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High-flow nasal cannulae for respiratory support in adult intensive care patients (Review)

Corley A, Rickard CM, Aitken LM, Johnston A, Barnett A, Fraser JF, Lewis SR, Smith AF

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[Intervention Review]

High-flow nasal cannulae for respiratory support in adult intensive care patients

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ABSTRACT

Background

High-flow nasal cannulae (HFNC) deliver high flows of blended humidified air and oxygen via wide-bore nasal cannulae and may be useful in providing respiratory support for adult patients experiencing acute respiratory failure in the intensive care unit (ICU).

Objectives

We evaluated studies that included participants 16 years of age and older who were admitted to the ICU and required treatment with HFNC. We assessed the safety and efficacy of HFNC compared with comparator interventions in terms of treatment failure, mortality, adverse events, duration of respiratory support, hospital and ICU length of stay, respiratory effects, patient-reported outcomes, and costs of treatment.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 3), MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Web of Science, proceedings from four conferences, and clinical trials registries; and we handsearched reference lists of relevant studies. We conducted searches from January 2000 to March 2016 and reran the searches in December 2016. We added four new studies of potential interest to a list of 'Studies awaiting classification' and will incorporate them into formal review findings during the review update.

Selection criteria

We included randomized controlled studies with a parallel or cross-over design comparing HFNC use in adult ICU patients versus other forms of non-invasive respiratory support (low-flow oxygen via nasal cannulae or mask, continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP)).

Data collection and analysis

Two review authors independently assessed studies for inclusion, extracted data, and assessed risk of bias.

Main results

We included 11 studies with 1972 participants. Participants in six studies had respiratory failure, and in five studies required oxygen therapy after extubation. Ten studies compared HFNC versus low-flow oxygen devices; one of these also compared HFNC versus CPAP, and another compared HFNC versus BiPAP alone. Most studies reported randomization and allocation concealment inadequately and provided inconsistent details of outcome assessor blinding. We did not combine data for CPAP and BiPAP comparisons with data for low-flow oxygen devices; study data were insufficient for separate analysis of CPAP and BiPAP for most outcomes. For the primary outcomes of treatment failure (1066 participants; six studies) and mortality (755 participants; three studies), investigators found no differences between HFNC and low-flow oxygen therapies (risk ratio (RR), Mantel-Haenszel (MH), random-effects 0.79, 95% confidence interval (CI) 0.49 to 1.27; and RR, MH, random-effects 0.63, 95% CI 0.38 to 1.06, respectively). We used the GRADE approach to downgrade the certainty of this evidence to low because of study risks of bias and different participant indications. Reported adverse events included nosocomial pneumonia, oxygen desaturation, visits to general practitioner for respiratory complications, pneumothorax, acute pseudo-obstruction, cardiac dysrhythmia, septic shock, and cardiorespiratory arrest. However, single studies reported adverse events, and we could not combine these findings; one study reported fewer episodes of oxygen desaturation with HFNC but no differences in all other reported adverse events. We downgraded the certainty of evidence for adverse events to low because of limited data. Researchers noted no differences in ICU length of stay (mean difference (MD), inverse variance (IV), random-effects 0.15, 95% CI -0.03 to 0.34; four studies; 770 participants), and we downgraded quality to low because of study risks of bias and different participant indications. We found no differences in oxygenation variables: partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) (MD, IV, random-effects 7.31, 95% CI -23.69 to 41.31; four studies; 510 participants); PaO_2 (MD, IV, random-effects 2.79, 95% CI -5.47 to 11.05; three studies; 355 participants); and oxygen saturation (SpO_2) up to 24 hours (MD, IV, random-effects 0.72, 95% CI -0.73 to 2.17; four studies; 512 participants). Data from two studies showed that oxygen saturation measured after 24 hours was improved among those treated with HFNC (MD, IV, random-effects 1.28, 95% CI 0.02 to 2.55; 445 participants), but this difference was small and was not clinically significant. Along with concern about risks of bias and differences in participant indications, review authors noted a high level of unexplained statistical heterogeneity in oxygenation effect estimates, and we downgraded the quality of evidence to very low. Meta-analysis of three comparable studies showed no differences in carbon dioxide clearance among those treated with HFNC (MD, IV, random-effects -0.75, 95% CI -2.04 to 0.55; three studies; 590 participants). Two studies reported no differences in atelectasis; we did not combine these findings. Data from six studies (867 participants) comparing HFNC versus low-flow oxygen showed no differences in respiratory rates up to 24 hours according to type of oxygen delivery device (MD, IV, random-effects -1.51, 95% CI -3.36 to 0.35), and no difference after 24 hours (MD, IV, random-effects -2.71, 95% CI -7.12 to 1.70; two studies; 445 participants). Improvement in respiratory rates when HFNC was compared with CPAP or BiPAP was not clinically important (MD, IV, random-effects -0.89, 95% CI -1.74 to -0.05; two studies; 834 participants). Results showed no differences in patient-reported measures of comfort according to oxygen delivery devices in the short term (MD, IV, random-effects 0.14, 95% CI -0.65 to 0.93; three studies; 462 participants) and in the long term (MD, IV, random-effects -0.36, 95% CI -3.70 to 2.98; two studies; 445 participants); we downgraded the certainty of this evidence to low. Six studies measured dyspnoea on incomparable scales, yielding inconsistent study data. No study in this review provided data on positive end-expiratory pressure measured at the pharyngeal level, work of breathing, or cost comparisons of treatment.

