


BMJ Open Effectiveness and harms of high-flow nasal oxygen (HFNO) for acute respiratory failure: a systematic review protocol

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To cite: Baldomero AK, Melzer A, Greer N, *et al*. Effectiveness and harms of high-flow nasal oxygen (HFNO) for acute respiratory failure: a systematic review protocol. *BMJ Open* 2020;**10**:e034956. doi:10.1136/bmjopen-2019-034956

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-034956>).

Received 15 October 2019
Revised 10 December 2019
Accepted 16 December 2019



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ABSTRACT

Introduction High-flow nasal oxygen (HFNO) use in adults hospitalised with acute respiratory failure (ARF) is increasing. However, evidence to support widespread use of HFNO compared with non-invasive ventilation (NIV) and conventional oxygen therapy (COT) is unclear. This protocol describes the methods for a systematic evidence review regarding the comparative effectiveness and harms of HFNO compared with NIV or COT for the management of ARF in hospitalised adult patients.

Methods and analysis We will search MEDLINE, Embase, CINAHL and Cochrane Library for randomised-controlled trials (RCTs) of adult patients hospitalised with ARF or who developed ARF while hospitalised. ARF will be defined as SpO₂ <90%, PaO₂:FiO₂ ratio ≤300, PaO₂ ≤60 mm Hg, or PaCO₂ ≥45 mm Hg. The intervention is HFNO (humidified oxygen, flow rate ≥20 L/min) compared separately to NIV or COT. The critical outcomes are: all-cause mortality, hospital-acquired pneumonia, intubation/reintubation (days of intubation), intensive care unit admission/transfers, patient comfort and hospital length of stay. The important outcomes are: delirium, 30-day hospital readmissions, barotrauma, compromised nutrition (enteral or parenteral nutrition), gastric dysfunction, functional independence at discharge and skin breakdown or pressure ulcers. We will calculate risk ratios and Peto ORs (for rare events) and corresponding 95% CIs for categorical outcomes. Mean and standardised mean difference will be calculated for continuous outcomes. Where possible and appropriate, meta-analysis will be performed for each outcome.

Conclusion This systematic review will provide a comprehensive evaluation of the evidence regarding the comparative effectiveness and harms of HFNO compared with NIV or COT for the management of ARF in hospitalised adult patients to inform clinical practice and to identify research gaps in the management of ARF in hospitalised adults. The results will inform the work of the American College of Physicians–Clinical Guidelines Committee in their development of a clinical guideline related to use of HFNO in adult patients with ARF.

Ethics and dissemination No ethical approval will be needed because we will be using data from previously published studies in which informed consent was obtained by the primary investigators. We will publish our results in a peer-reviewed journal.

PROSPERO registration number CRD42019146691

Strengths and limitations of this study

- We will compare high-flow nasal oxygen (HFNO) with both non-invasive ventilation and conventional oxygen therapy.
- We will evaluate the efficacy and harms of HFNO in a wide range of clinical conditions (eg, chronic obstructive pulmonary disease, cardiogenic pulmonary oedema, immunosuppressed, postsurgery, postextubation and so on) and multiple clinical settings (emergency department, intensive care unit, intermediate/step-down unit and hospital ward).
- The comprehensive list of clinically relevant outcomes that will be evaluated in this systematic evidence review was developed with input from physician and nonphysician public representatives.
- This systematic evidence review of HFNO will be limited to studies evaluating patients who meet criteria for acute respiratory failure.
- We will exclude studies that evaluated HFNO for oxygenation support before (preoxygenation) and during intubation.

INTRODUCTION

High-flow nasal oxygen (HFNO) therapy is a mode of non-invasive oxygen support that has been used in neonatal and paediatric settings for over a decade. In recent years, HFNO use in adults hospitalised with acute respiratory failure (ARF) has been increasing. HFNO delivers warmed, humidified oxygen with fraction of inspired oxygen (FiO₂) up to 1.0 and maximum flow rate of 60L/min. Several potential physiologic advantages of HFNO over non-invasive ventilation (NIV) and conventional oxygen therapy (COT) have been proposed.^{1 2} These include patient comfort,^{3–5} improved oxygenation and ventilation,^{6 7} clearance of airway secretions^{8 9} and reduced work of breathing.^{4 10 11} These theoretical benefits are attributed to HFNO delivery through small, pliable nasal cannula, washout of anatomic dead space,¹² high oxygen flow

rates,^{13 14} generation of low level positive-end expiratory pressure (PEEP),^{15–19} and heated humidification.

