Noninvasive ventilation strategies for patients with severe or critical COVID-19

A rapid evidence review of clinical outcomes: Executive summary and Summary of Findings

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Declarations of Interests

None declared.

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Protocol/Topic Registration:

This rapid evidence review was registered with the National Collaborating Centre for Methods and Tools (NCCMT) in May 2021 (https://www.nccmt.ca/covid-19/covid-19-evidence-reviews/428).

Abbreviations

AHRF	acute hypoxemic respiratory failure
ARDS	acute respiratory distress syndrome
BiPAP	bilevel positive airway pressure
CPAP	continuous positive airway pressure
HFNC	high flow nasal cannula
HFNO	high flow nasal oxygen
IMV	invasive mechanical ventilation
MA	meta-analysis
NIV	noninvasive mechanical ventilation
NMA	network meta-analysis
NPPV	negative positive pressure ventilation
ROB	risk of bias
RCT	randomized controlled trial
RR	rapid review[1]
SOT	standard oxygen therapy
SR	systematic review
WHO	World Health Organization

[1] RR abbreviation in Summary of Findings tables represents a relative risk/risk ratio

KEY FINDINGS

We located four RCTs reporting outcomes of interest in hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure not needing emergent intubation (direct PICO).

In hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure not needing emergent intubation, high flow nasal oxygen and continuous positive airway pressure ventilation may decrease mortality, invasive mechanical ventilation, and hospital or intensive care unit length of stay compared to standard oxygen therapy but findings are based on low quality of evidence.

Helmet noninvasive ventilation probably decreases invasive mechanical ventilation (moderate quality of evidence) but may increase patient discomfort compared to high flow nasal oxygen (low quality of evidence). Helmet noninvasive ventilation may decrease mortality and hospital or intensive care unit length of stay compared to high flow nasal oxygen but findings are based on low quality of evidence. We are uncertain whether continuous positive airway pressure ventilation increases or decreases mortality, invasive mechanical ventilation, and hospital or intensive care unit stay compared to high flow nasal oxygen.

We located 22 RCTs reporting outcomes of interest in hospitalized patients with acute respiratory distress syndrome (ARDS) and acute hypoxemic respiratory failure (AHRF) not needing emergent intubation (indirect PICO).

Additional data were available to compare helmet and facemask noninvasive ventilation and helmet and facemask continuous positive airway pressure for some outcomes, but evidence was not available for all comparisons of interest.

Compared to standard oxygen therapy:

- High flow nasal oxygen probably decreases mortality at 28 days, invasive mechanical ventilation and hospital length of stay (moderate quality of evidence).
- Facemask noninvasive ventilation probably decreases mortality at 30 days, invasive mechanical ventilation, and hospital or intensive care unit length of stay (moderate quality of evidence).
- Helmet continuous positive airway pressure may decrease in-hospital mortality and IMV but increase hospital length of stay (low quality of evidence).
- Facemask continuous positive airway pressure may decrease IMV and hospital length of stay (low quality of evidence) but we are uncertain whether in-hospital mortality is increased or decreased.

Compared to high flow nasal oxygen:

- Facemask noninvasive ventilation may increase mortality at 90 days, invasive mechanical ventilation and intensive care unit length of stay (low quality of evidence).

Helmet noninvasive ventilation may reduce mortality at 90 days and at one year, and hospital length of stay compared to facemask noninvasive ventilation (low quality of evidence).

Rapid evidence review approach for the direct PICO

Research question

In patients with severe or critical COVID-19, to what extent does high flow nasal oxygen (HFNO), continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) impact the need for invasive mechanical ventilation (IMV), hospital length of stay, and death compared to standard oxygen therapy (SOT) or against each other?

Methods overview

We conducted a rapid review of the evidence for noninvasive ventilation strategies and implemented the population, intervention, comparator, outcomes (PICO) framework to formulate the research question (Table E1):

Table E1: PICO framework

Population	Hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure not needing emergent intubation[a]
Intervention	• High flow nasal oxygen • Continuous positive airway pressure (facemask or helmet) • Noninvasive ventilation via facemask (or other non-helmet interfaces including nasal, oronasal, and full facial mask) • Noninvasive ventilation via helmet
Comparators	• Standard oxygen therapy • Any intervention
Outcomes	**Primary:** Mortality (within 30, 60, 90 days, and longer if data available), need for invasive mechanical ventilation, hospital length of stay **Secondary:** Intensive care unit length of stay **Patient-identified outcomes of interest:** Patient comfort, satisfaction with care
Eligible study designs	Systematic/rapid reviews[b] to identify eligible trials, randomized controlled trials[c]

a-patients weaned off IMV or who require respiratory support following IMV are not in scope.
b-eligible SR/RRs had to directly address ventilation support for two or more interventions/comparators in the PICO.
c-eligible RCTs had to directly compare two or more interventions/comparators in the PICO and at least one outcome.

