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Clinical Review

# HIGH FLOW NASAL CANNULA OXYGEN VS. CONVENTIONAL OXYGEN THERAPY AND NONINVASIVE VENTILATION IN EMERGENCY DEPARTMENT PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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☐ **Abstract—Background: Acute respiratory failure (ARF) is a common cause of presentation to the Emergency Department (ED). High flow nasal cannula (HFNC) has been introduced as an alternative way to administer oxygen. Objectives: We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing HFNC with conventional oxygen therapy (COT) and noninvasive ventilation (NIV) exclusively in the ED setting. Methods: Inclusion criteria were: RCTs on adults with ARF admitted to the ED, investigating HFNC vs. COT or other modes of ventilation. Trials that compared HFNC support outside the ED, were published as an abstract, or nonrandomized were excluded. Results: Four RCTs comparing HFNC with COT and one HFNC to NIV met the criteria. Overall, 775 patients were included. The meta-analysis of the studies comparing HFNC and COT showed no differences in intubation requirement, treatment failure, hospitalization, or mortality. Intolerance was significantly higher with HFNC (risk ratio 6.81 95% confidence interval 1.18–39.19; $p$ = 0.03). In the only available RCT comparing HFNC with NIV, no difference was found for intubation rate, treatment failure, tolerance, and dyspnea. Conclusions: We did not find any benefit of HFNC compared with COT and NIV in terms of intubation requirement, treatment failure, hospitalization, and mortality; COT was better tolerated.** © 2019 Elsevier Inc. All rights reserved.

☐ **Keywords—emergency department; high flow nasal cannula; acute respiratory failure; oxygen therapy; noninvasive ventilation**

## INTRODUCTION

Acute respiratory failure (ARF) is a common presentation to the emergency department (ED). Oxygen therapy is a treatment in cases that involve hypoxia (1,2). However, conventional oxygen therapy (COT) presents some drawbacks, including limited and lack of precision of exact oxygen delivery, insufficient heating and humidifying, and poor tolerance (3).

Recently, high flow nasal cannula (HFNC) has been introduced as an alternative way to administer oxygen therapy and overcome COT limitations: HFNC can deliver heated, humidified oxygen at high flow (up to 60 L/min), maintaining the set oxygen fraction (4–6).

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Several physiological positive effects and clinical benefits have been proposed when treating ARF of different etiologies in various settings (4–6). The role of HFNC in adult patients affected by ARF, compared with COT and noninvasive ventilation (NIV), has been assessed in randomized controlled trials (RCTs) and meta-analyses. However, the reported findings were contradictory, with some meta-analyses concluding superiority of HFNC compared with COT and NIV in terms of failure rate, intubation rate, or patient comfort, whereas others did not find any benefits (7–11).

Furthermore, none of the published meta-analyses was focused on ED patients: on the contrary, most of the analyzed RCTs were performed in other settings, particularly in the intensive care unit (ICU): the generalizability of their findings to ED patients is questionable and could be misleading. ED patients can be quite different from ICU patients, above all in terms of severity of illness, cause of ARF, and level of assistance; as a consequence, a treatment like HFNC could be advantageous for ICU patients but ineffective or detrimental for ED patients. To reliably assess the efficacy and safety of HFNC compared with COT and NIV for ED patients, we therefore performed a systematic review and meta-analysis of RCTs comparing these different treatments exclusively in the ED setting.

## MATERIALS AND METHODS

We performed the systematic review and meta-analysis in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (12). Three authors (VT, SF, LF) independently searched PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials databases, and Google Scholar for RCTs investigating HFNC use in adult patients with acute respiratory failure admitted to an ED published prior to October 26, 2018. The computer-based searches combined terms related to HFNC (e.g., high flow nasal cannula, high flow oxygen therapy), and randomized evidence (e.g., randomized controlled trial) in humans, without any language restriction. Detailed search strategy is reported in the Supplementary Material (available online).

Inclusion criteria were: 1) studies on adult patients with acute respiratory failure (author definition) admitted and treated in the ED, 2) investigating HFNC use vs. conventional oxygen therapy or other modes of ventilation, 3) presenting outcomes of interest, 4) randomized controlled trials. Trials comparing HFNC vs. oxygen or ventilation support outside the ED, studies published as a meeting abstract, or nonrandomized studies were excluded.