Authors' conclusions

We were unable to demonstrate whether HFNC was a more effective or safe oxygen delivery device compared with other oxygenation devices in adult ICU patients. Meta-analysis could be performed for few studies for each outcome, and data for comparisons with CPAP or BiPAP were very limited. In addition, we identified some risks of bias among included studies, differences in patient groups, and high levels of statistical heterogeneity for some outcomes, leading to uncertainty regarding the results of our analysis. Consequently, evidence is insufficient to show whether HFNC provides safe and efficacious respiratory support for adult ICU patients.

PLAIN LANGUAGE SUMMARY

High-flow nasal cannulae for breathing support in adult intensive care patients

Background

A common reason for intensive care unit (ICU) admission is the need for breathing (or respiratory) support. HFNC are small plastic tubes that sit inside the nostrils and deliver a heated mix of air and oxygen at high flow rates to patients requiring breathing support. They are used frequently in the ICU, yet no clear evidence shows whether they provide patients with long-term benefits such as reduced ICU stay or improved chances of survival.

Study characteristics

The evidence is current to March 2016. We included in the review 11 studies with 1972 participants. Most participants had respiratory failure, or had just been taken off an artificial breathing machine. Included studies compared HFNC with low-flow oxygen given through face masks, through low-flow cannulae, or through devices that use mild pressure to aid oxygen delivery. We reran the search in December 2016 and will deal with any studies of interest when we update the review.

Key results

We found no evidence that HFNC reduced the rate of treatment failure or risk of death compared with low-flow oxygen devices. We found no evidence of any advantages for HFNC in terms of adverse event rates, ICU length of stay, or duration of respiratory support. We observed no differences in participants' blood oxygen levels or carbon dioxide blood levels, and we noted that any differences in breathing rates were small and were not considered clinically important. Studies reported no differences in patient-rated measures of comfort. Only one study found evidence of less dry mouth when HFNC was used.

Quality of evidence

Most studies had reported methods inadequately, and we did not know whether risk of bias may have affected study results. We identified few eligible studies and noted some differences among participants within our included studies, particularly in reasons for requiring respiratory support. We used the GRADE system to rate the evidence for each of our outcomes, and we judged all evidence to be of low or very low quality.

Conclusion

We were not able to collect sufficient evidence from good quality studies to determine whether HFNC offer a safe and effective way of delivering respiratory support for adults in the ICU.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

High-flow nasal cannulae versus low-flow oxygen for respiratory support in adult intensive care patients

Patient or population: adult intensive care patients requiring respiratory support
Settings: intensive care unit
Intervention: high-flow nasal cannulae (HFNC) vs low-flow oxygen

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Low-flow oxygen	High-flow nasal cannulae				
Failure of treatment as indicated by the need for non-invasive positive-pressure ventilation or invasive ventilation	**236 per 1000**	**187 per 1000** (116 to 300)	**RR 0.79** (0.49 to 1.27)	1066 (6 studies)	⊕⊕◯◯ low[a]	
In-hospital mortality up to 90 days	**119 per 1000**	**74 per 1000** (44 to 123)	**RR 0.62** (0.37 to 1.03)	755 (3 studies)	⊕⊕◯◯ low[b]	
Adverse events Incidence of nosocomial pneumonia; visits to GP for respiratory complications up to day 28; episodes of oxygen desaturation; pneumothorax, acute pseudo-obstruction; cardiac dysrhythmia; septic	See comment	See comment	Not estimable	See comment	⊕⊕◯◯ low[c]	Each adverse event reported by individual study authors; therefore insufficient data for pooling

shock; cardiorespiratory arrest					
Length of ICU stay in days	Mean length of stay ranged from 1.39 days to 11.7 days	Mean length of ICU stay in days in the intervention group was **0.15 days longer** than in the control group (0.03 shorter to 0.34 longer)		770 (5 studies)	⊕⊕◯◯ low[b]
PaO_2/FiO_2 ratio up to 24 hours after initiation of therapy	Mean PaO_2/FiO_2 ratio ranged from 130 to 287.5	Mean PaO_2/FiO_2 ratio up to 24 hours after initiation of therapy in the intervention group was **7.31 higher** than in the control group (23.69 lower to 41.31 higher)		510 (4 studies)	⊕◯◯◯ very low[d]
Patient-reported outcomes - short-term comfort Scale from 0 to 10	Mean scores ranged from 1.11 to 5.2	Mean comfort score in the intervention group was **0.14 points higher** (0.65 lower to 0.93 higher)		462 (3 studies)	⊕⊕◯◯ low[e]
Patient-reported outcomes - long-term comfort Scale from 0 to 10	Mean scores ranged from 1.5 to 3.06	Mean comfort score in the intervention group was **0.36 points lower** (3.70 lower to 2.98 higher)		445 (2 studies)	⊕⊕◯◯ low[f]