Table E2 provides a summary of the methods used for this rapid evidence assessment. Additional details are provided in the full rapid evidence report.

Table E2: Summary of Methods

Search (systematic review/rapid reviews) *May 2-3, 2021*	Systematic/rapid reviews used to identify eligible trials Targeted search of COVID-19 meta-databases • WHO COVID-19 database • Living Overviews of Evidence (L.OVE) platform • COVID-END inventory of best evidence syntheses for clinical management
Search (randomized controlled trials) *May 15, 2021*	Top-up of recent RCTs published since date of last systematic review/rapid review search • WHO COVID-19 register • Cochrane COVID-19 register • Clinicaltrials.gov • International Clinical Trials Registry Platform[a] (Citation tracking and included references checked July 29, 2021)
Screening and selection	Single reviewer screened records using Covidence When they met the population, intervention, comparator, outcome: • Completed randomized controlled trials from systematic/rapid reviews were included in this review • Completed randomized controlled trials identified during the top-up search were included in this review
Data tabulation	Single reviewer with checking by a second reviewer Study characteristics and reported outcome data carried forward from the systematic/rapid reviews where possible • Top-up randomized controlled trials extracted *de novo*
Quality/ROB	Single reviewer with checking by a second Systematic/rapid reviews rapidly assessed using 'Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 2' tool Randomized controlled trial risk of bias assessments were retrieved and carried forward for eligible randomized controlled trials from the systematic/rapid reviews New randomized controlled trials with no previous risk of bias assessment were rapidly appraised by single reviewer with checking by a second and assisted by RobotReviewer[b]
Synthesis	Meta-analysis (pairwise for each primary and secondary outcome) Descriptive synthesis of patient-identified outcomes
Summary of findings	Single reviewer with checking by a second reviewer Summary of Findings tables created with focus on indirectness, imprecision, and risk of bias
Involvement of citizen partners	Reviewed and provided input on the population, intervention, comparator, and outcome. Added patient-reported outcomes. Review and co-author related report sections. Co-produce a patient-specific knowledge translation product

a: Planned but not executed due to availability of the database.
b: https://www.robotreviewer.net/ (last accessed August 4, 2021). Use of this software was planned but not executed due to availability of the application.

Rapid evidence review findings for the direct PICO

We located **four randomized controlled trials (RCTs)[1-4]** of noninvasive ventilation strategies in hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure not requiring emergent intubation.

This evidence was collected using the included study lists of **three relevant systematic reviews[29-33], four rapid reviews[34-37] and a top-up search** of bibliographic databases for more recent RCTs.

Complete results are presented in the rapid evidence report and the available evidence for noninvasive ventilation strategies is summarized using Summary of Findings tables for the direct PICO.

PICO = population, intervention, comparator, outcome

Identified systematic reviews

Three systematic reviews (SRs) reported in five records were identified[29-33].

Identified rapid reviews

Four additional rapid reviews (RRs) using a range of accepted 'rapid review' methods were identified for inclusion[34-37]. No randomized controlled trials (RCTs) directly evaluating the use of noninvasive ventilation strategies in COVID-19 patients were identified from the RRs.

Results from the top-up search

A top-up search identified one RCT of helmet NIV compared to HFNO in patients with COVID-19[4]. Of the 847 potentially relevant study registration records retrieved, none reported RCTs relevant to the PICO that were reported to be complete with results available.

Evidence from identified randomized controlled trials

Table E3 includes an overview of key study and patient characteristics for the four included RCTs[1-4].

Table E3: Summary of included RCTs

Study/Design	Population	Country/Setting	Interventions	Outcomes reported
Li et al. 2020[3] two-arm, parallel RCT N=72	Patients with severe coronavirus pneumonia complicated with acute respiratory failure	China, isolation ward of a single centre	HFNO [n=37] Standard oxygen therapy [n=35]	Mechanical ventilation at 12 h No patient-reported outcomes
Grieco et al. 2021[4] HENIVOT	Patients admitted to the intensive care unit with COVID-19–induced	Italy, ICUs in four centres	Helmet NIV [n=55] HFNO [n=54]	Intubation, 28 d Hospital LOS

