidal Volume | Follow-up Period |
|---|---|---|---|---|---|
| Azoulay 2018 | *N* = 776<br>HFNC: *n* = 388<br>Conventional $O_2$: *n* = 388 | Multicenter, randomized, parallel-group trial | Immunocompromised subjects admitted to ICU with AHRF with $P_{aO_2} \leq 60$ mm Hg or $S_{pO_2} \leq 90\%$ on room air, tachypnea > 30 breaths/min, labored breathing or respiratory distress; need for $O_2$ flow of ≥ 6 L/min | Continuous high-flow $O_2$ therapy, initiated at 50 L/min and $F_{IO_2} = 1.0$, with a subsequent flow increase to achieve $S_{pO_2} = 95\%$ | 28 d |
| Frat 2015 | *N* = 310<br>Conventional $O_2$: *n* = 94<br>HFNC: *n* = 106<br>NIV + HFNC: *n* = 110 | Multicenter, prospective RCT | Adult subjects with frequency ≥ 25 breaths/minute, $P_{aO_2}/F_{IO_2} \leq 300$ while the patient was breathing $O_2$ at a flow of ≥ 10 L/min for at least 15 min, $P_{aCO_2} \leq 45$ mm Hg, and absence of clinical history of underlying chronic respiratory failure | High-flow $O_2$ gas flow of 50 L/min and $F_{IO_2} = 1.0$ at initiation<br>NIV: pressure-support level was adjusted with to obtain an expired tidal volume of 7–10 mL/kg predicted body weight, with initial PEEP of 2–10 cm $H_2O$ | 90 d |
| Azevedo 2015 | *N* = 30<br>HFNC: *n* = 14<br>NIV: *n* = 16 | Single-center RCT | Adult subjects admitted to surgical ICU between December 2013 and March 2015, with AHRF defined as $S_{pO_2} < 95\%$ while receiving $O_2$ through a face mask at an estimated $F_{IO_2} = 0.50$ | HFNC: delivered via a high-flow delivery system and an air-$O_2$ blender that delivered a gas flow of ≤ 60 L/min to a heated humidifier<br>NIV: full face mask connected to an ICU ventilator with a NIV mode operating in pressure support mode | NA |
| Lemiale 2015 | *N* = 100<br>Venturi mask group: *n* = 48<br>HFNC: *n* = 52 | Multicenter, parallel-group RCT in 4 ICUs | Immunocompromised adult subjects with ARF defined as the need for ≥ 6 L/min of $O_2$ or symptoms of respiratory distress including tachypnea, intercostal retractions, or dyspnea at rests | Venturi mask group: $F_{IO_2} = 60\%$ (15 L/min) initially, adjusted as needed to maintain $S_{pO_2} \geq 95\%$<br>HFNC: initial flow was 40–50 L/min with an $F_{IO_2} = 1.0$, adjusted as needed to maintain $S_{pO_2} > 95\%$ | Not reported |
| Lemiale 2015 | *N* = 374<br>Conventional $O_2$: *n* = 183<br>NIV: *n* = 191 | Multicenter, randomized trial | Immunocompromised adult subjects with AHRF defined as $P_{aO_2} < 60$ mm Hg on room air, tachypnea > 30/min, labored breathing, respiratory distress, or dyspnea at rest | NIV: pressure-support level adjusted to obtain an expired tidal volume of 7–10 = mL/kg ideal body weight, with initial PEEP = 2–10 cm $H_2O$ | 28 d |
| Brambilla 2014 | *N* = 81<br>Conventional $O_2$: *n* = 41<br>NIV: *n* = 40 | Multicenter, open-label, parallel-group RCT | Adult subjects with a diagnosis of pneumonia as the only cause of AHRF, $P_{aO_2}/F_{IO_2} \leq 250$ evaluated during $O_2$ therapy supplied for at least 15 min through a Venturi mask ($F_{IO_2} \geq 0.50$), and either breathing frequency ≥ 30 breaths/min or respiratory distress | NIV: CPAP delivered through a high-flow generator with a helmet, with initial PEEP = 10 cm $H_2O$ and $F_{IO_2}$ set to maintain $S_{pO_2} \geq 92\%$ and PEEP = 10 cm $H_2O$ | Until hospital discharge |

(*continued*)