Two researchers (VT, LC) independently screened the titles and abstracts of all initially identified studies according to the selection criteria. Full-text articles of studies that met all selection criteria were retrieved. Reference lists of the selected studies, relevant reviews, and meta-analyses identified on the topic were manually searched for additional articles.

Two authors (VT, EF) independently extracted data using a standardized data extraction form, and a consensus was reached in case of any inconsistency with involvement of a third author (SF). The data extracted included first author, year of publication, journal, sample size, clinical context, outcomes of interest, timing of HFNC initiation, and complications.

The primary outcome was intubation requirement. The secondary outcomes were the rate of treatment intolerance (i.e., interruption of treatment required by the patient for discomfort), dyspnea improvement, treatment failure, hospitalization, and longest follow-up all-cause mortality.

Two authors (LB, EF) assessed the risk of bias using the Cochrane Collaboration's Risk of Bias tool (13). Due to the nature of the studied intervention, blinding of participants and personnel was not feasible, therefore we did not consider this as a potential risk of bias. We therefore determined the risk of bias of the included RCTs using the following criteria: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Summary measure was presented as risk ratio (RR) with 95% confidence interval (CI). The Mantel-Haenszel method was used to combine summary measures using random-effects model to minimize the effect of between-study heterogeneity. We evaluated heterogeneity between studies using Cochran's Q (represented as $\chi^2$ and $p$ values) and the $I^2$ statistic, which describes the percentage of variation between studies that is due to heterogeneity. In accordance with Cochrane guidance, we did not analyze publication bias because our search identified fewer than 10 studies for each data comparison. Data from each trial were considered as per the intention-to-treat principle. All statistical tests were two-sided and used a significance level of $p < 0.05$. MedCalc (MedCalc Statistical Software version 18.9; MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018) was used for all statistical analyses.

The present systematic review has been registered on the PROSPERO register (registration number CRD42018111280).

## RESULTS

Our search identified 1287 articles. After screening based on titles and abstracts, 26 articles remained for full-text assessment. Five of them met the inclusion criteria and

**Table 1. Risk of Bias in the Included Trials**

| Study | Bias | Author's Judgment | Support for Judgment |
|---|---|---|---|
| Bell et al., 2015 (16) | Random sequence generation | Low | Computer-generated random number sequence |
| | Allocation concealment | Low | Opaque envelope system |
| | Blinding of participants and personnel | High | Due to the nature of the intervention blinding of personnel was not possible. |
| | Blinding of outcome assessment | High | Unblinded treating nurse in emergency department assessed the primary outcome. |
| | Incomplete outcome data | Low | All patients were included in the analysis. |
| | Selective reporting | Low | Apparently free of selecting reporting. |
| | Other bias | High | Seven of 52 patients in the control group were escalated to HFNC. There was a larger proportion of patients with heart failure in the intervention group, which was not statistically significant. |
| Jones et al., 2016 (14) | Random sequence generation | Low | A purpose-built program in Microsoft Access 2003 based on a random number generator was used for randomization. |
| | Allocation concealment | Low | A series of sealed opaque envelopes with treatment allocation. |
| | Blinding of participants and personnel | High | Participants, treating clinical staff, and those responsible for data entry were not blinded to the interventions; however, treatment allocation was masked prior to analysis. |
| | Blinding of outcome assessment | High | Look just above. |
| | Incomplete outcome data | High | Seven patients in the HFNC group and 12 patients in the control group were excluded from the analysis. |
| | Selective reporting | Low | Apparently free of selecting reporting. |
| | Other bias | High | Sixteen patients in the HFNC group were placed on standard $O_2$ therapy. Four patients in HFNC group did not receive allocated therapy. The trial did not achieve the initially estimated sample size (303 analyzed vs. 390 planned patients) |
| Makdee et al., 2017 (15) | Random sequence generation | Low | The randomization was performed in a 1:1 ratio permuted block of 4. |
| | Allocation concealment | Low | Sealed opaque envelopes |
| | Blinding of participants and personnel | High | Due to the nature of the intervention, blinding of personnel was not possible. |
| | Blinding of outcome assessment | High | The primary outcome was assessed by unblinded investigators. |
| | Incomplete outcome data | High | Six patients in the HFNC group and 2 patients in the control group were excluded from the analysis. |
| | Selective reporting | Low | Apparently free of selecting reporting. |
| | Other bias | Unclear | Apparently free of other bias. |
| Rittayamai et al., 2015 (17) | Random sequence generation | Unclear | Not stated. |
| | Allocation concealment | Low | Blind envelope pull. |
| | Blinding of participants and personnel | High | Due to the nature of the intervention, blinding of personnel was not possible. |
| | Blinding of outcome assessment | Unclear | Not stated. |
| | Incomplete outcome data | High | One patient in the HFNC group and 1 patient in the control group were excluded from the analysis. |
| | Selective reporting | Low | Apparently free of selecting reporting. |
| | Other bias | High | There was a 1.5-h delay, on average, between the screening period and the trial protocol initiation. Arterial blood gas analysis was not controlled during the trial. |
| Doshi et al., 2018 (18) | Random sequence generation | Low | A computer-generated block-randomization schedule was used to produce the randomization sequence. |
| | Allocation concealment | Low | Sealed, sequentially numbered envelopes. |
| | Blinding of participants and personnel | High | Due to the nature of the intervention, blinding of personnel was not possible. |
| | Blinding of outcome assessment | Unclear | Not stated. |
| | Incomplete outcome data | High | Twelve patients in the HFNC group and 12 patients in the control group were excluded from the analysis. |
| | Selective reporting | Low | Apparently free of selecting reporting. |
| | Other bias | High | There were 23 HFNC crossover patients to $O_2$ therapy, and 6 $O_2$ therapy crossover patients to HFNC. |