Study/Design	Population	Country/Setting	Interventions	Outcomes reported
two-arm, parallel RCT N=109	moderate to severe hypoxemic respiratory failure			ICU LOS Patient-reported: Device-related discomfort
Perkins et al. 2021[2] RECOVERY-RS three-arm, adaptive RCT N=1272	Hospitalized adults with acute respiratory failure due to COVID-19 were deemed suitable for tracheal intubation if treatment escalation was required	United Kingdom, 75 hospitals	CPAP [n=380] HFNO [n=417] Standard oxygen therapy [n=475] (primary comparisons were CPAP to standard oxygen and HFNO to standard oxygen)	Mortality, 30 d Intubation, 30 d Tracheal intubation during the study period Critical care (ICU) LOS Hospital LOS No patient-reported outcomes
Teng et al. 2021[1] two-arm, parallel RCT N= 22	Patients diagnosed with severe COVID-19.	China, single centre	HFNO [n=12] Standard oxygen therapy [n=10]	Mortality (indirect) Hospital LOS ICU LOS No patient-reported outcomes

d=days; h=hours; HFNO=high flow nasal oxygen; ICU=intensive care unit; LOS=length of stay; RCT=randomized controlled trial; QoL=quality of life.

Summary of findings tables for the direct PICO

HFNO vs SOT[1-3]

Population: Hospitalized patients with severe or critical COVID 19 and AHRF not needing emergent intubation
Intervention: HFNO
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates SOT	Absolute effect estimates HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality, 30 d	Relative risk: **0.95 (CI 95% 0.75 - 1.19)** Based on data from 807 patients in 2 studies	**195** per 1000	**185** per 1000 Difference: **10 fewer per 1000** (CI 95% 49 fewer - 37 more)	**Low** Due to serious imprecision, inconsistency[1]	HFNO may decrease mortality at 30 days
IMV	Relative risk: **0.96 (CI 95% 0.81 - 1.13)** Based on data from 854 patients in 2 studies	**395** per 1000	**379** per 1000 Difference: **16 fewer per 1000** (CI 95% 75 fewer - 51 more)	**Low** Due to serious inconsistency, imprecision[2]	HFNO may decrease IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 804 patients in 2 studies	**16.85** days Mean	**16.34** days Mean Difference: **0.51 fewer** (CI 95% 3.65 fewer - 2.55 more)	**Low** Due to serious imprecision and inconsistency[3]	HFNO may decrease hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 804 patients in 2 studies	**7.2** days Mean	**6.99** days Mean Difference: **0.21 fewer** (CI 95% 2.0 fewer - 1.58 more)	**Low** Due to serious imprecision and inconsistency[4]	HFNO may decrease ICU LOS

1. **Inconsistency: serious.** Point estimates vary widely (One RCT not estimable due to zero events in both study arms); **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals;
2. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 67%.; **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals;
3. **Risk of Bias: no serious.** One RCT high risk of selection bias. Second RCT has unclear risk of bias for LOS due to no reported outcome denominators in largest study. Estimates were calculated using denominators from other study reported outcomes (incomplete data), Incomplete data and/or large loss to follow up; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 65%; **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals, Wide confidence intervals;
4. **Risk of Bias: no serious.** One RCT high risk of selection bias. Second RCT has unclear risk of bias for LOS due to no reported outcome denominators in largest study. Estimates were calculated using denominators from other study reported outcomes (incomplete data); **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 65%; **Imprecision: serious.** SD larger than mean.

CPAP vs SOT[2]

Population: Hospitalized patients with severe or critical COVID 19 and AHRF not needing emergent intubation
Intervention: CPAP
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOT	CPAP		
Mortality, 30 d	Relative risk: **0.87 (CI 95% 0.64 - 1.18)** Based on data from 737 patients in 1 studies	**192** per 1000	**167** per 1000 Difference: **25 fewer per 1000** (CI 95% 69 fewer - 35 more)	**Moderate** Due to serious imprecision[1]	CPAP probably decreases mortality at 30 days
IMV	Relative risk: **0.81 (CI 95% 0.67 - 0.98)** Based on data from 733 patients in 1 studies	**413** per 1000	**335** per 1000 Difference: **78 fewer per 1000** (CI 95% 136 fewer - 8 fewer)	**Moderate** Due to serious imprecision[2]	CPAP probably decreases IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 737 patients in 1 studies	**17.3** days Mean	**16.34** days Mean Difference: **0.96 fewer** (CI 95% 3.59 fewer - 1.67 more)	**Moderate** Due to serious imprecision[3]	CPAP probably decreases hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 737 patients in 1 studies	**9.6** days Mean	**9.52** days Mean Difference: **0.08 fewer** (CI 95% 2.23 fewer - 2.07 more)	**Moderate** Due to serious imprecision[4]	CPAP probably has little or no difference on ICU LOS

1. **Inconsistency: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals, Only data from one study;
2. **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Only data from one study;
3. **Risk of Bias: no serious.** Unclear risk of bias for LOS due to no reported outcome denominators in largest study. Estimates were calculated using denominators from other study reported outcomes (incomplete data); **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals, Only data from one study;
4. **Risk of Bias: no serious.** Unclear risk of bias for LOS due to no reported outcome denominators in largest study. Estimates were calculated using denominators from other study reported outcomes (incomplete data); **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals, only data from one study.

