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High-flow nasal oxygen (HFNO) for hospitalized patients: a systematic review protocol

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PROTOCOL:

High-flow nasal oxygen (HFNO) for hospitalized patients: a systematic review protocol

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HFNO for hospitalized patients: a systematic review protocol
Date: 10/15/19

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Date: 10/15/19

ABSTRACT

Introduction

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

Methods and analysis

We searched MEDLINE®, Embase, CINAHL, and Cochrane Library for randomized-controlled trials (RCTs) of adult patients hospitalized with ARF defined as SpO_2 <90%, PaO_2:FiO_2 ratio ≤300, PaO_2 ≤60 mmHg, or $PaCO_2$ ≥45 mmHg. The intervention is HFNO (humidified oxygen, flow rate ≥20 L/min) compared to NIV or COT. The critical outcomes are: mortality, hospital-acquired pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU) admission and ICU transfers, patient comfort, and hospital length of stay. The important outcomes are: delirium, 30-day hospital readmissions, barotrauma, compromised nutrition, gastric dysfunction, independence at discharge, discharge, and skin breakdown or pressure ulcers. 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 to NIV or COT for the management of ARF in hospitalized adult patients to inform clinical practice and to identify

research gaps in the management of acute respiratory failure in hospitalized 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.

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: Submitted on August 8, 2019.

MeSH keywords: systematic review; oxygen inhalation therapy; respiratory failure; respiratory tract diseases; positive-pressure respiration; high-flow nasal oxygen

Word count: 1,484

Strengths and limitations of this study:

- This protocol describes the methods for a systematic evidence review that will comprehensively evaluate the comparative effectives and harms of high-flow nasal oxygen (HFNO) compared to noninvasive ventilation (NIV) or conventional oxygen therapy (COT) for the management of acute respiratory failure in hospitalized adult patients to inform clinical practice and to identify research gaps in the management of acute respiratory failure in hospitalized adults.
- The list of patient-centered outcomes that will be evaluated in this systematic evidence review was developed with input from nonphysician public representatives.

- The relative heterogeneity of the populations, diagnoses, settings, and outcome measures assessed by the individual studies that will be included in this systematic review may preclude meaningful subgroup analyses.

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INTRODUCTION

High-flow nasal oxygen (HFNO) therapy is a mode of noninvasive oxygen support that has been used in neonatal and pediatric settings for over a decade. In recent years, HFNO use in adults hospitalized 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 60 L/min. Several potential physiologic advantages of HFNO over noninvasive ventilation (NIV) and conventional oxygen therapy (COT) have been proposed. These include patient comfort (1, 2), improved oxygenation and ventilation (3, 4), clearance of airway secretions (5, 6), and reduced work of breathing (2, 7, 8). These theoretical benefits are attributed to HFNO delivery through small, pliable nasal cannula, washout of anatomic dead space (9), high oxygen flow rates (10, 11), generation of positive-end expiratory pressure (PEEP) (12-16), 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 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 to NIV or COT for the management of ARF in hospitalized adult patients. With input from the ACP-Clinical Guidelines Committee (ACP-CGC) (17) 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 hospitalized 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 hospitalized 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 (PROSPERO) on August 8, 2019. We will report our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 statement (18).

Eligibility criteria

All studies included in this systematic review will be selected in accordance with the PICOTS (Population, Intervention, Comparison, Outcomes, Timing, Study Design) framework:

Population

We will include all adult patients (age ≥18 years) with ARF at the time of study enrollment, defined as SpO_2 <90%, PaO_2:FIO_2 ratio ≤300, PaO_2 ≤60 mmHg, or $PaCO_2$ ≥45 mmHg.

Intervention

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

Comparators

We will compare HFNO to NIV (continuous or bilevel positive airway pressure ventilation [CPAP or BiPAP®]) or COT (e.g. oxygen delivered through nasal cannula, simple face mask, air-entrainment mask, partial rebreathing mask, non-rebreather mask, etc).

Outcome measures

We will examine several patient-related outcomes and intermediate outcomes. With input from the ACP-CGC that included nonphysician public representatives, outcomes were identified as critical or important. The critical outcomes are: mortality, hospital-acquired pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU) admission and ICU 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, PaO_2/FiO_2 ratio, SpO_2, pH, PaO_2, and PCO_2.

Timing

We will include patients hospitalized for ARF or who developed ARF while hospitalized, including patients with ARF post-extubation or post-surgery. We will exclude studies evaluating HFNO for oxygenation support before (preoxygenation) and during intubation.

Setting

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

Study design

Randomized controlled trials (RCTs) with full-text reports in English will be included. We will exclude non-randomized trials and observational studies.

Data sources and search strategy

We searched MEDLINE®, Embase, CINAHL, and Cochrane Library from January 2000 to August 2019. The literature search will be updated prior to preparation of the final report. The search strategy for the MEDLINE® search is provided in Appendix A. We will search references of the primary studies and published systematic reviews for relevant studies. We will also search ClinicalTrials.gov and conference proceedings for unpublished 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 SpO_2, respiratory rate, PaO_2/FiO_2 ratio, pH, PaO_2, and PCO_2); and outcome data (patient-centered outcomes and intermediate outcomes). The data extraction form with the full list of information that will be extracted is provided in Appendix B. Data extraction will be stratified by setting; depending on data availability, we will also stratify data by comparator and by diagnosis or underlying disease.

Data synthesis and analysis

We will examine the clinical and methodological heterogeneity to determine appropriateness of quantitative synthesis. 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 odds ratios (for rare events) and corresponding 95% confidence intervals for categorical outcomes. Mean and standardized mean difference will be calculated for continuous outcomes. Heterogeneity will be assessed by using the I^2 test. An I^2 statistic of 75 or greater may indicate substantial heterogeneity. If heterogeneity exists, we will conduct sensitivity analyses to explore potential causes of heterogeneity. We will pool studies with clinically homogeneous (population, intervention, setting, outcome measures) studies with sufficient outcomes information. We will also pool data from studies deemed of low to moderate risk of bias (ROB). We will extract data from high ROB studies and include them in sensitivity analyses. If quantitative synthesis is not appropriate, findings will be summarized narratively.