HFNC = high flow nasal cannula.

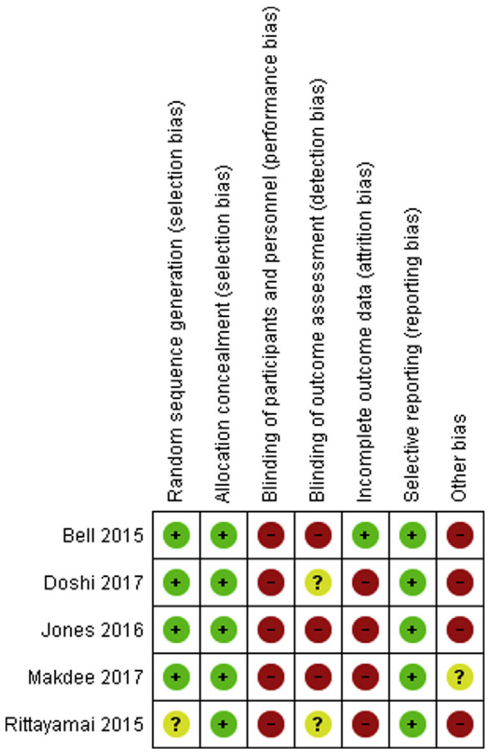


**Figure 1. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias (14–18).**

were included in the systematic review: four compared HFNC to COT and one HFNC to NIV (14–18). Overall, 775 patients with ARF of heterogeneous origin were analyzed: 400 in HFNC groups, 275 in COT groups, and 100 in NIV group. Details of the key characteristics of the trials are presented in Table 1 (14–18). Figure 1 reports the risk of bias for each study (explanation in Table 1).

We performed a meta-analysis of the primary and secondary outcomes of the four studies comparing HFNC and COT, which included 296 HFNC and 275 COT patients (14–17). There were no differences between groups in the intubation requirement (RR 0.69, 95% CI 0.12–4.12, $p$ for effect = 0.68; $p$ for heterogeneity = 0.28; $I^2$ = 21%; with four included trials; Figure 2), rate of treatment failure (RR 1.49, 95% CI 0.33–6.82, $p$ for effect = 0.60; $p$ for heterogeneity = 0.03; $I^2$ = 72%; with four included trials; Figure 3), rate of hospitalization (RR 0.99, 95% CI 0.81–1.19, $p$ for effect = 0.88; $p$ for heterogeneity = 0.28; $I^2$ = 21%; with three included trials; Figure 4), and longest reported follow-up all-cause mortality rate (RR 1.20, 95% CI 0.58–2.48, $p$ for effect = 0.62; $p$ for heterogeneity = 0.55; $I^2$ = 0%; with two included trials; Figure 5) (14–17). The rate of treatment intolerance was significantly higher in the HFNC group, as compared with the control group (RR 6.81, 95% CI 1.18–39.19, $p$ for effect = 0.03; $p$ for heterogeneity = 0.47; $I^2$ = 0%; with four included trials; Figure 6) (14–17). We did not include dyspnea improvement scores due to the heterogeneity in the dyspnea estimation scales among the included RCTs.