HELMET NIV vs HFNO[4]

Population: Hospitalized patients with severe or critical COVID 19 and AHRF not needing emergent intubation
Intervention: Helmet NIV
Comparator: HFNO

Outcome	Study results and measurements	Absolute effect estimates HFNO	Absolute effect estimates Helmet NIV	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality, 28 d	Relative risk: **0.8 (CI 95% 0.34 - 1.87)** Based on data from 110 patients in 1 study	**182** per 1000	**146** per 1000 Difference: **36 fewer per 1000** (CI 95% 120 fewer - 158 more)	**Low** Due to very serious imprecision[1]	Helmet NIV may decrease mortality at 28 days
Mortality, 60 d	Relative risk: **1.1 (CI 95% 0.55 - 2.2)** Based on data from 110 patients in 1 study	**236** per 1000	**260** per 1000 Difference: **24 more per 1000** (CI 95% 106 fewer - 283 more)	**Low** Due to very serious imprecision[2]	Helmet NIV may decrease mortality at 60 days
IMV	Relative risk: **0.54 (CI 95% 0.32 - 0.89)** Based on data from 110 patients in 1 study	**509** per 1000	**275** per 1000 Difference: **234 fewer per 1000** (CI 95% 346 fewer - 56 fewer)	**Moderate** Due to serious imprecision[3]	Helmet NIV probably decreases IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 110 patients in 1 study	**22** days Median	**16** days Median Difference: **6 fewer** (CI 95% 14 fewer - 1 more)	**Low** Due to serious risk of bias, imprecision[4]	Helmet NIV may decrease hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 110 patients in 1 study	**10** days Median	**4** days Median Difference: **6 fewer** (CI 95% 13 fewer - 1 more)	**Low** Due to serious risk of bias, imprecision[5]	Helmet NIV may decrease ICU LOS
Device-related discomfort	Measured by: Scale: - Lower better Based on data from 110 patients in 1 study	**1.8** VAS points Mean	**3.7** VAS points Mean Difference: **1.9 higher** (CI 95% 1.4 higher - 2.5 higher)	**Low** Due to serious risk of bias, imprecision[6]	Helmet NIV may increase device-related discomfort
Mortality, 90 d	No studies were found that looked at mortality at 90 days[7]				

1. **Risk of Bias: no serious.** Selective outcome reporting; **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
2. **Risk of Bias: no serious.** Selective outcome reporting; **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
3. **Imprecision: serious.** Only data from one study, Low number of patients;
4. **Risk of Bias: serious.** Incomplete data (medians/IQR by group reported with absolute difference in means compared); **Imprecision: serious.** Low number of patients, Only data from one study;
5. **Risk of Bias: serious.** Incomplete data (medians/IQR by group reported with absolute difference in means compared); **Imprecision: serious.** Low number of patients, Only data from one study;

6. **Risk of Bias: serious.** post hoc outcome assessment, multiple time points collected, but not reported; **Imprecision: serious.** Low number of patients, Only data from one study;
7. **Risk of Bias: very serious.** Selective outcome reporting (outcome planned but not reported).

CPAP vs HFNO

One three-arm pragmatic RCT reported outcomes for CPAP and HFNO[2] but did not compare these interventions directly in the planned analyses. All patients did not have the opportunity to be randomized to all arms due to the availability of these interventions by centre (thereby making direct comparison unfeasible). To inform the clinical guideline panel discussions, we have provided an exploratory estimate for CPAP compared to HFNO using an indirect treatment comparison.

Population: Hospitalized patients with severe or critical COVID 19 and AHRF not needing emergent intubation
Intervention: CPAP
Comparator: HFNO