Assessment of bias in individual studies

We will assess the risk of bias using a modification of the Cochrane guidance for randomized trials (19). 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 do not anticipate that there will be sufficient studies by population, intervention, and outcome to conduct funnel plots assessing for publication bias across studies. 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 (GRADE) methodology to rate overall certainty of evidence for the critical outcomes identified by the ACP as high, moderate, low, or very low (20, 21).

Patient and public involvement

The list of patient-centered 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 to NIV or COT for the management of ARF in hospitalized adult patients to inform clinical practice and to identify research gaps in the management of acute respiratory failure in hospitalized 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.

Author contributions: TJW is the guarantor. AKB, AM, NG, BNM, 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.

Support: 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.

Acknowledgements: The evidence review team would like to acknowledge the ACP-CGC, the public representatives, and the technical expert panel (TEP) members who have provided valuable feedback on the protocol development. The TEP members are: Charles Carpati, MD; Andrew Dunn, MD, MPH, SFHM, MACP; Matthew G. Drake, MD; and Robert C. Hyzy, MD.

Competing interests: TJW is Chair of the ACP-CGC. He will be recused from voting on or authoring the ACP guidelines. All other authors have no conflict of interests to declare.

Data statement: Data sharing is not applicable as no datasets were generated and/or analyzed for this protocol paper.

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Appendix A. MEDLINE® search strategy

1 (high flow nasal adj2 (cannula$ or oxygen$ or therap$ or insufflation$)).mp.
2 high flow therapy.mp.
3 nasal high flow.mp.
4 high flow oxygen.mp.
5 (humidified high flow or humidified oxygen).mp.
6 (HFNC or HHFNC or HFNT or NHF or HFNO or HFOT or HFNOT).ti,ab.
7 (Vapotherm or Optiflow or "Comfort Flo").ti,ab.
8 or/1-7
9 remove duplicates from 8
10 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab.
11 (random$ adj (enroll$ or assign$ or allocat$)).ti,ab.
12 ((randomi#ed or controlled or clinical) adj2 trial$).ti,ab.
13 or/10-12
14 9 and 13
15 (meta-analy$ or metaanaly$ or meta analy$).ti,ab.
16 exp Meta-Analysis/
17 (systematic adj2 (review$ or overview$)).ti,ab.
18 (rapid review or meta synthesis or metasynthesis or meta-synthesis or umbrella review or integrative review or data synthesis or review of reviews).ti,ab.
19 or/15-18
20 9 and 19
21 limit 14 to english language
22 limit 21 to yr="1995 -Current"
23 limit 22 to "all child (0 to 18 years)"
24 limit 23 to "all adult (19 plus years)"
25 22 not 23
26 24 or 25
27 limit 20 to english language
28 limit 27 to yr="2015 -Current"
29 limit 28 to "all child (0 to 18 years)"
30 limit 29 to "all adult (19 plus years)"
31 28 not 29
32 30 or 31

Appendix B. Data extraction tables

Table 1. Study Characteristics

Author, year **Country** **Funding** **Setting** **Special population** **Risk of Bias**	**Inclusion/Exclusion Criteria**	**Intervention (n)** **Comparator (n)** **Follow-up (primary outcome)**	**Demographics**
	Inclusion: Exclusion:	Intervention: Comparator: Follow-up:	N= Age (mean): Race/ethnicity (%): White: Black: Other: Gender (% male): Comorbidities (%): Chronic Respiratory Failure: COPD: Congestive Heart Failure: Comorbidity Index: Baseline characteristics: SpO_2: Respiratory Rate: PaO_2/FiO_2 ratio: pH: PaO_2: $PaCO_2$:

Table 2. Risk of Bias Assessment for Included Studies

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias

Table 3. Treatment Characteristics

Author Year Setting Follow-up Comparator	Adherence to treatment—describe measure		Treatment Settings				Treatment Weaning Criteria	
			Protocol		Received			
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
			Flow Rate: FiO2: Temperature: Duration:	Flow Rate: FiO2: Temperature: Duration:	Flow Rate: FiO2: Temperature: Duration:	Flow Rate: FiO2: Temperature: Duration:		

Table 4: Patient-Centered Outcomes, Part 1

Author Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N)		ICU Admissions and/or Transfers (mean # of days)		Length of Hospital Stay (mean # of days)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

Table 5: Patient-Centered Outcomes, Part 2

Author Year Setting Follow-up Comparator	Hospital-acquired Pneumonia % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Patient Comfort (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

Table 6: Patient-Centered Outcomes, Part 3

Author Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)—describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control

Table 7: Patient-Centered Outcomes, Part 4

Author Year Setting Follow-up Comparator	Compromised Nutrition				Gastric Dysfunction			
	% (n/N)		# days w/o nutrition		% (n/N) with placement of nasogastric tube		% (n/N) with nausea, vomiting, or abdominal distension	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

Table 8: Patient-Centered Outcomes, Part 5

Author Year Setting Follow-up Comparator	Barotrauma % (n/N)		Skin Breakdown or Pressure Ulcers % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control

Table 9: Intermediate Outcomes, Part 1

Author Year Setting Follow-up Comparator	**Respiratory Rate (mean, SD)**		**PaO_2/FiO_2 ratio (mean, SD)**		**SpO_2 (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**

Table 10: Intermediate Outcomes, Part 2

Author Year Setting Follow-up Comparator	**pH (mean, SD)**		**PaO_2 (mean, SD)**		**$PaCO_2$ (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - **Moher D, Stewart L & Shekelle P:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	71. Awaiting registration number.
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	25-31
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	250-255
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	257-260
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	257-260
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	257-260
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	92-107

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	110-117
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	125-167
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	169-174
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	169-174
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	184-197
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	176-182
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	184-197
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	184-197
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	142-154
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	213-225
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	199-211
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	199-211

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	199-211
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	211
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	220-225
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	227-230