Table 1. Continued

| Study | Number of Subjects, Total and by Group | Study Design | Inclusion Criteria | Flow of $O_2$ in HFNC and NIV Setting With Goal of Tidal Volume | Follow-up Period |
|---|---|---|---|---|---|
| Wermke 2012 | $N = 86$<br>Conventional $O_2$: $n = 44$<br>NIV: $n = 42$ | Single-center RCT | Adult subjects undergoing hematopoietic stem cell transplantation with ARF defined as a breathing frequency $> 25$ breaths/min, $P_{aO_2}/F_{IO_2} < 300$, or $S_{pO_2} < 92\%$ on room air | NIV: PEEP = 7.1 cm $H_2O$, pressure support = 15.29 cm $H_2O$ | 100 d |
| Zhan 2012 | $N = 40$<br>Conventional $O_2$: $n = 19$<br>NIV: $n = 21$ | Multicenter, prospective RCT | Adult subjects with acute onset respiratory distress; $P_{aO_2}/F_{IO_2} < 300$ mm Hg but $> 200$ mm Hg while breathing $O_2$ delivered via conventional Venturi device at a maximum concentration (50%); presence of bilateral pulmonary infiltrates on posteroanterior chest radiograph; and no evidence of left heart failure as assessed with echocardiography and/or a pulmonary artery wedge pressure of $< 18$ mm Hg | NIV: expiratory positive airway pressure initially set at 4 cm $H_2O$ and increased by increments of 1–2 cm $H_2O$ up to a patient's maximum tolerance; $F_{IO_2}$ set to maintain $S_{pO_2} = 92\%$–$96\%$ | Until hospital discharge |
| Squadrone 2010 | $N = 40$<br>Conventional $O_2$: $n = 20$<br>NIV: $n = 20$ | Single-center RCT | Immunocompromised adult subjects with respiratory failure defined as $S_{pO_2} < 90\%$ while breathing room air, and breathing frequency $> 25$ breaths/min with bilateral pulmonary nodules | NIV: CPAP with a pressure = 10 cm $H_2O$ and $F_{IO_2} = 0.5$<br>Venturi mask set at $F_{IO_2} = 0.5$ | 6 mo |
| Cosentini 2010 | $N = 47$<br>Conventional $O_2$: $n = 27$<br>NIV: $n = 20$ | Multicenter, prospective RCT in parallel groups | Adult subjects with diagnosis of CAP as the only cause of ARF, breathing frequency $< 35$ breaths/min, and $P_{aO_2}/F_{IO_2} > 200$ and $< 300$ evaluated during $O_2$ therapy supplied for at least 15 min through a Venturi mask | NIV: CPAP with initial PEEP = 10 cm $H_2O$ and $F_{IO_2}$ set to maintain a pulse oximetry $> 92\%$ | Until hospital discharge |
| Ferrer 2003 | $N = 105$<br>Conventional $O_2$: $n = 39$<br>NIV: $n = 36$ | Multicenter, prospective RCT | Adult subjects with severe AHRF, defined as $P_{aO_2}$ persistently ($\geq$ 6–8 h) $< 60$ mm Hg or $S_{pO_2}$ persistently $< 90\%$ while breathing $O_2$ via conventional Venturi mask at maximum concentration (50%)<br>Subjects with pulmonary edema as a cause of AHRF were excluded in the primary analysis (15 patients in each group). | NIV: ventilator set in bi-level positive airway pressure mode; $F_{IO_2}$ was set to achieve $S_{pO_2} > 92\%$ or a $P_{aO_2} > 65$ mm Hg | 90 d |
| Hilbert 2001 | $N = 52$<br>Conventional $O_2$: $n = 26$<br>NIV: $n = 26$ | Single-center, prospective, randomized trial | Immunocompromised subjects admitted to ICU with fever, pulmonary infiltrates, and AHRF. | NIV: pressure support set with a target tidal volume = 7–10 mL/kg body weight and breathing frequency $< 25$ breaths/min; PEEP and $F_{IO_2}$ adjusted to a target $S_{pO_2} > 90\%$ | Until hospital discharge |
| Antonelli 2000 | $N = 40$<br>Conventional $O_2$: $n = 15$<br>NIV: $n = 16$ | Single-center, prospective, randomized trial | Adult recipients of solid organ transplant admitted to ICU with acute respiratory distress; breathing frequency $> 35$ breaths/min, $P_{aO_2}/F_{IO_2} < 200$ while the subject was breathing $O_2$ through a Venturi mask; and active contraction of the accessory muscles of respiration or paradoxical abdominal motion<br>Subjects with pulmonary edema were excluded from the primary analysis (4 subjects in the NIV group and 5 subjects in conventional $O_2$ group). | NIV: pressure support was set with a target tidal volume = 8–10 mL/kg, breathing frequency $< 25$ breaths/min, and relief of respiratory distress signs and symptoms; PEEP and $F_{IO_2}$ adjusted to achieve appropriate oxygenation | Until hospital discharge |