Outcome	Study results and measurements	Absolute effect estimates HFNO	 CPAP	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality, 30 d	Relative risk**: 0.95 (CI 95% 0.52 - 1.71)** Based on data from 793 patients in 1 study	**188** per 1000	**179** per 1000 Difference: **9 fewer per 1000** (CI 95% 90 fewer - 133 more)	**Very low** Due to serious risk of bias, indirectness, and imprecision[1]	We are uncertain whether CPAP increases or decreases mortality at 30 days
IMV	Relative risk**: 0.69 (CI 95% 0.43 - 1.09)** Based on data from 791 patients in 1 study	**411** per 1000	**284** per 1000 Difference: **127 fewer per 1000** (CI 95% 234 fewer - 37 more)	**Very low** Due to serious risk of bias, indirectness, and imprecision[2]	We are uncertain whether CPAP increases or decreases IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 791 patients in 1 study	**18.3** days Mean	**16.63** days Mean Difference: **1.67 fewer** (CI 95% 5.43 fewer - 2.09 more)	**Very low** Due to serious risk of bias, indirectness, and imprecision[3]	We are uncertain whether CPAP increases or decreases hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 791 patients in 1 study	**10.5** days Mean	**9.48** days Mean Difference: **1.02 fewer** (CI 95% 3.97 fewer - 1.93 more)	**Very low** Due to serious risk of bias, indirectness, and serious imprecision[4]	We are uncertain whether CPAP increases or decreases ICU LOS

1. **Risk of Bias: serious.** Incomplete data and post hoc comparison: CPAP and HFNO were not available to all study participants and this comparison was not made in the RCT.; **Indirectness: serious.** Direct comparisons not available; **Imprecision: serious.** Only data from one study;
2. **Risk of Bias: serious. Indirectness: serious.** Direct comparisons not available; **Imprecision: serious.** Only data from one study;
3. **Risk of Bias: serious. Indirectness: serious.** Direct comparisons not available; **Imprecision: serious.** Low number of patients, Only data from one study, Wide confidence intervals;
4. **Risk of Bias: serious. Indirectness: serious.** Direct comparisons not available; **Imprecision: serious.** Only data from one study.

Rapid evidence review approach for the indirect PICO

Research Question

In patients with acute respiratory distress syndrome (ARDS) and acute hypoxemic respiratory failure (AHRF), to what extent does high flow nasal oxygen (HFNO), continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) impact the need for invasive mechanical ventilation (IMV), hospital length of stay and death compared to standard oxygen therapy (SOT) or against each other?

Methods overview

Due to the uncertainty in the randomized controlled trial (RCT) evidence in severe or critical COVID-19 populations, we completed an additional rapid evidence review for noninvasive ventilation strategies in non-COVID patients with ARDS and AHRF. We implemented the population, intervention, comparator, outcomes (PICO) framework to formulate the research question (Table E4):

Table E4: PICO framework

Population	Patients hospitalized with acute respiratory distress syndrome and acute hypoxemic respiratory failure that do not require emergent intubation[a]
Intervention	• High flow nasal oxygen • Continuous positive airway pressure • Noninvasive ventilation via facemask (or other non-helmet interfaces including nasal, oronasal, and full facial mask) • Noninvasive ventilation via helmet
Comparators	Standard of care (conventional oxygen therapy) or any other intervention
Outcomes	**Primary:** Mortality (within 30, 60, 90 days, and longer if data available), need for invasive mechanical ventilation, hospital length of stay **Secondary:** ICU length of stay **Patient-identified outcomes of interest:** Patient comfort, satisfaction with care
Eligible study designs	Systematic/rapid reviews [b] to identify eligible trials, randomized controlled trials[c]

a-patients weaned off IMV or who require respiratory support following IMV are not in scope.
b-eligible SR/RRs had to directly address ventilation support for two or more interventions/comparators in the PICO.
c-eligible RCTs had to directly compare two or more interventions/comparators in the PICO and at least one outcome.

We followed a similar rapid evidence review approach as for hospitalized patients with severe or critical COVID-19 and AHRF, with differences summarized below in Table E5.

Table E5: Methods overview: Differences from direct PICO

Search (Systematic reviews/rapid reviews) ***May 18, 2021***	Systematic reviews/rapid reviews used to identify relevant randomized controlled trials A targeted search of meta-databases • Epistemonikos database[2] of systematic reviews for health decision-making (includes Cochrane reviews) • Living Overviews of Evidence (L.OVE) Platform
Search (randomized controlled trials) *May 19, 2021*	Top-up of recent randomized controlled trials published since date of last systematic/rapid review search • Clinicaltrials.gov • International Clinical Trials Registry Platform[a] • Cochrane CENTRAL (Citation tracking and included randomized controlled trial reference lists checked July 29, 2021) *Date of latest systematic review/rapid review search in included randomized controlled trials for top-up: December 1, 2020*

a: Planned but not executed due to availability of the database. COCHRANE CENTRAL searched instead as a post hoc study registry substitution.

[2] https://www.epistemonikos.org/en/about_us/methods

Rapid evidence review findings for the indirect PICO

We located **22 completed randomized controlled trials (RCTs)[5-26] in 24 reports[5-28]** of non-invasive ventilation support in hospitalized patients with acute respiratory distress syndrome (ARDS) and acute hypoxemic respiratory failure (AHRF) not requiring emergent intubation.