BMJ Open

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

Journal:	*BMJ Open*
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Complete List of Authors:	Baldomero, Arianne; Minneapolis VA Health Care System; University of Minnesota, Pulmonary, Allergy, Critical Care, and Sleep Medicine Melzer, Anne; Minneapolis VA Health Care System; University of Minnesota, Pulmonary, Allergy, Critical Care, and Sleep Medicine Greer, Nancy; Minneapolis VA Health Care System, Center for Care Delivery and Outcomes Research Majeski, Brittany; Minneapolis VA Health Care System, Center for Care Delivery and Outcomes Research Macdonald, Roderick; Minneapolis VA Health Care System, Center for Care Delivery and Outcomes Research Wilt, Timothy; Minneapolis VA Health Care System, Center for Care Delivery and Outcomes Research; University of Minnesota, Department of Medicine
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Respiratory medicine, Intensive care, Evidence based practice
Keywords:	RESPIRATORY MEDICINE (see Thoracic Medicine), INTERNAL MEDICINE, INTENSIVE & CRITICAL CARE, Adult thoracic medicine < THORACIC MEDICINE, GENERAL MEDICINE (see Internal Medicine), Adult intensive & critical care < INTENSIVE & CRITICAL CARE

PROTOCOL:

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

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ABSTRACT

Introduction

High-flow nasal oxygen (HFNO) use in adults hospitalized with acute respiratory failure (ARF) is increasing. However, evidence to support widespread use of HFNO compared to noninvasive 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 to NIV or COT for the management of ARF in hospitalized adult patients.

Methods and analysis

We will search MEDLINE®, Embase, CINAHL, and Cochrane Library for randomized-controlled trials (RCTs) of adult patients hospitalized with ARF or who developed ARF while hospitalized. ARF will be defined as SpO_2 <90%, PaO_2:FiO_2 ratio ≤300, PaO_2 ≤60 mmHg, or $PaCO_2$ ≥45 mmHg. 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 (ICU) 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 odds ratios (for rare events) and corresponding 95% confidence intervals for categorical outcomes. Mean and standardized 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 to NIV or COT for the management of ARF in hospitalized adult patients to inform clinical practice and to identify research gaps in the management of ARF in hospitalized 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.

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: CRD42019146691

MeSH keywords: systematic review; oxygen inhalation therapy; respiratory failure; respiratory tract diseases; positive-pressure respiration; high-flow nasal oxygen

Word count: 1,969

Strengths and limitations of this study:

- We will compare high-flow nasal oxygen (HFNO) to both noninvasive ventilation and conventional oxygen therapy.
- We will evaluate the efficacy and harms of HFNO in a wide-range of clinical conditions (e.g. chronic obstructive pulmonary disease, cardiogenic pulmonary edema, immunosuppressed, post-surgery, post-extubation, etc.) 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 noninvasive oxygen support that has been used in neonatal and pediatric settings for over a decade. In recent years, HFNO use in adults hospitalized 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 60 L/min. Several potential physiologic advantages of HFNO over noninvasive 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 to NIV or COT for the management of ARF in hospitalized adult patients. Compared to 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 acute respiratory failure. With input from the ACP-Clinical Guidelines Committee (ACP-CGC) (20) 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 hospitalized 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 hospitalized 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 (PROSPERO) on August 8, 2019. We will report our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 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 (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: SpO_2 <90%, PaO_2:FIO_2 ratio ≤300, PaO_2 ≤60 mmHg, or $PaCO_2$ ≥45 mmHg.

Intervention

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

Comparators

We will compare HFNO vs. NIV (continuous or bilevel positive airway pressure ventilation [CPAP or BiPAP®]) and HFNO vs. COT (e.g. oxygen delivered through nasal cannula, simple face mask, air-entrainment mask, partial rebreathing mask, non-rebreather mask, etc.).

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, PaO_2/FiO_2 ratio, SpO_2, pH, PaO_2, PCO_2, treatment escalation, and device intolerance. If multiple points are reported, we will categorize 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 hospitalized for ARF or who developed ARF while hospitalized, including patients with ARF post-extubation or post-surgery. We will exclude studies evaluating HFNO for oxygenation support before (preoxygenation) and during intubation.

Setting

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

Study design

Randomized controlled trials (RCTs) including crossover RCTs and cluster RCTs with full-text reports in English will be included. We will exclude non-randomized 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 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 SpO_2, respiratory rate, PaO_2/FiO_2 ratio, pH, PaO_2, and PCO_2); and outcome data (patient-centered outcomes and intermediate outcomes). The data extraction form with the full list of information that will be extracted is provided in 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 odds ratios (for rare events) and corresponding 95% confidence intervals for categorical outcomes. Mean and standardized mean difference will be calculated for continuous outcomes. Heterogeneity will be assessed by using the I^2 statistic, Chi-squared test, and visual inspection of the forest plots. An I^2 statistic of 75 or greater may indicate substantial heterogeneity. If heterogeneity exists, we will conduct sensitivity analyses to explore potential causes of heterogeneity. We will pool clinically homogeneous (population, intervention, setting, outcome measures) studies with sufficient outcomes information. We will also pool data from studies deemed of low to moderate risk of bias (ROB). We will extract data from high ROB studies and include them in sensitivity analyses. If quantitative synthesis is not appropriate, findings will be summarized narratively.

Subgroup analysis

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

We hypothesize 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, post-extubation, and post-surgical patients; (4) HFNO is less effective than NIV in cardiogenic pulmonary edema 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 (>30 L/min) is more effective, but is less comfortable, than lower flow (≤30 L/min) settings. If subgroup analyses are performed, we will assess subgroup effects with an I^2 statistic for subgroup differences. The I^2 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 randomized trials (22). 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 (GRADE) methodology to rate overall certainty of evidence for the critical outcomes identified by the ACP as high, moderate, low, or very low (23, 24).

Patient and public involvement

The list of patient-centered 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 to NIV or COT for the management of ARF in hospitalized adult patients to inform clinical practice and to identify research gaps in the management of acute respiratory failure in hospitalized 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.

Author contributions: TJW is the guarantor. AKB, AM, NG, BNM, 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.

Support: 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.