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a] Evidence downgraded by two levels, as statistical heterogeneity between studies was moderate, some studies had high or unclear risk of bias, and some studies showed indirectness including participants requiring respiratory support for different purposes

[b] Evidence downgraded by two levels, as some studies had high or unclear risk of bias in some domains and some studies showed indirectness including participants requiring respiratory support for different purposes

[c] Evidence for each reported adverse event from single studies only. Not possible to combine in analysis; quality of data downgraded by two levels for imprecision

[d] Evidence downgraded by three levels. Level of statistical heterogeneity between studies (I^2 = 86%) was substantial; indirectness, with studies including participants requiring respiratory support for different purposes, and very wide confidence intervals in the effect estimate

[e] Evidence downgraded by two levels: Effect estimate includes data from only three studies with some unclear risk of bias within studies

[f] Evidence downgraded by three levels: Effect estimate includes data from only two studies with some unclear risk of bias within studies and high level of statistical heterogeneity

BACKGROUND

Description of the condition

Acute respiratory failure and the subsequent need for respiratory support, is a frequent cause of admission of adults to an intensive care unit (ICU) (Behrendt 2000). For such patients, respiratory support is required owing to hypoxaemia, ventilatory failure, or both (Shelly 1999). This respiratory support can be provided to the patient in an invasive or non-invasive manner.

Invasive mechanical ventilation involves the insertion of an artificial airway (an endotracheal or tracheostomy tube). Although this is regarded as a life-saving treatment, it comes with multiple inherent risks to patients. These risks include development of ventilator-induced lung injury (Gattinoni 2012), ventilator-associated pneumonia (Muscadere 2008), neurocognitive sequelae associated with prolonged sedation (Morandi 2011; Nelson 2000), and increased length of ICU and hospital stay (Safdar 2005). When possible, therefore, invasive mechanical ventilation should be avoided, although intubation and mechanical ventilation are inevitable if the patient has stopped breathing or is unable to maintain his or her airway (Nava 2009).

Non-invasive respiratory support, when possible, is the preferred method of respiratory support and can be delivered via any of the following approaches.

- Low-flow nasal cannulae (LFNC).
- Simple face mask.
- Venturi mask.
- Non-rebreather mask.
- Non-invasive positive-pressure ventilation (NIPPV).
- High-flow nasal cannulae (HFNC).

The type of delivery device chosen depends largely on the severity and the cause of the patient's acute respiratory failure, and each device provides benefits and drawbacks that determine its usefulness in clinical practice.

Physicians use LFNC for patients requiring minimal respiratory support in the form of supplemental oxygen to maintain adequate oxygenation. These cannulae deliver dry oxygen at 1 to 6 litres per minute via small prongs approximately 1.5 cm long, which sit just inside the nares of the nose (O'Driscoll 2008). Although they are generally well tolerated by patients (Zevola 2001), delivery of higher flows of oxygen through LFNC is not practicable owing to the drying and irritating effects of cold dry gas on the mucosa (Lellouche 2002).

Delivery of oxygen via a face mask is necessary if the patient has higher oxygen requirements than can be achieved with LFNC. Simple face masks can deliver 5 to 10 litres per minute of oxygen. For patients requiring increased oxygen and higher flows to maintain adequate oxygenation, non-rebreather masks can deliver 10 to 15 litres per minute of oxygen (O'Driscoll 2008). Oxygen may be supplemented with humidification by some devices. Simple face masks and non-rebreather masks are capable of delivering relatively high oxygen concentrations; therefore they are generally unsuitable for patients with chronic obstructive pulmonary disease (COPD), who may retain carbon dioxide. For hypercapnoeic patients with COPD, oxygen concentration can be regulated by a Venturi mask, which can deliver between 24% and 60% oxygen at a flow of 2 to 15 litres per minute (O'Driscoll 2008). Although face masks are effective for delivering oxygen to patients with mild to moderate acute respiratory failure, they can be poorly tolerated when compared with nasal cannulae owing to discomfort and feelings of claustrophobia, leading to reduced compliance as a result of frequent removal and subsequent treatment interruption (Sasaki 2003).