This evidence was collected using the included study lists of **four systematic reviews (SRs)[32,38-40]. A top-up search** of study registry databases found no eligible RCTs.

Complete results for clinical outcomes are presented in the rapid evidence report and the available evidence for noninvasive ventilation strategies for the indirect PICO is summarized using Summary of Findings tables.

None of the included SRs included RCTs relevant to the indirect PICO with patient-reported outcomes such as comfort or satisfaction with care.

PICO = population, intervention, comparator, outcome

Identified systematic reviews

We identified four relevant systematic reviews (SRs) (included in 7 published reports)[32,38-43].

Evidence from randomized controlled trial eligibility

After screening all individual RCTs included in the four relevant SRs (n=74), a total of 22 RCTs (in 24 reports)[5-28] matching our indirect PICO were included in the rapid evidence review for the indirect PICO.

A top-up search for literature published between Dec 1, 2020 and June 1, 2021, identified a total of 1926 records. No additional RCTs were identified.

Summary of findings tables for the indirect PICO

HNFO vs SOT[5,8,14,18,19,27]

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: HFNO
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates SOT	Absolute effect estimates HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality, 28 d	Relative risk: **0.99 (CI 95% 0.82 - 1.19)** Based on data from 776 patients in 1 study	**361** per 1000	**357** per 1000 Difference: **4 fewer per 1000** (CI 95% 65 fewer - 69 more)	**Moderate** Due to serious imprecision[1]	HFNO probably decreases mortality at 28 days
Mortality, 90 d	Relative risk: **0.92 (CI 95% 0.63 - 1.32)** Based on data from 522 patients in 2 studies	**189** per 1000	**174** per 1000 Difference: **15 fewer per 1000** (CI 95% 70 fewer - 60 more)	**Low** Due to serious inconsistency, imprecision[2]	HFNO may decrease mortality at 90 days
IMV	Relative risk: **0.74 (CI 95% 0.56 - 0.99)** Based on data from 668 patients in 4 studies	**207** per 1000	**153** per 1000 Difference: **54 fewer per 1000** (CI 95% 91 fewer - 2 fewer)	**Moderate** Due to serious indirectness[3]	HFNO probably decreases IMV
Mortality, any[4]	Relative risk: **0.98 (CI 95% 0.83 - 1.15)** Based on data from 1344 patients in 4 studies	**291** per 1000	**285** per 1000 Difference: **6 fewer per 1000** (CI 95% 49 fewer - 44 more)	**Low** Due to serious indirectness, imprecision[5]	HFNO may decrease mortality
Hospital LOS	Measured by: Scale: - Lower better Based on data from 998 patients in 2 studies	**16.26** days Median	**15.09** days Median Difference: **1.17 fewer** (CI 95% 3.16 fewer - 0.83 more)	**Moderate** Due to serious imprecision[6]	HFNO probably decreases hospital LOS
ICU LOS	Based on data from 996 patients in 2 studies	Studies were not pooled		**Low** Due to very serious inconsistency[7]	HFNO may have little or no difference on ICU LOS

1. **Imprecision: serious.** Wide confidence intervals, Only data from one study;
2. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 80%.; **Imprecision: serious.** Wide confidence intervals;
3. **Indirectness: serious.** Differences between the population of interest and those studied;
4. Longest duration mortality data available, includes mix of hospital and end of study (EOS) outcomes
5. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was moderate, with I^2: 44%.; **Indirectness: serious.** Differences between the population of interest and those studied (some mixed, some immunocompromised), Differences between the outcomes of interest (timing); **Imprecision: serious.** Wide confidence intervals;
6. **Imprecision: serious.** Wide confidence intervals;
7. **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high, with I^2: 85%, the direction of the effect is not consistent between the included studies.

FACEMASK NIV vs SOT [6,10,13-17,20,24-27]