Given the increasing use of HFNO and the lack of robust evidence to support its widespread use in adult patients with ARF, the Minnesota Evidence Synthesis and Dissemination Center was commissioned by the American College of Physicians (ACP) to systematically review the evidence regarding the comparative effectiveness and harms of HFNO compared with NIV or COT for the management of ARF in hospitalised adult patients. Compared with existing reviews in this area, this systematic evidence review will include a broader scope that will compare HFNO to both NIV and COT, assess a wider range of clinical conditions in multiple clinical settings, and evaluate a more comprehensive list of key clinical outcomes. Furthermore, an updated review will include evidence from recently published clinical trials. This systematic review will be used by the ACP-Clinical Guidelines Committee (ACP-CGC) to develop a clinical practice guideline for the use of HFNO in ARF. With input from the ACP-CGC²⁰ and a technical expert panel (TEP), we developed the following key questions (KQ):

KQ 1. What is the comparative effectiveness of HFNO versus NIV or COT for hospitalised patients with ARF? Does comparative effectiveness of HFNO vary by patient characteristics, disease/diagnosis characteristics, protocol/device settings or location of administration?

KQ 2. What are the harms of HFNO versus NIV or COT for hospitalised patients with ARF? Do harms vary by patient characteristics, disease/diagnosis, protocol/device settings or location of administration?

METHODS

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews on 8 August 2019. We will report our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 statement.²¹

Eligibility criteria

All studies that will be included in this systematic review will be selected in accordance with the PICOTS (Population, Intervention, Comparison, Outcomes, Timing, Study Design) framework (online supplementary appendix A). A study will be included if at least 75% of the participants meet the inclusion criteria.

Population

We will include all adult patients (age ≥ 18 years) with ARF at the time of study enrollment. A study will be included if at least one criterion for ARF is met: $\text{SpO}_2 < 90\%$, $\text{PaO}_2/\text{FIO}_2$ ratio ≤ 300 , $\text{PaO}_2 \leq 60$ mm Hg or $\text{PaCO}_2 \geq 45$ mm Hg.

Intervention

The intervention of interest is HFNO, defined as humidified oxygen with flow rates ≥ 20 L/min.

Comparators

We will compare HFNO versus NIV (continuous or bilevel positive airway pressure ventilation (CPAP or BiPAP)) and HFNO versus COT (eg, oxygen delivered through nasal cannula, simple face mask, air-entrainment mask, partial rebreathing mask, non-rebreather mask and so on).

Outcome measures

We will examine several patient-related outcomes and intermediate outcomes. With input from the ACP-CGC that included physician and nonphysician public representatives, outcomes were identified as critical or important. The critical outcomes are: all-cause mortality (in-hospital and the longest available through 90 days), hospital-acquired pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU) admission/transfers, patient comfort and hospital length of stay. The important outcomes are: delirium, 30-day hospital readmissions, barotrauma (pneumothorax, pneumomediastinum, pneumoperitoneum or ventilator-induced lung injury), compromised nutrition (enteral or parenteral nutrition), gastric dysfunction (placement of nasogastric tube, abdominal distension, nausea or vomiting), functional independence at discharge, discharge disposition (home, assisted-living facility, nursing home or long-term care hospital) and skin breakdown or pressure ulcers. Intermediate outcomes are: respiratory rate, $\text{PaO}_2/\text{FiO}_2$ ratio, SpO_2 , pH, PaO_2 , PCO_2 , treatment escalation and device intolerance. If multiple points are reported, we will categorise these as ‘short’ (first time point) and ‘longer’ (last time point) term outcomes. We will also explore analyses based on commonly reported time points.