NIPPV can be used in patients who not only require supplemental oxygen but also need support for the mechanical process of ventilation (Mehta 2001). A blend of oxygen and air is delivered at a prescribed fraction of inspired oxygen (FiO_2) via a tight-fitting mask (nasal mask, oronasal mask, or full face mask). Additionally, continuous positive airway pressure (CPAP) or bilevel positive airway pressure ventilation (BiPAP) is delivered to improve alveolar recruitment, improve gas exchange, and decrease the work of breathing (Mehta 2001). Although CPAP is not a true ventilatory mode, it is often referred to as NIPPV in clinical practice (Nava 2009). Substantial available data show that NIPPV improves outcomes among patients requiring respiratory support owing to cardiogenic pulmonary oedema or acute exacerbations of COPD, and also among patients weaning from invasive mechanical ventilation (Nava 2009). However, its relevance for patients with hypoxaemic acute respiratory failure is less clearly defined (Nava 2009). Despite showing clear benefit for certain conditions, NIPPV inhibits mobilization, is associated with gastric distension, restricts effective communication and oral nutrition, and is poorly tolerated by some patients owing to discomfort (Gregoretti 2002; Mehta 2001).

Although the conventional non-invasive delivery devices listed above provide important therapies in the range of respiratory support available to treat patients with acute respiratory failure, it is evident that they have limitations that can impact their usefulness in clinical practice. Failure of these devices to provide adequate respiratory support and to correct acute respiratory failure often results in the need for required intubation and mechanical ventilation.

Description of the intervention

HFNC, which have been used in the neonatal setting for some years (Wilkinson 2011), are a relatively new method of delivering respiratory support to adults experiencing acute respiratory failure. Cannulae are approximately 1.5 cm long and 0.5 cm in diameter and, as with LFNC, sit just inside the nares. A gas flow of up to 60 litres per minute can be delivered because the gas is warmed and humidified, making it less irritating to the nasal mucosa. For the purposes of this review, HFNC will be defined as humidified

oxygen delivered via nasal cannulae at a rate greater than 20 litres per minute. Very few adverse reactions have been reported with HFNC use, and those reported consist of minor complaints of a runny nose (Price 2008) and some discomfort with heat or flow rate (Roca 2010).

How the intervention might work

HFNC can deliver blended humidified air and oxygen via wide-bore nasal cannulae at a prescribed FiO_2 at high flow rates. HFNC do not need to be removed during oral hygiene care or when patients talk, eat, or drink, resulting in less frequent interruptions to therapy. In the growing body of evidence gathered when effects of HFNC are investigated, improvements in oxygenation (Corley 2011; Parke 2009; Roca 2010; Sztrymf 2011; Sztrymf 2011a), respiratory rate (Corley 2011; Roca 2010; Sztrymf 2011; Sztrymf 2011a), dyspnoea (Corley 2011; Roca 2010; Sztrymf 2011), and patient comfort (Corley 2011; Roca 2010; Tiruvoipati 2010) have been reported in recent observational studies.

Suggested mechanisms of action of HFNC consist of:

- flushing of anatomical dead space due to high gas flow, functionally reducing dead space and improving respiratory efficiency (Dysart 2009);
- generation of positive airway pressure (Corley 2011; Groves 2007; Parke 2009), which increases functional residual capacity and improves alveolar recruitment;
- improved ability to meet high inspiratory flow demands among patients requiring respiratory support and to deliver a more accurate FiO_2 through less dilution by entrainment of room air (Dysart 2009); and
- ability to deliver optimal humidification, leading to enhanced mucociliary transport (Salah 1988) and improved patient comfort (Chanques 2009).

We conducted this review to compare the efficacy and safety of HFNC versus other methods of non-invasive respiratory support in adult patients admitted to the ICU.

Why it is important to do this review

It has been demonstrated that HFNC offer some immediate physiological benefit for patients requiring respiratory support, but it remains to be determined whether they offer any clinically important benefit and improve patient outcomes, such as by preventing progression to invasive mechanical ventilation and reducing mortality. Individual studies may tend to focus on surrogate outcomes or may be underpowered to detect effects on clinically important outcomes. By performing this review, we can extract data on important clinical outcomes and can conduct meta-analyses on effects of the intervention on these outcomes with greater statistical power to detect meaningful patient differences should they exist.

As HFNC gain in popularity as a treatment modality for providing respiratory support, it is important to perform this review to synthesize the existing evidence base and to provide clear conclusions regarding the efficacy and safety of HFNC. In this way, clinicians can make decisions about how this form of respiratory support can best be incorporated into the current suite of treatment options; and for whom this treatment can be used most efficaciously.

OBJECTIVES

We evaluated studies that included participants 16 years of age and older who were admitted to the ICU and required treatment with HFNC. We assessed the safety and efficacy of HFNC compared with comparator interventions in terms of treatment failure, mortality, adverse events, duration of respiratory support, hospital and ICU length of stay, respiratory effects, patient-reported outcomes, and costs of treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized, parallel, and quasi-randomized studies (including cross-over studies) that compared HFNC versus other forms of non-invasive respiratory support for selected outcome measures. We included quasi-randomized trials in this review owing to the current scarcity of randomized controlled trials (RCTs) in this area.