(*continued*)

Table 1. Continued

| Study | Number of Subjects, Total and by Group | Study Design | Inclusion Criteria | Flow of $O_2$ in HFNC and NIV Setting With Goal of Tidal Volume | Follow-up Period |
|---|---|---|---|---|---|
| Delclaux 2000 | *N* = 123<br>Conventional $O_2$: *n* = 40<br>NIV: *n* = 41 | Multicenter, prospective RCT | Adult subjects with acute respiratory insufficiency and the presence of bilateral lung infiltrates on a posteroanterior chest radiograph<br>Subjects with heart failure were excluded from the primary analysis (21 subjects in each group). | NIV: CPAP initiated at 7.5 cm $H_2O$; CPAP could be decreased to 5 cm $H_2O$ or increased to 10 cm $H_2O$ as needed based on the clinical response and tolerance | Until hospital discharge |
| Confalonieri 1999 | *N* = 56<br>Conventional $O_2$: *n* = 28<br>NIV: *n* = 28 | Multicenter, prospective RCT | Adult subjects who met ≥ 1 of the ATS non-respiratory criteria for severe CAP and ≥ 2 of the following criteria for ARF: (1) frequency > 35 breaths/min and/or active contraction of the accessory muscles of respiration or paradoxical abdominal motion; (2) $P_{aO_2} < 68$ mm Hg while receiving $F_{IO_2} > 0.4$, or $P_{aO_2}/F_{IO_2} < 250$ while receiving $F_{IO_2} > 0.5$<br>Subjects with COPD and/or $P_{aCO_2} \geq 45$ mm Hg were excluded (11 subjects in conventional and 12 subjects in NIV). | NIV: initial ventilator settings at CPAP 0 cm $H_2O$ and PSV = 5–10 cm $H_2O$; PSV was increased to obtain an exhaled tidal volume > 6 mL/kg, breathing frequency < 25 breaths/min, disappearance of accessory muscle activity, and patient comfort | 60 d |
| Wysocki 1993 | *N* = 41<br>Conventional $O_2$: *n* = 20<br>NIV: *n* = 21 | Single-center, prospective RCT | Adult subjects who were intubated in ICU with a breathing frequency ≥ 25 breaths/min, $P_{aO_2} < 60$ mm Hg breathing room air or < 80 mm Hg with additional $O_2$, $P_{aCO_2} \geq 50$ mm Hg, and arterial pH ≤ 7.38 | Noninvasive PSV: during the first 24 h, noninvasive PSV was maintained continuously until clinical and oxygenation status improved; noninvasive PSV was then administered discontinuously, for several periods of 3 h in the day and of 6 h during the night, and the length was reduced progressively to ≥ 6 h/d | Until hospital discharge |

HFNC = high-flow nasal cannula
NIV = noninvasive ventilation
RCT = randomized, controlled trial
AHRF = acute hypoxemic respiratory failure
ARF = acute respiratory failure
CAP = community-acquired pneumonia
PSV = pressure support ventilation
ATS = American Thoracic Society