Timing

We will include patients hospitalised for ARF or who developed ARF while hospitalised, including patients with ARF postextubation or postsurgery. We will exclude studies evaluating HFNO for oxygenation support before (preoxygenation) and during intubation.

Setting

We will include studies that randomised patients in the hospital (including hospital wards, intermediate/step-down units and intensive care units) and emergency department (ED).

Study design

Randomised controlled trials (RCTs) including crossover RCTs and cluster RCTs with full-text reports in English will be included. We will exclude non-randomised trials and observational studies.

Data sources and search strategy

We will search MEDLINE, Embase, CINAHL and Cochrane Library from January 2000 to August 2019. HFNO was not widely used in adults prior to 2000. The literature search will be updated prior to preparation of the final report. The search strategy for the MEDLINE search is provided in online supplementary appendix B. We will search

references of the primary studies and published systematic reviews for relevant studies. We will also search ClinicalTrials.gov for recently completed or ongoing clinical trials.

Study selection process

We will conduct the study selection in two stages: stage one is abstract triage and stage two is full-text triage. All studies in stage one and stage two of the study selection process will be reviewed independently by two members of the review team. Abstracts included by one reviewer will move on to full-text review. At the full-text review stage, both reviewers must agree on study inclusion or exclusion. Disagreements will be resolved through discussion and evaluation by a third reviewer, if needed.

Data extraction and management

Data extraction forms will be piloted by three members of the review team. Final data extraction will be conducted by one investigator with verification by a second team member. Disagreements in data extraction will be resolved by consensus that includes the senior investigator (TJW). Data that will be extracted include information related to study characteristics (primary author, year published, country, funding source, setting and study population); participant inclusion and exclusion criteria; descriptions of intervention and comparator (oxygen therapy or NIV settings, adjustment parameters and follow-up duration); participant demographics (age, race/ethnicity, gender, comorbidities and baseline physiologic parameters such as SpO₂, respiratory rate, PaO₂/FiO₂ ratio, pH, PaO₂ and PCO₂) and outcome data (patient-centred outcomes and intermediate outcomes). The data extraction form with the full list of information that will be extracted is provided in online supplementary appendix C. Data will be extracted similarly for all eligible studies and then subgroup analyses will be performed.

Data synthesis and analysis

We will examine the clinical and methodological heterogeneity to determine appropriateness of quantitative synthesis. Cluster RCTs will be evaluated for statistical measures that adjust for clustering. Analyses will be conducted by a systematic review methodologist. We will use Comprehensive Meta Analysis V.3 or R for pooled analyses. We will calculate risk ratios and Peto ORs (for rare events) and corresponding 95% CIs for categorical outcomes. Mean and standardised mean difference will be calculated for continuous outcomes. Heterogeneity will be assessed by using the I² statistic, χ^2 test and visual inspection of the forest plots. An I² statistic of 75% or greater may indicate substantial heterogeneity. If heterogeneity exists, we will conduct subgroup analyses to explore potential causes of heterogeneity. We will pool clinically homogeneous (population, intervention, setting, outcome measures) studies with sufficient outcomes information. Our primary analysis will include studies deemed of low-to-moderate risk of bias. We will conduct sensitivity analyses that include data from studies deemed to be high risk of bias. For analyses involving two

subgroups, χ^2 test will be used to assess differences between the groups. If applicable, when there are more than two subgroups, meta-regression will be applied to explore the relationship between the subgroup characteristics and the treatment effects.²² Meta-regression will only be considered if there are more than 10 studies in a meta-analysis. Meta-regression will be performed using the 'metafor' package for R. If quantitative synthesis is not appropriate, findings will be summarised narratively.

Subgroup analysis

If sufficient data allow, we plan to perform analysis on the following subgroups of interest: (1) NIV versus COT; (2) ED, ICU, hospital ward/step down, or mixed settings; (3) de novo versus post-extubation respiratory failure; (4) chronic obstructive pulmonary disease (COPD), cardiogenic pulmonary oedema/acute decompensated heart failure, pneumonia, obese, post-extubation, post-surgical, immunocompromised (5) hypoxic, hypercapnic and mixed (hypoxic or hypercapnic) respiratory failure; (6) treatment duration <6vs ≥6hours and (7) lower (≤30L/min) versus higher (>30L/min) flow settings.