Owing to the inability of randomized cross-over studies to detect long-term patient outcomes, we included this trial design only for the secondary outcome measures of positive end-expiratory pressure, oxygenation, carbon dioxide clearance, respiratory rate, work of breathing, and patient-reported outcomes.

We did not impose a language restriction, and we considered studies written in any language.

We excluded retrospective studies and prospective cohort or observational studies, as we wanted to focus on evidence of the highest quality from randomized studies.

Types of participants

We included studies that enrolled adult patients (16 years of age or older) requiring respiratory support and admitted to the ICU. We excluded participants younger than 16 years of age. Two already published Cochrane reviews have assessed the effectiveness of HFNC in preterm infants (Wilkinson 2011) and in the paediatric population (Mayfield 2012).

We also excluded patients not admitted to an ICU.

Types of interventions

We included humidified oxygen delivered via the nasal route at a rate greater than 20 litres per minute as the experimental intervention.

We included the following forms of non-invasive respiratory support as comparison interventions.

- Low-flow oxygen via nasal cannulae or mask (≤ 15 litres per minute).
- Continuous positive airway pressure (CPAP).
- Bilevel positive airway pressure (BiPAP).

Types of outcome measures

The outcome measures in this review are a mix of surrogate and clinical outcomes. We recognize that while there may be a correlation between the surrogate and clinical outcomes, it is the clinical outcomes which will provide the strongest evidence regarding the safety and efficacy of HFNC. As a result, we chose the clinical outcome of failure of treatment as indicated by the need for NIPPV or invasive ventilation as one of our primary outcome measures

Primary outcomes

1. Treatment failure as indicated by the need for NIPPV or invasive ventilation (up to 28 days)
2. In-hospital mortality (up to 90 days)
3. Adverse events

Secondary outcomes

1. Duration in hours of any form of respiratory support (mechanical ventilation, NIPPV, HFNC, standard oxygen)
2. Length of stay in days (ICU and hospital)
3. Respiratory effects as indicated by any of the following
   - Degree of atelectasis on radiological examination
   - Positive end-expiratory pressure measured at the pharyngeal level (cm H_2O)
   - Oxygenation (partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio, PaO_2, oxygen saturation of arterial blood (SaO_2), and oxygen saturation (SpO_2))
   - Carbon dioxide clearance (partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and partial pressure of carbon dioxide (PCO_2))
   - Respiratory rate
   - Work of breathing (joules per litre)
4. Patient-reported outcomes as indicated by any of the following
   - Dyspnoea
   - Comfort
   - Dry mouth
   - Patient refusal to continue with treatment
5. Cost comparison of treatment (in Australian dollars)

We assessed all outcomes at the time points reported in included studies. For patient-reported outcomes, we accepted study authors' definitions.

Search methods for identification of studies

Electronic searches

We searched the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2016, Issue 3); see Appendix 1.
- MEDLINE, OvidSP (January 2000 to March 2016); see Appendix 2.
- Cumulative Index to Nursing and Allied Health Literature (CINAHL), EBSCOhost (January 2000 to March 2016); see Appendix 3.
- Embase, OvidSP (January 2000 to March 2016); see Appendix 4.
- Institute for Scientific Information (ISI) Web of Science (January 2000 to March 2016); see Appendix 5.

We restricted the search start date to 2000, as HFNC have been available for use in the adult population only since the mid-2000s. We adapted the MEDLINE search strategy for searches of all other databases.

We (Amanda Corley (AC)) searched for published abstracts from conference proceedings for the European Society of Intensive Care Medicine, the Australia and New Zealand Intensive Care Society, the Society of Critical Care Medicine, and the American Thoracic Society (2000 to May 2014).

For trials not yet completed, we searched clinical trials registries (clinicaltrials.gov; controlled-trials.com; anzctr.org.au; and who.int/ictrp). We (AC) contacted trial authors to determine whether any data were available for inclusion in the review; however, we received no responses.

We reran database searches in December 2016. We added new studies of potential interest to Characteristics of studies awaiting classification and will incorporate them into formal review findings during the review update.

Searching other resources

We screened the reference lists of eligible trials to identify any previously unidentified studies.

Data collection and analysis

Selection of studies

We included in the review all randomized, parallel-group, and quasi-randomized controlled trials (including randomized cross-over trials) meeting review criteria. Two review authors (of AC, Claire M Rickard (CMR), Sharon R Lewis (SRL), Andrew F Smith (AFS)) independently examined published titles and abstracts obtained during the search and screened them for suitability. Each review author completed a study selection form (see Appendix 6), and if the study was to be excluded, we detailed the reasons for exclusion. All review authors reached consensus regarding study inclusion.

Data extraction and management

Two review authors (of AC, CMR, SRL, AFS) independently extracted data from each study onto the data extraction form (see Appendix 7) and compared data extraction forms for each study. Review authors reached consensus regarding extracted data through discussion.

Assessment of risk of bias in included studies

Two review authors (of AC, CMR, SRL, AFS) independently assessed the risk of bias of each study. Review authors reported no disagreements regarding assessment of risk of bias. We (AC) contacted some trial authors if we needed more information to assess risk of bias.