Table 2. Baseline Demographic and Clinical Characteristics of Subjects

| Study | Study Groups | Subjects, *n* | Age, y | Male, % | Hematological and/or Solid Malignancy, % | SAPS II Score | Frequency, breaths/min | $P_{aO_2}/F_{IO_2}$ | $P_{aCO_2}$ |
|---|---|---|---|---|---|---|---|---|---|
| Azoulay 2018 | HFNC | 388 | 64 (55–70) | 69.6 | 75.8 | 36 (28–46) | 33 (28–39) | 136 (96–187) | NA |
| | Conventional | 388 | 63 (56–71) | 63.6 | 82.2 | 37 (28–48) | 32 (27–38) | 128 (92–164) | NA |
| Frat 2015 | NIV | 110 | 61 ± 17 | 67 | 23.6 | 27 ± 9 | 33 ± 7 | 149 ± 72 | 34 ± 6 |
| | HFNC | 106 | 61 ± 16 | 71 | 24.5 | 25 ± 9 | 33 ± 6 | 157 ± 89 | 36 ± 6 |
| | Conventional | 94 | 59 ± 17 | 67 | 23 | 24 ± 9 | 32 ± 6 | 161 ± 73 | 35 ± 5 |
| Azevedo 2015 | HFNC | 14 | 61.4 ± 13.7 | 43 | NA | NA | NA | NA | NA |
| | NIV | 16 | 72.3 ± 19.0 | 50 | NA | NA | NA | NA | NA |
| Lemiale 2015 | HFNC | 52 | 59.3 (43–70) | 73.1 | 88.4 | 42 (30–52) | 26 (22–31) | 128 (48–178) | NA |
| | Conventional | 48 | 64.5 (53–72) | 66.7 | 79.2 | 37.5 (32–47) | 27 (22–32) | 100 (40–156) | NA |
| Lemiale 2015 | NIV | 191 | 61 (52–70) | 61.3 | 84.8 | NA | 27 (21–31) | 156 (95–248) | NA |
| | Conventional | 183 | 64 (53–72) | 57.4 | 84.7 | NA | 25 (21–30) | 130 (86–205) | NA |
| Brambilla 2014 | NIV | 40 | 64.9 ± 16.1 | 60 | 22.5 | 34.7 ± 7.6 | 34.7 ± 6.4 | 134 ± 32 | 32.1 ± 4.6 |
| | Conventional | 41 | 69.5 ± 15.8 | 70.7 | 29.3 | 35.8 ± 9.9 | 32.9 ± 6.9 | 148 ± 44 | 34.1 ± 7.3 |
| Wermke 2012 | NIV | 42 | NA | NA | 100 | NA | NA | NA | NA |
| | Conventional | 44 | NA | NA | 100 | NA | NA | NA | NA |
| Zhan 2012 | NIV | 21 | 43.8 ± 13.7 | 76.2 | 0 | NA | 28.8 ± 7.2 | 225.4 ± 17.4 | 31.3 ± 6.0 |
| | Conventional | 19 | 49.1 ± 13.7 | 42.1 | 5.3 | NA | 30.4 ± 6.3 | 234.4 ± 26.6 | 32.7 ± 5.6 |
| Squadrone 2010 | NIV | 20 | 49 ± 14 | 55 | 100 | 42 ± 7 | 29 ± 5 | 256 ± 52 | 41 ± 3 |
| | Conventional | 20 | 49.5 ± 14 | 60 | 100 | 41.3 ± 6 | 30 ± 4 | 282 ± 41 | 42 ± 3 |
| Cosentini 2010 | NIV | 20 | 65 ± 17 | 70 | NA | 21 ± 7.4 | 27 ± 4.5 | 249 ± 25 | 34 ± 6 |
| | Conventional | 27 | 72 ± 13 | 59 | NA | 21 ± 5.7 | 27 ± 4.4 | 246 ± 20 | 36 ± 5 |
| Ferrer 2003 | NIV | 36 | 61 ± 17 | 58 | NA | 34 ± 10 | 37 ± 6 | 102 ± 21 | 37 ± 7 |
| | Conventional | 39 | 62 ± 18 | 52 | NA | 33 ± 8 | 37 ± 6 | 103 ± 23 | 36 ± 6 |
| Hilbert 2001 | NIV | 26 | 48 ± 14 | 69 | 58 | 45 ± 10 | 35 ± 3 | 141 ± 24 | 37 ± 4 |
| | Conventional | 26 | 50 ± 12 | 73 | 58 | 42 ± 9 | 36 ± 3 | 136 ± 23 | 38 ± 5 |
| Antonelli 2000 | NIV | 16 | 45 ± 19 | 65 | 0 | NA | 38 ± 3 | NA | 42 ± 10 |
| | Conventional | 15 | 44 ± 10 | 60 | 0 | NA | 37 ± 1 | NA | 38 ± 9 |
| Delclaux 2000 | NIV | 40 | 56 (19–85) | 61 | NA | 32 (6–87) | 34 (20–60) | 140 (59–288) | 36 (26–66) |
| | Conventional | 41 | 60 (18–88) | 66 | NA | 32 (6–102) | 32 (12–52) | 148 (62–283) | 35 (22–47) |
| Confalonieri 1999 | NIV | 16 | 66 ± 14 | 82 | NA | NA | 37 ± 5 | 183 ± 36 | 50 ± 21 |
| | Conventional | 17 | 61 ± 21 | 61 | NA | NA | 36 ± 6 | 167 ± 47 | 47 ± 18 |
| Wysocki 1993 | NIV | 14 | 64 ± 18 | 57 | NA | 17 ± 7 | 35 ± 8 | NA | 44 ± 13 |
| | Conventional | 10 | 62 ± 11 | 60 | NA | 12 ± 5 | 35 ± 8 | NA | 42 ± 14 |