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Competing interests: TJW is Chair of the ACP-CGC. He will be recused from voting on or authoring the ACP guidelines. All other authors have no conflict of interests to declare.

Data statement: Data sharing is not applicable as no datasets were generated and/or analyzed for this protocol paper.

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Appendix A. Key Questions and PICOTS

KEY QUESTIONS

1) What is the comparative effectiveness of high flow nasal oxygen versus noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen for hospitalized patients?

1a) Does comparative effectiveness of high flow nasal oxygen vary by patient characteristics, disease/diagnosis characteristics, protocol/device settings, or location of administration?

2) What are the harms of high flow nasal oxygen versus noninvasive positive pressure ventilation (CPAP, BiPAP®), invasive mechanical ventilation, or conventional oxygen for hospitalized patients?

2a) Do harms vary by patient characteristics, disease/diagnosis, protocol/device settings, or location of administration?

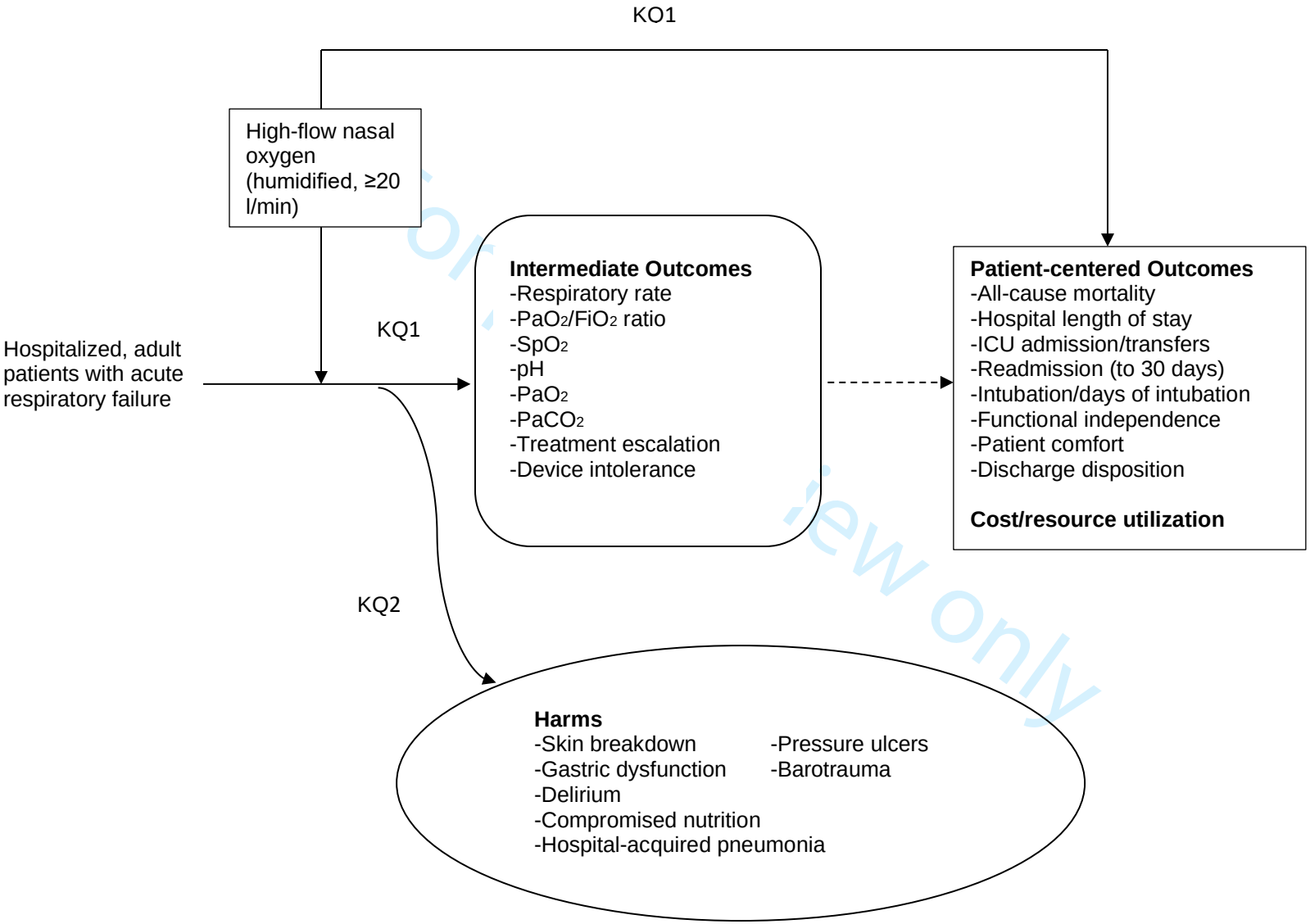
PICOTS	
Population:	Hospitalized adult patients with acute respiratory failure (ARF). ARF defined as SpO_2 <90%, PaO_2:FiO_2 ratio ≤300, PaO_2 ≤60 mmHg, or $PaCO_2$ ≥45 mmHg
Intervention:	High flow nasal oxygen (humidified, ≥20 l/min)
Comparators:	Noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen (e.g., simple, Venturi, or nonrebreather oxygen masks)
Outcomes:	**Patient-centered Outcomes:** all-cause mortality (in-hospital and 90 day), intubation/reintubation (days of intubation), hospital length of stay, ICU admissions/transfers (ICU days), patient comfort, hospital readmissions (30 day) (e.g., all-cause, pneumonia), functional independence at discharge (e.g., scale scores, measures of independence/activities of daily living), discharge disposition **Intermediate Outcomes:** respiratory rate, PaO_2/FiO_2 ratio, SpO_2, pH, PaO_2, $PaCO_2$, treatment escalation, device intolerance **Cost/resource utilization** **Harms:** skin breakdown or pressure ulcers, gastric dysfunction, hospital-acquired pneumonia, compromised nutrition (enteral or parenteral nutrition), delirium, barotrauma
Timing:	Hospitalization for ARF or development of ARF while hospitalized; immediate post-extubation; post-surgery. Exclude pre-intubation/pre-oxygenation and HFNO oxygenation support during intubation
Setting:	Hospital (including ICU, step down units, hospital wards), emergency department
Study Design:	Randomized controlled trials, including crossover RCTs and cluster RCTs
Subgroups:	Patient characteristics: age, race, gender Disease/diagnosis (e.g. COPD, cardiogenic pulmonary edema, immunosuppressed, post-extubation, post-surgery; hypoxic, hypercapnic, or mixed [hypoxic or hypercapnic] respiratory failure) Protocol/device settings (e.g., flow rate ≤30 vs. >30 L/min; treatment duration <6 vs. ≥6 hours)