We conducted assessment of risk of bias in included studies by using the 'Risk of bias' tool, as per the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using the quality assessment form (see Appendix 8). We assessed trials as having low risk of bias if we assessed all of the following areas as adequate. We assessed trials as having high risk of bias if we assessed one or more of these areas as not adequate or unclear.

We assessed risk of bias in the following domains.

Random sequence generation (selection bias)

We assessed allocation of interventions as adequate if allocation was performed in a truly unpredictable manner (e.g. computerized random number generator, random number table, shuffled envelope system, coin toss, roll of the die).

We assessed allocation as inadequate if it was based on non-random methods (e.g. day of the week, alternate patients, patient characteristics such as date of birth, hospital identifier) or if the method of allocation was unclear.

Allocation concealment (selection bias)

We assessed allocation concealment as adequate if study personnel and participants were unaware of the treatment allocation of the next participant (e.g. central or telephone randomization, sequentially numbered sealed opaque envelopes, on-site computer accessed only after patient enrolment).

Inadequate allocation concealment included randomization methods deemed inadequate above (e.g. unsealed or non-sequential envelopes, open allocation sequence) or unclear methods of allocation concealment.

Blinding of outcome assessors (performance and detection bias)

It is not possible to blind the participant or the clinical staff to treatment allocation for this intervention; therefore, we limited assessment of risk of bias to blinding of outcome assessors. For interventions such as oxygen delivery devices for which it is not possible to blind participants or clinical staff, some performance bias is inevitable.

We assessed blinding as adequate when outcome assessors were definitely blinded to treatment allocation. If blinding was not mentioned, we deemed blinding as not adequate.

When blinding of outcome assessors was not always possible (e.g. respiratory rate, oxygenation, carbon dioxide clearance, work of breathing), we assessed whether this would have been likely to have introduced bias. If measurement of the outcome was unlikely to have been influenced by lack of blinding, we assumed that blinding was adequate.

When the participant was the outcome assessor (i.e. for patient-reported outcomes), we deemed blinding as adequate if strategies to reduce potential bias were evident (e.g. standardized questioning strategy used for all patient-reported outcomes, questioning carried out by non-study staff).

Incomplete outcome data, intention-to-treat (attrition bias)

We deemed outcome data as adequate if all withdrawals, protocol deviations, and losses to follow-up were reported and incomplete data were proportionate across groups. If this was not reported, we assessed outcome data as inadequately dealt with.

Selective reporting

We assessed outcome reporting as adequate if all previously stated outcomes were fully reported. We assessed outcome reporting as inadequate if all previously stated outcomes were not reported, if outcomes were not fully reported, or if outcomes were reported but were not previously mentioned.

Measures of treatment effect

We performed statistical analyses using Review Manager 5 (RevMan 5.3). We expressed dichotomous data as risk ratio (RR), risk difference (RD), and number needed to treat for an additional beneficial outcome (NNTB). We expressed continuous data as the difference between means. We reported the 95% confidence interval (CI) for all estimates. We treated ordinal data (e.g. mouth dryness on a scale of 0 to 10) as continuous data. To cope with non-

normally distributed data, we used the generalized linear model framework while assuming a gamma distribution.

Unit of analysis issues

The unit of analysis for all included studies was the participant, and our meta-analysis was based on summary statistics derived from participant level data.

We identified three cross-over trials as eligible for inclusion (Chanques 2013; Rittayamai 2014; Schwabbauer 2014). The study author for one study (Schwabbauer 2014) did not report data for the first cross-over period; therefore, we included no data from this study in the analysis. Study authors from the other two studies (Chanques 2013; Rittayamai 2014) provided data from the first treatment period for inclusion in the review.

Included studies measured many of the secondary outcomes (oxygenation (PaO_2, PaO_2/FiO_2 ratio, SpO_2), carbon dioxide clearance, respiratory rate, dyspnoea, mouth dryness, and patient comfort) at multiple time points. To overcome the potential for unit of analysis error, we took a simple approach to analysis of these outcomes on the advice of the statistical editor. We reported outcome data as short-term and longer-term effects, with short-term effects resulting from initiation of therapy up to 24 hours, and longer-term effects occurring more than 24 hours after initiation of therapy. For short-term effects, we used the closest data point to 24 hours. Only two studies (Maggiore 2014; Parke 2013a) assessed outcomes for longer than 24 hours. Both studies measured outcomes at 48 hours after initiation of therapy; therefore, we used this time point as the longest follow-up data.

We identified two studies that had three arms (Frat 2015; Schwabbauer 2014). Both comparison arms were relevant for this review. We included no data for Schwabbauer 2014, as stated above. For Frat 2015, we used the halving method (as described by Higgins 2011) to divide dichotomous data for the HFNC group equally for each comparison group. It was not possible to do this for continuous data; therefore, we included only the comparison arm that gave the most conservative estimate for each outcome.