We hypothesise that: (1) HFNO is more beneficial than COT, but is as effective, though less comfortable, than NIV; (2) the efficacy of HFNO is likely the same as NIV, but better than COT, in different settings; (3) HFNO is as effective as NIV in COPD, pneumonia, postextubation and postsurgical patients; (4) HFNO is less effective than NIV in cardiogenic pulmonary oedema and obesity due to lower level of PEEP; (5) HFNO is more effective than COT in most disease states; (6) HFNO is more effective and less harmful than NIV in hypoxic respiratory failure but is less effective in hypercapnic and mixed hypoxic and hypercapnic respiratory failure; and (7) higher flow (>30L/min) is more effective, but is less comfortable, than lower flow (≤30L/min) settings. If subgroup analyses are performed, we will assess subgroup effects with an I² statistic for subgroup differences. The I² statistic delineates the percentage of variability in the estimates of effect between the different subgroups that is due to real subgroup differences (as opposed to sampling error).

Assessment of bias in individual studies

We will assess the risk of bias using a modification of the Cochrane guidance for randomised trials.²³ Individual elements will be rated low, unclear or high risk of bias. Our modification of the tool is to identify overall study risk of bias as low, moderate or high. A study with unclear elements will be considered moderate risk of bias. Components of risk of bias assessment will include sequence generation, allocation concealment, blinding, attrition and appropriateness of analytic methods. One reviewer will conduct risk of bias assessments at the study level and will be verified by a second reviewer. Disagreements will be resolved through discussion and evaluation by a third reviewer. If appropriate, we may conduct sensitivity analyses excluding high risk of bias studies.

We will attempt to reduce the risk of publication bias by doing a comprehensive search across multiple data bases and with input from ACP-CGC and TEP members. We will conduct funnel plot analysis to assess for publication bias across studies if sufficient studies are found. We will look at protocol papers, where available, to assess whether outcomes were pre-specified and whether all outcomes are reported.

Assessment of the certainty of the body of evidence

We will use the Grading of Recommendations, Assessment, Development, and Evaluation methodology to rate overall certainty of evidence for the critical outcomes identified by the ACP as high, moderate, low or very low.^{24 25}

Patient and public involvement

The list of patient-centred outcomes that will be evaluated in this systematic evidence review was developed and rated as critical or important with input from nonphysician public representatives.

Ethics and dissemination

No ethical approval will be needed because we will be using data from previously published studies in which informed consent was obtained by the primary investigators. We will publish our results in a peer-reviewed journal.

CONCLUSION

This systematic review will provide a comprehensive evaluation of the evidence regarding the comparative effectiveness and harms of HFNO compared with NIV or COT for the management of ARF in hospitalised adult patients to inform clinical practice and to identify research gaps in the management of ARF in hospitalised adults. The results will inform the work of the ACP-CGC in their development of a clinical guideline related to use of HFNO in adult patients with ARF.

Correction notice This article has been corrected since it was published. The Funding section has been updated.

Contributors TJW is the guarantor. AKB, AM, NG, BNM and TJW contributed to study design and the PROSPERO protocol. NG developed the search strategy and the risk of bias assessment strategy. BNM and NG developed the data extraction tables. AKB drafted the protocol manuscript. AKB and AM provided expertise on acute respiratory failure management. RM provided statistical expertise. All authors provided critical revisions and approved the final manuscript.

Funding This review is funded by a contract with the American College of Physicians (ACP). The ACP-Clinical Guideline Committee (CGC) assisted in the development of key questions, study inclusion criteria, and outcome measures of interest but will not be involved in data collection, analysis, or manuscript preparation. This material is the result of work supported by and conducted at the Minneapolis VA Health Care System.

Competing interests TJW is Chair of the ACP-CGC. He will be recused from voting on or authoring the ACP guidelines.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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