Only one multicenter study compared HFNC (104 patients) with NIV (100 patients): no difference was found in terms of intubation rate, treatment failure, vital signs, tolerance and dyspnea, and clinicians assigned better scores in HFNC group for respiratory response, patient comfort, and ease of the treatment (18).

## DISCUSSION

In this first systematic review and meta-analysis focused on the value of HFNC vs. COT in treating ARF in the ED setting, we did not find any difference in terms of intubation requirement, treatment failure, hospitalization, and mortality. COT proved to be superior to HFNC for better comfort, with fewer patients interrupting the treatment for discomfort.

Prior studies and analyses have demonstrated improved outcomes using HFNC, but the studies were performed in a variety of situations and predominantly in the ICU (4–11). For these reasons, we performed the present study limited to the ED setting.

The feasibility and efficacy of HFNC for ARF in the ED were evaluated in 70 patients in a prospective study by Lenglet et al.: HFNC was proven feasible, easy to use, and with beneficial effects on dyspnea, pulse oximetry, and respiratory rate (3). Furthermore, most caregivers considered HFNC more effective and better tolerated than COT, but only 9 patients reported their opinion, and 8 preferred HFNC. The authors concluded that HFNC could be the first-line therapy in severe ARF in the ED. However, a single, small, observational study is clearly not sufficient to lead to an evidence-based recommendation, nor can the results be extended to other populations like ICU patients. Actually, it can be misleading and detrimental.

Our findings suggest that HFNC does not offer any benefit in ED patients presenting for ARF compared with COT and NIV, even with weaker evidence in the latter. On the contrary, COT could be better tolerated than HFNC: this finding was the only significant difference, with a trend against HFNC in three out of four analyzed studies (14,15,17). A recent study found that when using HFNC, a lower temperature (31°C) can be better tolerated compared with 37°C: in the two RCTs comparing HFNC and COT and reporting the delivered flow temperature, HFNC flow was delivered at 37°C, and this may explain the worse patient comfort (14,17,19).

On the other hand, HFNC could be an alternative to the more complex NIV.