Dealing with missing data

We contacted some study authors via email for further information regarding study methods and data. Study authors did not identify missing data in addition to those reported in the published review, and we were unable to tabulate missing data and perform sensitivity analyses to determine the influence of missing data on effect estimates, as planned in the protocol.

Assessment of heterogeneity

Using clinical judgement, we assessed participants, interventions, and outcomes for clinical heterogeneity. We assessed methodological heterogeneity during risk of bias assessments and by visual inspection of forest plots. We assessed statistical heterogeneity by using the I^2 statistic (on a scale of 0% to 100%) and the Chi^2 test (Higgins 2011).

Assessment of reporting biases

As fewer than 10 trials were available for the meta-analysis, we did not assess publication bias in this review.

Data synthesis

We conducted meta-analyses for outcomes for which we had comparable study data. We performed separate analyses for comparisons of low-flow oxygen devices and for comparisons of CPAP and BiPAP. If studies selected for inclusion did not have moderate to substantial levels of heterogeneity (clinical, methodological, or statistical), we would have used a fixed-effect model to calculate effects estimates. We classified the level of heterogeneity using the I^2 statistic as 0% to 40% not important; 30% to 60% moderate heterogeneity; 50% to 90% substantial heterogeneity; and 75% to 100% considerable heterogeneity (Higgins 2011). We selected a random-effects model, rather than a fixed-effect model, owing to heterogeneity and overall small sample sizes for our outcome data. We conducted analyses for outcomes using Review Manager 5 (RevMan 5.3).

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis for studies that included participants requiring respiratory support for respiratory failure and participants requiring respiratory support after extubation.

Sensitivity analysis

To determine the sensitivity of findings to the way in which we had conducted the analysis, we performed sensitivity analysis based on risk of bias judgements and statistical models used for effect estimates.

Summary of findings table and GRADE

We used the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with the specific outcomes listed below.

- Failure of treatment as indicated by the need for NIPPV or invasive ventilation.
- In-hospital mortality.
- Adverse events.
- Length of stay in days (ICU).
- PaO_2/FiO_2 ratio up to 24 hours after initiation of therapy.
- Patient-reported outcomes - comfort over the short term.
- Patient-reported outcomes - comfort over the long term.

We constructed a 'Summary of findings' table using GRADE software as a guide. The GRADE approach appraises the quality of a

body of evidence on the basis of the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias. See Summary of findings for the main comparison.

RESULTS

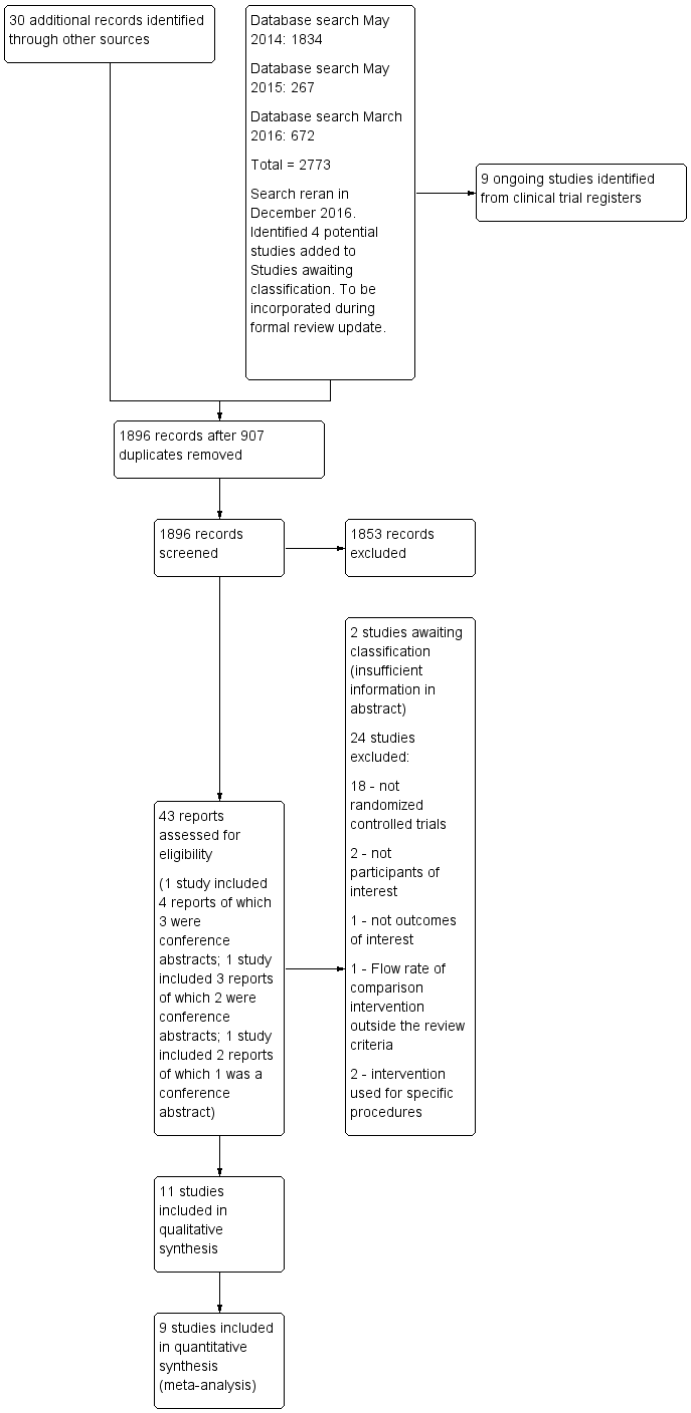
Description of studies

See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies.