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Facemask NIV
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates SOT	Absolute effect estimates Facemask NIV	Certainty of the Evidence (Quality of evidence)	Plain language summary
IMV	Relative risk: **0.74 (CI 95% 0.64 - 0.86)** Based on data from 1166 patients in 10 studies	**416** per 1000	**308** per 1000 Difference: **108 fewer per 1000** (CI 95% 150 fewer - 58 fewer)	**Moderate** Due to serious inconsistency[1]	Facemask NIV probably decreases IMV
Mortality, 30 d	Relative risk: **0.88 (CI 95% 0.62 - 1.25)** Based on data from 374 patients in 1 study	**273** per 1000	**240** per 1000 Difference: **33 fewer per 1000** (CI 95% 104 fewer - 68 more)	**Moderate** Due to serious imprecision[2]	Facemask NIV probably decreases mortality at 30 days
Mortality, 60 d	Relative risk: **0.7 (CI 95% 0.31 - 1.58)** Based on data from 56 patients in 1 study	**357** per 1000	**250** per 1000 Difference: **107 fewer per 1000** (CI 95% 246 fewer - 207 more)	**Low** Due to very serious imprecision[3]	Facemask NIV may decrease mortality at 60 days
Mortality, 90 d	Relative risk: **0.87 (CI 95% 0.58 - 1.3)** Based on data from 395 patients in 3 studies	**375** per 1000	**326** per 1000 Difference: **49 fewer per 1000** (CI 95% 158 fewer - 113 more)	**Very low** Due to serious inconsistency, indirectness, imprecision[4]	We are uncertain whether facemask NIV increases or decreases mortality at 90 days
Mortality, any	Relative risk: **0.83 (CI 95% 0.71 - 0.96)** Based on data from 1254 patients in 11 studies	**347** per 1000	**288** per 1000 Difference: **59 fewer per 1000** (CI 95% 101 fewer - 14 fewer)	**Moderate** Due to serious indirectness[5]	Facemask NIV probably decreases mortality
Hospital LOS	Measured by: Scale: - Lower better Based on data from 829 patients in 6 studies	**20.51** days Median	**18.49** days Median Difference: **2.02 fewer** (CI 95% 4.39 fewer - 0.35 more)	**Moderate** Due to serious inconsistency[6]	Facemask NIV probably decreases hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 1152 patients in 10 studies	**9.43** days Median	**7.82** days Median Difference: **1.61 fewer** (CI 95% 3.21 fewer - 0.03 fewer)	**Moderate** Due to serious inconsistency[7]	Facemask NIV probably decreases ICU LOS

1. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 57%. Variation in timepoint IMV outcome was assessed at;
2. **Indirectness: no serious.** Differences between the population of interest and those studied (100% immunocompromised population); **Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study;
3. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
4. **Inconsistency: serious.** The magnitude of statistical heterogeneity was moderate, with I^2: 58%.; **Indirectness: serious.** Direct comparisons not made in one RCT and so crude data used to estimate the comparison; **Imprecision: serious.** Wide confidence intervals;

5. **Indirectness: serious.** Combined in-hospital and longer duration mortality at varying time points;
6. **Inconsistency: serious.** The magnitude of statistical heterogeneity was moderate, with I^2:55%;
7. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 75%.

HELMET CPAP vs SOT[9,11,23]

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Helmet CPAP
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOT	Helmet CPAP		
IMV	Relative risk: **0.45 (CI 95% 0.15 - 1.34)** Based on data from 168 patients in 3 studies	**102** per 1000	**46** per 1000 Difference: **56 fewer per 1000** (CI 95% 87 fewer - 35 more)	**Low** Due to serious inconsistency, imprecision[1]	Helmet CPAP may decrease IMV
In-hospital mortality	Relative risk: **0.23 (CI 95% 0.1 - 0.55)** Based on data from 168 patients in 3 studies	**250** per 1000	**58** per 1000 Difference: **192 fewer per 1000** (CI 95% 225 fewer - 112 fewer)	**Low** Due to serious indirectness, imprecision[2]	Helmet CPAP may decrease in-hospital mortality
Hospital LOS	Measured by: Scale: - Lower better Based on data from 81 patients in 1 study	**14** days Median	**14.5** days Median Difference: **0.5 more** (CI 95% 3.75 fewer - 4.75 more)	**Low** Due to very serious imprecision[3]	Helmet CPAP may increase hospital LOS
ICU LOS	No studies were found that looked at ICU LOS				

1. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 55%; **Imprecision: serious.** Low number of patients, Wide confidence intervals;
2. **Risk of Bias: no serious.** One trial stopped earlier than scheduled, potential for overestimating benefits; **Indirectness: serious.** One trial of patients with hematologic malignancies, Differences between the outcomes of interest (30d or longer) and those reported (in-hospital); **Imprecision: serious.** Low number of patients;
3. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

FACEMASK CPAP vs SOT[12]

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Facemask CPAP
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOT	Facemask CPAP		
In-hospital mortality	Relative risk**: 0.71 (CI 95% 0.38 - 1.32)** Based on data from 123 patients in 1 study	**295** per 1000	**209** per 1000 Difference: **86 fewer per 1000** (CI 95% 183 fewer - 94 more)	**Very low** Due to serious indirectness and very serious imprecision[1]	We are uncertain whether facemask CPAP increases or decreases in-hospital mortality
IMV	Relative risk**: 0.86 (CI 95% 0.54 - 1.37)** Based on data from 123 patients in 1 study	**393** per 1000	**338** per 1000 Difference: **55 fewer per 1000** (CI 95% 181 fewer - 145 more)	**Low** Due to very serious imprecision[2]	Facemask CPAP may decrease IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 81 patients in 1 study	**16** days Median	**14** days Median Difference: **2 fewer** (CI 95% 17.5 fewer - 13.5 more)	**Low** Due to very serious imprecision[3]	Facemask CPAP may decrease hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 81 patients in 1 study	**9** days Median	**9** days Median Difference: **0 fewer** (CI 95% 8.89 fewer - 8.89 more)	**Low** Due to very serious imprecision[4]	Facemask CPAP may have little or no difference on ICU LOS