BiPAP=Bilevel Positive Airway Pressure; CPAP=continuous positive airway pressure; ICU=intensive care unit; COPD= chronic obstructive pulmonary disease

LITERATURE SEARCH

RCTs: We will search MEDLINE, Embase, CINAHL, and Cochrane Library from 2000 to August 2019
Clinicaltrials.gov for recently completed and/or on-going trials
Reference lists from relevant systematic reviews for references missed by our database searches

Analytic Framework



Appendix B. MEDLINE® search strategy

1 (high flow nasal adj2 (cannula$ or oxygen$ or therap$ or insufflation$)).mp.
2 high flow therapy.mp.
3 nasal high flow.mp.
4 high flow oxygen.mp.
5 (humidified high flow or humidified oxygen).mp.
6 (HFNC or HHFNC or HFNT or NHF or HFNO or HFOT or HFNOT).ti,ab.
7 (Vapotherm or Optiflow or "Comfort Flo").ti,ab.
8 or/1-7
9 remove duplicates from 8
10 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab.
11 (random$ adj (enroll$ or assign$ or allocat$)).ti,ab.
12 ((randomi#ed or controlled or clinical) adj2 trial$).ti,ab.
13 or/10-12
14 9 and 13
15 (meta-analy$ or metaanaly$ or meta analy$).ti,ab.
16 exp Meta-Analysis/
17 (systematic adj2 (review$ or overview$)).ti,ab.
18 (rapid review or meta synthesis or metasynthesis or meta-synthesis or umbrella review or integrative review or data synthesis or review of reviews).ti,ab.
19 or/15-18
20 9 and 19
21 limit 14 to english language
22 limit 21 to yr="1995 -Current"
23 limit 22 to "all child (0 to 18 years)"
24 limit 23 to "all adult (19 plus years)"
25 22 not 23
26 24 or 25
27 limit 20 to english language
28 limit 27 to yr="2015 -Current"
29 limit 28 to "all child (0 to 18 years)"
30 limit 29 to "all adult (19 plus years)"
31 28 not 29
32 30 or 31

Appendix C. Data extraction forms

Table 1. Study Characteristics

Author, year **Country** **Funding** **Setting** **Special population** **Risk of Bias rating**	**Inclusion/Exclusion Criteria**	**Intervention (n)** **Comparator (n)** **Follow-up (primary outcome)**	**Demographics**
	Inclusion: Exclusion:	Intervention: Comparator: Follow-up:	N= Age (mean): Race/ethnicity (%): White: Black: Other: Gender (% male): Comorbidities (%): Chronic Respiratory Failure: COPD: Congestive Heart Failure: Comorbidity Index: Baseline characteristics: SpO_2: Respiratory Rate: PaO_2/FiO_2 ratio: pH: PaO_2: $PaCO_2$:

Table 2. Risk of Bias Assessment for Included Studies

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias

Table 3. Treatment Characteristics

Author Year Setting Follow-up Comparator	Adherence/Intolerance describe measure		Treatment Settings				Treatment Weaning Criteria		
			Protocol		Received				
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported

COT=conventional oxygen therapy; HFFM=high-flow face mask; HFNC=high-flow nasal cannula; NIV=non-invasive ventilation; NR=not reported; PEEP=positive end-expiratory pressure

Table 4: Patient-Centered Outcomes, Part 1

Author Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N)		ICU Admissions and/or Transfers (mean # of days)		Length of Hospital Stay (mean # of days)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HR=hazard ratio; ICU=intensive care unit; IQR=interquartile range; NIV=Non-invasive ventilation; N/A=not applicable; NR=not reported; RD=risk difference; SD=standard deviation

Table 5: Patient-Centered Outcomes, Part 2

Author Year Setting Follow-up Comparator	Treatment Escalation (describe) % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported

CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HR=hazard ratio; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; VAS=visual analog scale

Table 6: Patient-Centered Outcomes, Part 3

Author Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)—describe measure		Patient Comfort (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; NS=not statistically significant

Discharge Disposition: home, assisted living facility, nursing home, long-term care hospital

Table 7: Patient-Centered Outcomes, Part 4

Author Year Setting Follow-up Comparator	Compromised Nutrition				Gastric Dysfunction			
	% (n/N)		# days w/o nutrition		% (n/N) with placement of nasogastric tube		% (n/N) with nausea, vomiting, or abdominal distension	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; NR=not reported

Compromised Nutrition: (enteral/parenteral nutrition or days without nutrition)
Gastric Dysfunction: (placement of a nasogastric tube for decompression or treatment of abdominal distension/nausea/vomiting)

Table 8: Patient-Centered Outcomes, Part 5

Author Year Setting Follow-up Comparator	Hospital-acquired Pneumonia % (n/N)		Barotrauma % (n/N)		Skin Breakdown or Pressure Ulcers % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; N/A=not applicable; NR=not reported

Barotrauma: (pneumothorax, pneumomediastinum, pneumoperitoneum, or ventilator-induced lung injury

Table 9: Intermediate Outcomes, Part 1

Author Year Setting Follow-up Comparator	Respiratory Rate (mean, SD)		PaO_2/FiO_2 ratio (mean, SD)		SpO_2 (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; NS=not statistically significant; SD=standard deviation

Table 10: Intermediate Outcomes, Part 2

Author Year Setting Follow-up Comparator	pH (mean, SD)		PaO_2 (mean, SD)		$PaCO_2$ (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; NR=not reported; SD=standard deviation