Data are presented as mean ± SD or median (interquartile range) unless otherwise noted.
SAPS II score = Simplified Acute Physiology Score II
HFNC = high-flow nasal cannula
NIV = noninvasive ventilation
NA = not available

PEEP that ranges from 2–3 cm $H_2O$, although this decreases with mouth opening.[33,35]

In our network meta-analysis, we found that the total intubation rate and short-term mortality rate were as high as 40% and 28%, respectively, which is consistent with previous studies.[7,8,27,29,34,36,37] NIV was associated with significant reductions of intubation rates in comparison to conventional oxygen therapy group. The rates of short- and long-term morality were lower in the NIV group compared to other groups, but the difference didn't reach statistical significance. These findings are reliable because they are derived from a large patient population from 16 different RCTs. A few RCTs enrolled a small proportion of subjects with pulmonary edema as a cause of acute hypoxemic respiratory failure without reporting the outcomes in this subgroup of subjects. In our sensitivity analysis, which was performed by excluding these studies,[17,19,22,30] we found that the rates of intubation remained significantly lower in the NIV group. Further well-controlled randomized trials that are conducted exclusively in subjects with de novo respiratory failure are needed to determine if the significant reduction in intubation and need for mechanical ventilation will translate into a mortality benefit. Furthermore, several risk factors are known to increase the risk of NIV failure, including high clinical severity scores, severe ARDS, older age, and pneumonia. Because we lacked subject-level data necessary to conduct a subgroup or

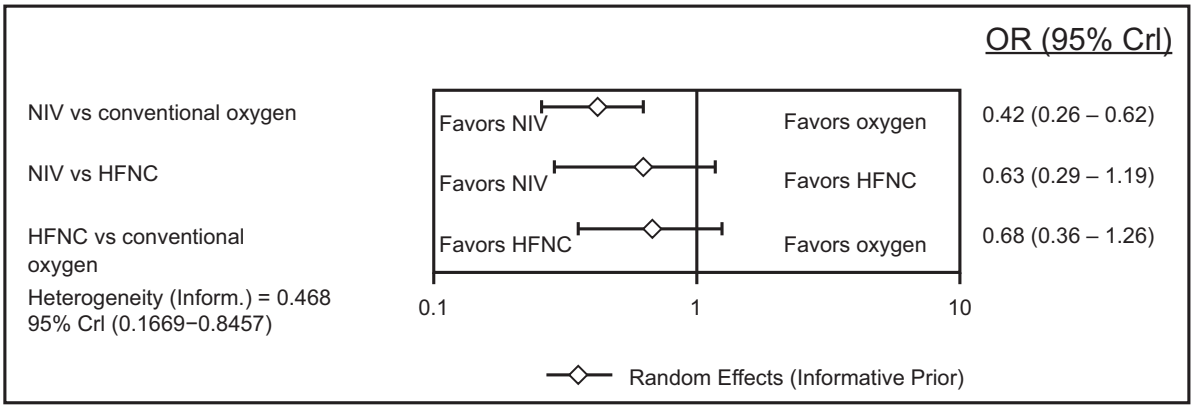


Fig. 3. Forest plots illustrating rate of intubation between the competing treatments. NIV = noninvasive ventilation; HFNC = high-flow nasal cannula; OR = odds ratio; CrI = credible interval.