1. **Indirectness: serious.** Differences between the outcomes of interest (30d or longer) and those reported (in-hospital); **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
2. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
3. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
4. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

FACEMASK NIV vs HFNO[7,14,22]

Population: hospitalized patients with ARDS and AHRF who do not need emergent intubation
Intervention: Facemask NIV
Comparator: HFNO

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		HFNO	**Facemask NIV**		
Mortality, 90 d	Relative risk: **2.3 (CI 95% 1.27 - 4.15)** Based on data from 216 patients in 1 study	**123** per 1000	**283** per 1000 Difference: **160 more per 1000** (CI 95% 33 more - 387 more)	**Low** Due to very serious imprecision[1]	Facemask NIV may increase mortality at 90 days
IMV	Relative risk: **1.22 (CI 95% 0.94 - 1.59)** Based on data from 316 patients in 3 studies	**364** per 1000	**444** per 1000 Difference: **80 more per 1000** (CI 95% 22 fewer - 215 more)	**Low** Due to serious risk of bias, imprecision[2]	Facemask NIV may increase IMV
In-hospital mortality	Relative risk: **1.15 (CI 95% 0.55 - 2.43)** Based on data from 70 patients in 1 study	**265** per 1000	**305** per 1000 Difference: **40 more per 1000** (CI 95% 119 fewer - 379 more)	**Very low** Due to serious indirectness, very serious imprecision[3]	We are uncertain whether facemask NIV increases or decreases in-hospital mortality
Hospital LOS	No studies were found that looked at hospital LOS				
ICU LOS	Measured by: Scale: - Lower better Based on data from 216 patients in 1 study	**12.8** days Median	**13.35** days Median Difference: **0.55 more** (CI 95% 3.16 fewer - 4.26 more)	**Low** Due to very serious imprecision[4]	Facemask NIV may increase ICU LOS

1. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
2. **Risk of Bias: serious.** two of three trials have unclear sequence generation and concealment of allocation during randomization process (one abstract only at high risk of bias with incomplete data); **Imprecision: serious.** Low number of patients, Wide confidence intervals;
3. **Indirectness: serious.** Differences between the outcomes of interest (30d or longer) and outcome reported (in-hospital); **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
4. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

HELMET NIV versus FACEMASK NIV[21,28]

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Helmet NIV
Comparator: Facemask NIV

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		Facemask NIV	Helmet NIV		
Mortality, 90 d	Relative risk: **0.6 (CI 95% 0.37 - 0.99)** Based on data from 83 patients in 1 studies	**564** per 1000	**338** per 1000 Difference: **226 fewer per 1000** (CI 95% 355 fewer - 6 fewer)	**Low** Due to very serious imprecision[1]	Helmet NIV may decrease mortality at 90 days
Mortality, 1 yr	Relative risk: **0.62 (CI 95% 0.42 - 0.93)** Based on data from 83 patients in 1 studies	**692** per 1000	**429** per 1000 Difference: **263 fewer per 1000** (CI 95% 401 fewer - 48 fewer)	**Low** Due to very serious imprecision[2]	Helmet NIV may decrease mortality at 1 year
IMV	Relative risk**: 0.3 (CI 95% 0.15 - 0.58)** Based on data from 83 patients in 1 studies	**615** per 1000	**185** per 1000 Difference: **430 fewer per 1000** (CI 95% 523 fewer - 258 fewer)	**Low** Due to very serious imprecision[3]	Helmet NIV may decrease IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 83 patients in 1 studies	**7.8** days Median	**2.7** days Median Difference: **5.1 fewer** (CI 95% 9.38 fewer - 0.82 fewer)	**Low** Due to very serious imprecision[4]	Helmet NIV may decrease hospital LOS
ICU LOS	No studies were found that looked at ICU LOS				

1. **Imprecision: very serious.** Low number of patients, Only data from one study;
2. **Imprecision: very serious.** Low number of patients, Only data from one study;
3. **Imprecision: very serious.** Low number of patients, Only data from one study;
4. **Imprecision: very serious.** Low number of patients, Only data from one study.

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