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	74	74
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	25-31
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	295-300
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	302-305
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	302-305
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	302-305
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	98-121

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	122-129
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	125-167
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	137-187
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	189-195
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	205-217
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	197-203
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	205-217
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	209-216 157-173
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	157-173
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	256-270
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	219-233

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	199-211
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	219-242
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	232-233
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	266-270
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	272-275

BMJ Open

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

Journal:	*BMJ Open*
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Respiratory medicine, Intensive care, Evidence based practice
Keywords:	RESPIRATORY MEDICINE (see Thoracic Medicine), INTERNAL MEDICINE, INTENSIVE & CRITICAL CARE, Adult thoracic medicine < THORACIC MEDICINE, GENERAL MEDICINE (see Internal Medicine), Adult intensive & critical care < INTENSIVE & CRITICAL CARE

PROTOCOL:

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

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ABSTRACT

Introduction

High-flow nasal oxygen (HFNO) use in adults hospitalized with acute respiratory failure (ARF) is increasing. However, evidence to support widespread use of HFNO compared to noninvasive 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 to NIV or COT for the management of ARF in hospitalized adult patients.

Methods and analysis

We will search MEDLINE®, Embase, CINAHL, and Cochrane Library for randomized-controlled trials (RCTs) of adult patients hospitalized with ARF or who developed ARF while hospitalized. ARF will be defined as SpO_2 <90%, PaO_2:FiO_2 ratio ≤300, PaO_2 ≤60 mmHg, or $PaCO_2$ ≥45 mmHg. 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 (ICU) 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 odds ratios (for rare events) and corresponding 95% confidence intervals for categorical outcomes. Mean and standardized 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 to NIV or COT for the management of ARF in hospitalized adult patients to inform clinical practice and to identify research gaps in the management of ARF in hospitalized 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.

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: CRD42019146691

MeSH keywords: systematic review; oxygen inhalation therapy; respiratory failure; respiratory tract diseases; positive-pressure respiration; high-flow nasal oxygen

Word count: 1,969

Strengths and limitations of this study:

- We will compare high-flow nasal oxygen (HFNO) to both noninvasive ventilation and conventional oxygen therapy.
- We will evaluate the efficacy and harms of HFNO in a wide-range of clinical conditions (e.g. chronic obstructive pulmonary disease, cardiogenic pulmonary edema, immunosuppressed, post-surgery, post-extubation, etc.) 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 noninvasive oxygen support that has been used in neonatal and pediatric settings for over a decade. In recent years, HFNO use in adults hospitalized 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 60 L/min. Several potential physiologic advantages of HFNO over noninvasive 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 to NIV or COT for the management of ARF in hospitalized adult patients. Compared to 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 acute respiratory failure. With input from the ACP-Clinical Guidelines Committee (ACP-CGC) (20) 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 hospitalized 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 hospitalized 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 (PROSPERO) on August 8, 2019. We will report our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 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 (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: SpO_2 <90%, PaO_2:FIO_2 ratio ≤300, PaO_2 ≤60 mmHg, or $PaCO_2$ ≥45 mmHg.

Intervention

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

Comparators

We will compare HFNO vs. NIV (continuous or bilevel positive airway pressure ventilation [CPAP or BiPAP®]) and HFNO vs. COT (e.g. oxygen delivered through nasal cannula, simple face mask, air-entrainment mask, partial rebreathing mask, non-rebreather mask, etc.).

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, PaO_2/FiO_2 ratio, SpO_2, pH, PaO_2, PCO_2, treatment escalation, and device intolerance. If multiple points are reported, we will categorize 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 hospitalized for ARF or who developed ARF while hospitalized, including patients with ARF post-extubation or post-surgery. We will exclude studies evaluating HFNO for oxygenation support before (preoxygenation) and during intubation.

Setting

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

Study design

Randomized controlled trials (RCTs) including crossover RCTs and cluster RCTs with full-text reports in English will be included. We will exclude non-randomized 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 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 SpO_2, respiratory rate, PaO_2/FiO_2 ratio, pH, PaO_2, and PCO_2); and outcome data (patient-centered outcomes and intermediate outcomes). The data extraction form with the full list of information that will be extracted is provided in 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 odds ratios (for rare events) and corresponding 95% confidence intervals for categorical outcomes. Mean and standardized mean difference will be calculated for continuous outcomes. Heterogeneity will be assessed by using the I^2 statistic, Chi-squared test, and visual inspection of the forest plots. An I^2 statistic of 75% or greater may indicate substantial heterogeneity. 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 includes data from studies deemed to be high risk of bias. For analyses involving two subgroups, Chi-squared 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 ten 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 summarized narratively.

Subgroup analysis

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

We hypothesize 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, post-extubation, and post-surgical patients; (4) HFNO is less effective than NIV in cardiogenic pulmonary edema 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 (>30 L/min) is more effective, but is less comfortable, than lower flow (≤30 L/min) settings. If subgroup analyses are performed, we will assess subgroup effects with an I^2 statistic for subgroup differences. The I^2 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 randomized 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 (GRADE) 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-centered 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 to NIV or COT for the management of ARF in hospitalized adult patients to inform clinical practice and to identify research gaps in the management of acute respiratory failure in hospitalized 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.

Author contributions: TJW is the guarantor. AKB, AM, NG, BNM, 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.

Acknowledgements: The evidence review team would like to acknowledge the ACP-CGC, the public representatives, and the technical expert panel (TEP) members who have provided valuable feedback on the protocol development. The TEP members are: Charles Carpati, MD; Andrew Dunn, MD, MPH, SFHM, MACP; Matthew G. Drake, MD; and Robert C. Hyzy, MD.

Competing interests: TJW is Chair of the ACP-CGC. He will be recused from voting on or authoring the ACP guidelines. All other authors have no conflict of interests to declare.

Data statement: Data sharing is not applicable as no datasets were generated and/or analyzed for this protocol paper.

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Appendix A. Key Questions and PICOTS

KEY QUESTIONS

1) What is the comparative effectiveness of high flow nasal oxygen versus noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen for hospitalized patients?