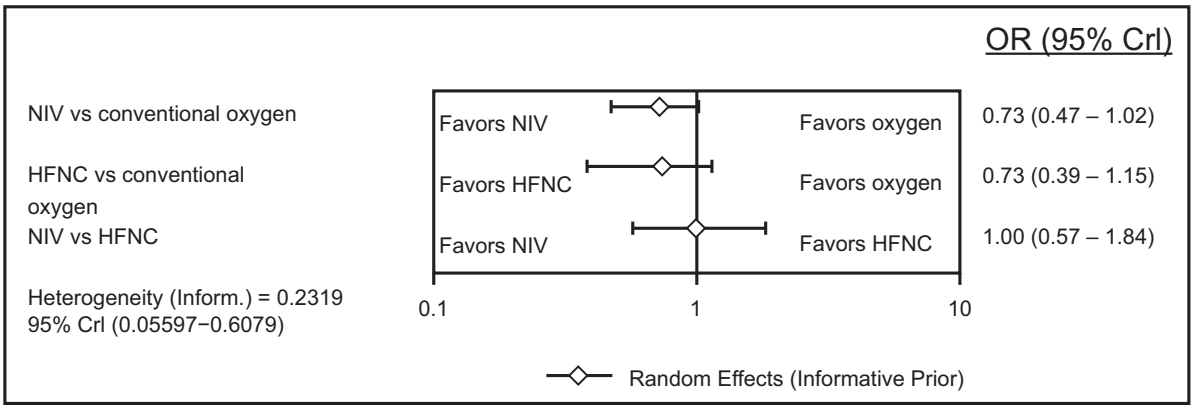


Fig. 4. Forest plots summarizing short-term all-cause mortality between the competing treatments. NIV = noninvasive ventilation; HFNC = high-flow nasal cannula; OR = odds ratio; CrI = credible interval.

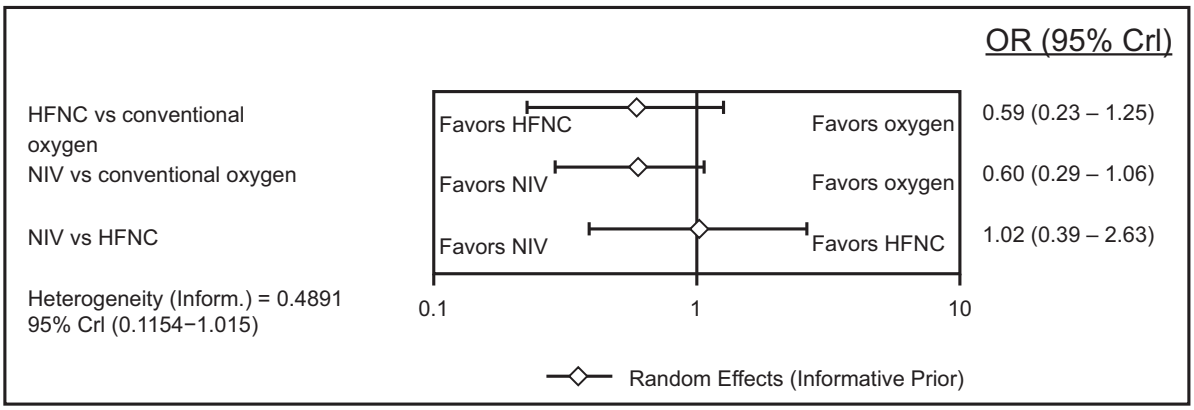


Fig. 5. Forest plots summarizing long-term all-cause mortality between the competing treatments. NIV = noninvasive ventilation; HFNC = high-flow nasal cannula; OR = odds ratio; CrI = credible interval.

sensitivity analysis with control for these risk factors, they should be addressed in further studies.

A small number studies have conducted a direct comparison between HFNC and NIV or conventional oxygen therapy, and of those performed, results have been controversial. Frat et al[5] conducted an RCT involving > 300 subjects and found a mortality benefit with HFNC in comparison to NIV and conventional oxygen therapy, although there was no significant reduction in intubation rates, which was reduced significantly in subjects with

$P_{aO_2}/F_{IO_2} < 200$. However, a delay of intubation and high tidal-volume delivered (> 9 mL/kg of ideal body weight) could have attributed to the higher intubation rate and increased mortality in the NIV group.[31,38] In contrast, several subsequent trials in different patient populations found no difference between HFNC and NIV in intubation rates.[18,19] In our network meta-analysis, we conducted direct and indirect comparisons between HFNC and NIV involving 1,168 subjects from the 16 included studies. Comparing HFNC and NIV, we found no significant difference in the need for intubation and invasive ventilation, nor any difference in short- or long-term mortality. Several pairwise meta-analyses with direct comparisons have reported similar results.[14,39] Further well-controlled trials conducting head-to-head comparisons between these oxygenation strategies in subjects with de novo respiratory failure are needed to determine the superiority between HFNC and NIV while controlling for causes and severity of acute hypoxemic respiratory failure.