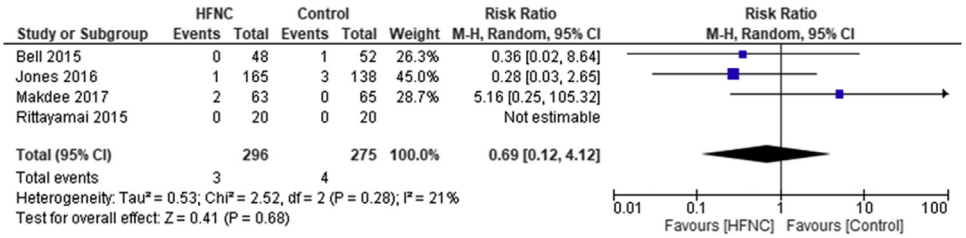


**Figure 2. Intubation requirement (14–17). CI = confidence interval; HFNC = high flow nasal cannula.**

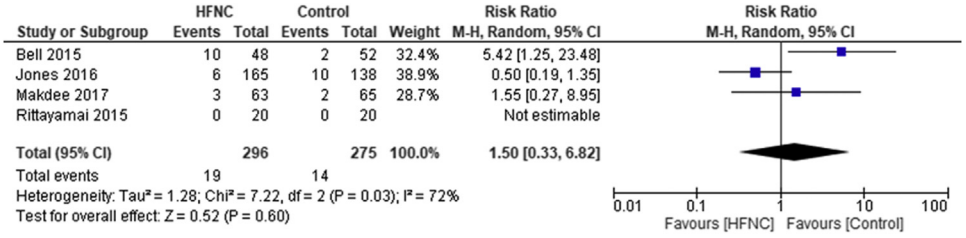


**Figure 3. Treatment failure (14–17). CI = confidence interval; HFNC = high flow nasal cannula.**

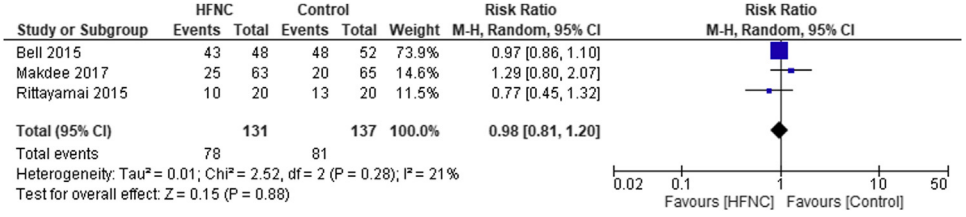


**Figure 4. Rate of hospitalization (15–17). CI = confidence interval; HFNC = high flow nasal cannula.**

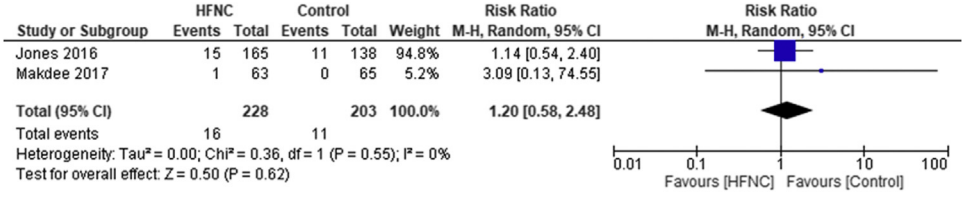


**Figure 5. All-cause mortality at the longest available follow-up (14,15). CI = confidence interval; HFNC = high flow nasal cannula.**

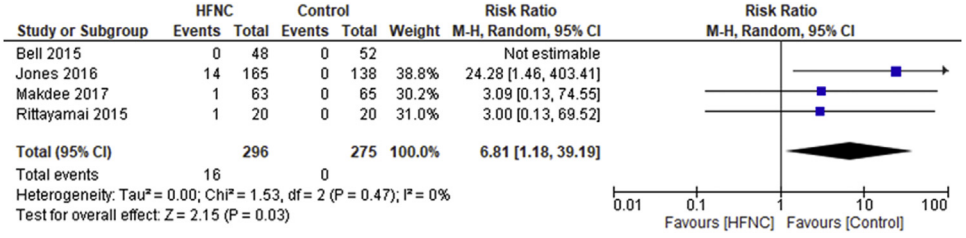


**Figure 6. Treatment intolerance (14–17). CI = confidence interval; HFNC = high flow nasal cannula.**

A randomized controlled clinical trial on this subject, including ED patients with ARF, would be advisable to confirm our conclusions in terms of clinical outcomes and patients' tolerability.

*Limitations*

The number of pertinent available RCTs was limited, and most of them were small. The absence of additional

information, like the cause and the type of ARF, and the criteria for failure and for intubation are further limitations; however, so far, our findings represent the best available evidence and they have clinical relevance.

## CONCLUSIONS

In the present meta-analysis on the value of HFNC vs. COT in treating ARF in ED patients, we did not find any benefit of HFNC compared with COT and NIV in terms of intubation requirement, treatment failure, hospitalization, and mortality. COT proved to be superior for patient tolerance. Further RCTs focused on ARF patients in the ED are required to gauge whether these treatment options affect patient outcome.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jemermed.2019.06.033.

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## ARTICLE SUMMARY

**1. Why is this topic important?**

Although acute respiratory failure (ARF) is one of the most common causes of presentation to the emergency department (ED), and despite the growing use of high flow nasal cannula (HFNC), this is the first systematic review focused on HFNC oxygen therapy compared with conventional oxygen therapy and noninvasive ventilation for ED patients presenting with acute respiratory failure.

**2. What does this review attempt to show?**

The aim of the present review is to reliably assess the efficacy and safety of HFNC compared with conventional oxygen therapy (COT) and noninvasive ventilation (NIV), for the first time exclusively in ED patients, which are quite different from intensive care unit patients, in terms of severity of illness, cause of ARF, and level of assistance.

**3. What are the key findings?**

In contrast with previous studies and meta-analysis not restricted to ED patients, our work suggests that HFNC does not offer any benefit in ED subjects presenting for ARF compared with COT and NIV, even with weaker evidence in the latter. On the contrary, COT could be better tolerated than HFNC; this finding was the only significant difference.

**4. How is patient care impacted?**

Our findings are relevant as they suggest a cautious use in the ED; moreover, unexpectedly, COT might be superior in terms of patient tolerance. When treating ARF patients, clinicians should avoid relying on a supposed superiority of HFNC compared with COT, and should maintain careful monitoring, to detect promptly a failure of the treatment or the appearance of intolerance.