1a) Does comparative effectiveness of high flow nasal oxygen vary by patient characteristics, disease/diagnosis characteristics, protocol/device settings, or location of administration?

2) What are the harms of high flow nasal oxygen versus noninvasive positive pressure ventilation (CPAP, BiPAP®), invasive mechanical ventilation, or conventional oxygen for hospitalized patients?

2a) Do harms vary by patient characteristics, disease/diagnosis, protocol/device settings, or location of administration?

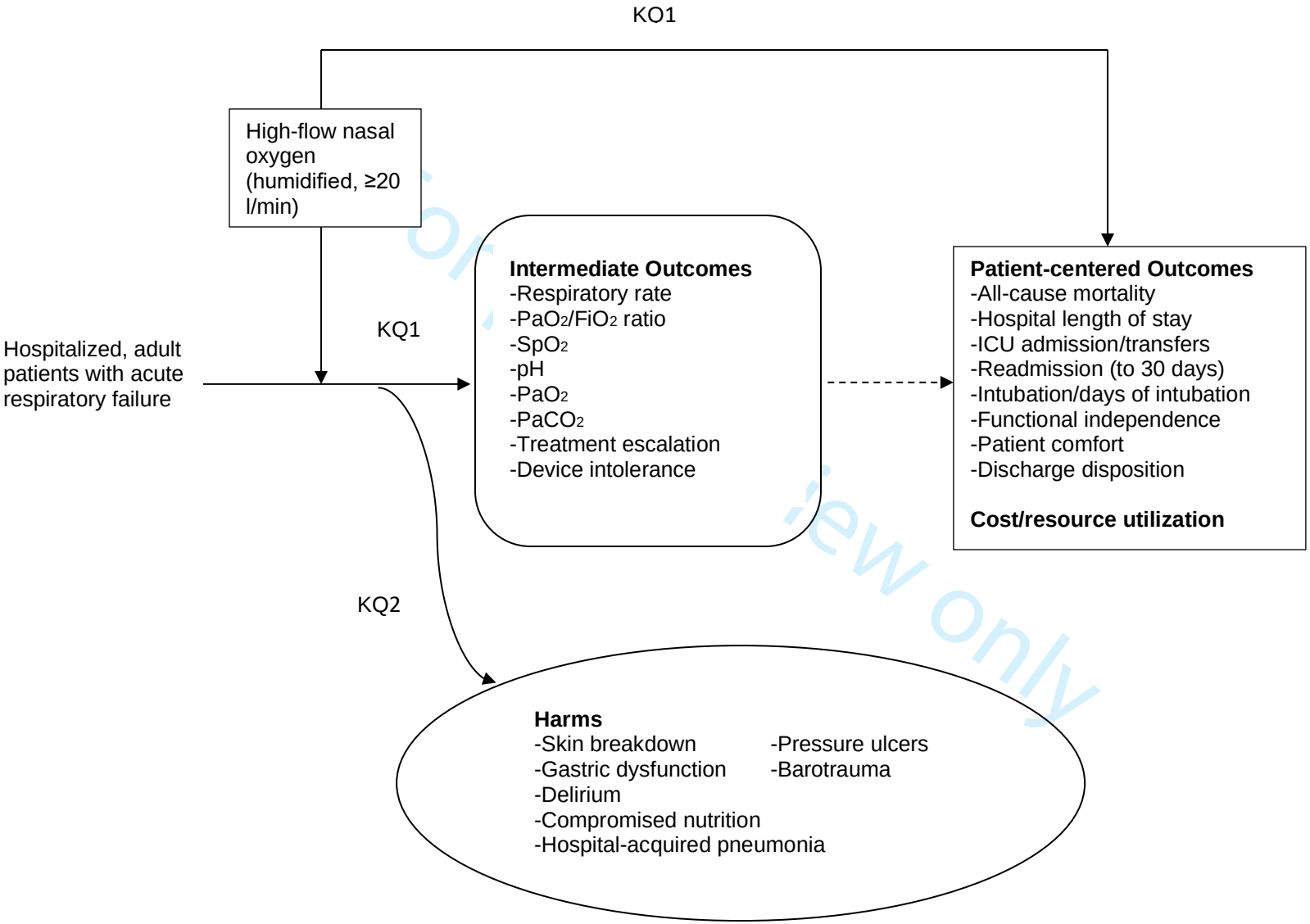
PICOTS	
Population:	Hospitalized adult patients with acute respiratory failure (ARF). ARF defined as SpO_2 <90%, PaO_2:FiO_2 ratio ≤300, PaO_2 ≤60 mmHg, or $PaCO_2$ ≥45 mmHg
Intervention:	High flow nasal oxygen (humidified, ≥20 l/min)
Comparators:	Noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen (e.g., simple, Venturi, or nonrebreather oxygen masks)
Outcomes:	**Patient-centered Outcomes:** all-cause mortality (in-hospital and 90 day), intubation/reintubation (days of intubation), hospital length of stay, ICU admissions/transfers (ICU days), patient comfort, hospital readmissions (30 day) (e.g., all-cause, pneumonia), functional independence at discharge (e.g., scale scores, measures of independence/activities of daily living), discharge disposition **Intermediate Outcomes:** respiratory rate, PaO_2/FiO_2 ratio, SpO_2, pH, PaO_2, $PaCO_2$, treatment escalation, device intolerance **Cost/resource utilization** **Harms:** skin breakdown or pressure ulcers, gastric dysfunction, hospital-acquired pneumonia, compromised nutrition (enteral or parenteral nutrition), delirium, barotrauma
Timing:	Hospitalization for ARF or development of ARF while hospitalized; immediate post-extubation; post-surgery. Exclude pre-intubation/pre-oxygenation and HFNO oxygenation support during intubation
Setting:	Hospital (including ICU, step down units, hospital wards), emergency department
Study Design:	Randomized controlled trials, including crossover RCTs and cluster RCTs
Subgroups:	Patient characteristics: age, race, gender Disease/diagnosis (e.g. COPD, cardiogenic pulmonary edema, immunosuppressed, post-extubation, post-surgery; hypoxic, hypercapnic, or mixed [hypoxic or hypercapnic] respiratory failure) Protocol/device settings (e.g., flow rate ≤30 vs. >30 L/min; treatment duration <6 vs. ≥6 hours)