HFNC is a more comfortable means of respiratory support and is associated with more relief of dyspnea compared to conventional oxygen therapy,[16,40] and HFNC is frequently used in patients with hypoxemic respiratory failure with $S_{pO_2} < 90$ despite being treated with conventional oxygen therapy during postextubation respiratory failure and during intubation.[11] In contrast to the trial by Frat et al,[5] other trials found no difference between HFNC and conventional oxygen therapy in subjects with hypoxemic respiratory failure.[12,16,17,40,41] However, HFNC showed superiority over conventional oxygen therapy in subjects with postextubation respiratory failure in terms of a reduction of intubation rates.[42,43] Additionally, HFNC is associated with a significantly higher lowest $S_{pO_2}$ when used during intubation.[44] In our pooled analysis, HFNC was not superior to conventional oxygen therapy with regard to reduction of intubation rates, short-term mortality, or long-term mortality among subjects with de novo respiratory failure. Our findings remained consistent because this direct meta-analysis was performed only between these interventions. Although our analysis included only subjects with de novo respiratory failure, inconsistent results were reported with previous meta-analyses that included subjects with different causes of acute hypoxemic respiratory failure, including postoperative and postextubation respiratory failure.[9,39,45] Furthermore, unlike the NIV and conventional oxygen therapy groups, large proportions of subjects treated with HFNC in our analysis were immunocompromised, which may underestimate the benefit of HFNC because immunocompromised patients are often less stable and have greater comorbidities. Further studies are needed to identify patients who would receive the greatest benefit from this new oxygenation modality, while also assessing different causes of acute hypoxemic respiratory failure and other risk factors.

Our results are similar to a previous meta-analysis[46] that showed no difference between HFNC when compared to NIV or conventional oxygen in subjects with hypoxemic respiratory failure. However, this earlier review included subjects with postoperative respiratory failure and subjects treated in the emergency department. Our results contradict a recently published meta-analysis[47] which reported that HFNC was associated with a reduction of intubation rates but not with any mortality benefit when compared to conventional oxygen. However, the included studies investigated subjects with acute hypoxemic respiratory failure secondary to any cause in the ICU and the emergency department. Our meta-analysis included larger patient populations from RCTs that were conducted only in the ICU and in subjects with hypoxemic respiratory failure excluding patients with COPD, cardiogenic pulmonary edema, postoperative respiratory failure, and postextubation respiratory failure. Furthermore, our results and conclusions were drawn from performing a network meta-analysis with direct and indirect analysis between the competing interventions. Additionally, we were able to conduct a comparison between HFNC and NIV despite the fact that few studies have conducted direct comparisons between these interventions.

Our analysis has several limitations. First, there were fewer subjects treated with HFNC in comparison to other competing interventions. Second, a large proportion of subjects treated with HFNC were immunocompromised. Third, there was a lack of studies that conducted direct comparison between HFNC and other oxygenation modalities in acute de novo hypoxemic respiratory failure. Fourth, blinding for the intervention for participants and personnel was impossible given the nature of the intervention, which could introduce bias. Fifth, NIV was delivered for different durations and with different settings. Finally, because we lacked subject-level data, we were unable to perform subgroup analysis based on severity and different reasons for respiratory failure.

## Conclusion

Among subjects with de novo hypoxemic respiratory failure, noninvasive ventilation was associated with a significant reduction in intubation rates but not with a significant reduction in short- or long-term mortality when compared with conventional oxygen therapy. Additionally, there was no significant difference between noninvasive ventilation and HFNC therapy regarding the primary and secondary outcomes. Similarly, we found HFNC to have no benefit in reducing intubation rates or mortality when compared to conventional oxygen therapy. Further RCTs conducting head-to-head comparisons between HFNC and NIV, while also controlling for risk factors such as clinical

severity scores, various etiologies of respiratory failure, and age, are needed.

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