BiPAP=Bilevel Positive Airway Pressure; CPAP=continuous positive airway pressure; ICU=intensive care unit; COPD= chronic obstructive pulmonary disease

LITERATURE SEARCH

RCTs: We will search MEDLINE, Embase, CINAHL, and Cochrane Library from 2000 to August 2019
Clinicaltrials.gov for recently completed and/or on-going trials
Reference lists from relevant systematic reviews for references missed by our database searches

Analytic Framework



Appendix B. MEDLINE® search strategy

1 (high flow nasal adj2 (cannula$ or oxygen$ or therap$ or insufflation$)).mp.
2 high flow therapy.mp.
3 nasal high flow.mp.
4 high flow oxygen.mp.
5 (humidified high flow or humidified oxygen).mp.
6 (HFNC or HHFNC or HFNT or NHF or HFNO or HFOT or HFNOT).ti,ab.
7 (Vapotherm or Optiflow or "Comfort Flo").ti,ab.
8 or/1-7
9 remove duplicates from 8
10 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab.
11 (random$ adj (enroll$ or assign$ or allocat$)).ti,ab.
12 ((randomi#ed or controlled or clinical) adj2 trial$).ti,ab.
13 or/10-12
14 9 and 13
15 (meta-analy$ or metaanaly$ or meta analy$).ti,ab.
16 exp Meta-Analysis/
17 (systematic adj2 (review$ or overview$)).ti,ab.
18 (rapid review or meta synthesis or metasynthesis or meta-synthesis or umbrella review or integrative review or data synthesis or review of reviews).ti,ab.
19 or/15-18
20 9 and 19
21 limit 14 to english language
22 limit 21 to yr="1995 -Current"
23 limit 22 to "all child (0 to 18 years)"
24 limit 23 to "all adult (19 plus years)"
25 22 not 23
26 24 or 25
27 limit 20 to english language
28 limit 27 to yr="2015 -Current"
29 limit 28 to "all child (0 to 18 years)"
30 limit 29 to "all adult (19 plus years)"
31 28 not 29
32 30 or 31

Appendix C. Data extraction forms

Table 1. Study Characteristics

Author, year **Country** **Funding** **Setting** **Special population** **Risk of Bias rating**	**Inclusion/Exclusion Criteria**	**Intervention (n)** **Comparator (n)** **Follow-up (primary outcome)**	**Demographics**
	Inclusion: Exclusion:	Intervention: Comparator: Follow-up:	N= Age (mean): Race/ethnicity (%): White: Black: Other: Gender (% male): Comorbidities (%): Chronic Respiratory Failure: COPD: Congestive Heart Failure: Comorbidity Index: Baseline characteristics: SpO_2: Respiratory Rate: PaO_2/FiO_2 ratio: pH: PaO_2: $PaCO_2$:

Table 2. Risk of Bias Assessment for Included Studies

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias

Table 3. Treatment Characteristics

Author Year Setting Follow-up Comparator	Adherence/Intolerance describe measure		Treatment Settings				Treatment Weaning Criteria		
			Protocol		Received				
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported

COT=conventional oxygen therapy; HFFM=high-flow face mask; HFNC=high-flow nasal cannula; NIV=non-invasive ventilation; NR=not reported; PEEP=positive end-expiratory pressure

Table 4: Patient-Centered Outcomes, Part 1

Author Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N)		ICU Admissions and/or Transfers (mean # of days)		Length of Hospital Stay (mean # of days)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HR=hazard ratio; ICU=intensive care unit; IQR=interquartile range; NIV=Non-invasive ventilation; N/A=not applicable; NR=not reported; RD=risk difference; SD=standard deviation

Table 5: Patient-Centered Outcomes, Part 2

Author Year Setting Follow-up Comparator	Treatment Escalation (describe) % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported

CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HR=hazard ratio; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; VAS=visual analog scale

Table 6: Patient-Centered Outcomes, Part 3

Author Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)—describe measure		Patient Comfort (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; NS=not statistically significant

Discharge Disposition: home, assisted living facility, nursing home, long-term care hospital

Table 7: Patient-Centered Outcomes, Part 4

Author Year Setting Follow-up Comparator	Compromised Nutrition				Gastric Dysfunction			
	% (n/N)		# days w/o nutrition		% (n/N) with placement of nasogastric tube		% (n/N) with nausea, vomiting, or abdominal distension	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; NR=not reported

Compromised Nutrition: (enteral/parenteral nutrition or days without nutrition)
Gastric Dysfunction: (placement of a nasogastric tube for decompression or treatment of abdominal distension/nausea/vomiting)

Table 8: Patient-Centered Outcomes, Part 5

Author Year Setting Follow-up Comparator	Hospital-acquired Pneumonia % (n/N)		Barotrauma % (n/N)		Skin Breakdown or Pressure Ulcers % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; N/A=not applicable; NR=not reported

Barotrauma: (pneumothorax, pneumomediastinum, pneumoperitoneum, or ventilator-induced lung injury

Table 9: Intermediate Outcomes, Part 1

Author Year Setting Follow-up Comparator	Respiratory Rate (mean, SD)		PaO_2/FiO_2 ratio (mean, SD)		SpO_2 (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; NS=not statistically significant; SD=standard deviation

Table 10: Intermediate Outcomes, Part 2

Author Year Setting Follow-up Comparator	pH (mean, SD)		PaO_2 (mean, SD)		$PaCO_2$ (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; NR=not reported; SD=standard deviation

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	4-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	74	74
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	7-31
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	301-306
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	308-311
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	308-311
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	308-311
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	98-121

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	122-129
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	137-188
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	190-196
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	190-196
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	206-218
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	198-204
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	206-218
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	210-217 158-174
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	158-174
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	262-276
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	220-238

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	220-238
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	231-260
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	238-239
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	272-276
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	278-281