Results of the search

We conducted electronic searches in May 2014, May 2015, and March 2016. We identified 2773 records, and by handsearching reference lists, we identified another 30 records. From these results, we identified 43 reports for which we sourced the full text and assessed eligibility against our review inclusion criteria. We found 11 studies, three of which provided six additional associated references. We were unable to classify two studies without further information, and we excluded 24 studies. See Figure 1.

Figure 1. Study flow diagram.



Included studies

We included 11 RCTs with 1972 randomized participants; eight used a parallel design (Corley 2014; Cuquemelle 2012; Frat 2015; Lemiale 2015; Maggiore 2014; Parke 2011; Parke 2013a; Stephan 2015), and three were randomized cross-over studies (Chanques 2013; Rittayamai 2014; Schwabbauer 2014). We were unable to gain data from one RCT for the outcomes of interest, so we included only narrative results (Cuquemelle 2012). This study included a four-hour cross-over period at the end of a 24-hour parallel assignment period; therefore we included in this review only narrative results from the initial 24-hour period. One of the randomized cross-over studies provided no data from the first treatment period (as per the review protocol, only data from the first treatment period were to be included in the review) (Schwabbauer 2014). Therefore, we were unable to include in the review any data from study authors' reported outcomes (oxygenation, patient-reported dyspnoea, and patient-reported comfort). We included data from seven RCTs (Corley 2014; Frat 2015; Lemiale 2015; Maggiore 2014; Parke 2011; Parke 2013a; Stephan 2015) and data from the first treatment period of two randomized cross-over studies (Chanques 2013; Rittayamai 2014) in the meta-analysis when applicable. Two review authors achieved complete agreement on study inclusion. We provided details of each of the included studies (inclusion and exclusion criteria, intervention details, reported outcomes, study dates, country, setting, funding sources, and declarations of interest) in the Characteristics of included studies table.

We included only studies that examined participants 16 years of age or older who were patients in the ICU requiring respiratory support. Participants in five studies had respiratory failure (Cuquemelle 2012; Frat 2015; Lemiale 2015; Parke 2011; Schwabbauer 2014), those in Stephan 2015 were at risk of acute respiratory failure, and those in the remaining five studies were given oxygen therapy after extubation (Chanques 2013; Corley 2014; Maggiore 2014; Parke 2013a; Rittayamai 2014). Participants in Corley 2014 had a body mass index (BMI) of at least 30 kg/m^2. No other studies included or excluded participants on the basis of BMI.

All included studies used the Optiflow HFNC system (Fisher & Paykel Healthcare) to deliver humidified high-flow nasal oxygen. By contacting the study authors listed below, we confirmed flow rates for the intervention group as between 35 and 50 litres per minute for five studies (Cuquemelle 2012; Maggiore 2014; Parke 2011; Parke 2013a; Rittayamai 2014). Some study authors reported flow rates up to a maximum of 50 L/min (Corley 2014; Frat 2015; Lemiale 2015; Stephan 2015). Schwabbauer 2014 reported flow rates at 55 L/min. Chanques 2013 tested each oxygen delivery device at 15, 30, and 45 L/min.

Three studies included two comparison groups (Chanques 2013; Frat 2015; Schwabbauer 2014). Comparisons with face masks used a simple face mask, nasal cannulae, a non-rebreather face mask or Venturi mask (Corley 2014; Frat 2015; Lemiale 2015; Maggiore 2014; Parke 2013a; Rittayamai 2014; Schwabbauer 2014), a high-flow face mask (Chanques 2013), and a high-flow face mask with humidifier (Parke 2011). Comparisons with NIPPV devices used Bossignac oxygen therapy (Chanques 2013) and bilevel positive airway pressure (BiPAP) (Stephan 2015), and two studies provided non-invasive ventilation (Frat 2015; Schwabbauer 2014). Cuquemelle 2012) described as the use of 'standard oxygen therapy'. All comparisons included low-flow oxygen delivery at $\leq$ 15 L/min. Chanques 2013 included comparisons with oxygen flow at 15, 30, and 45 L/min, but we included data only for the 15 L/min group.

We contacted eight study authors by email to request additional details, including outcome data not available in the published report and information for risk of bias assessment (Chanques 2013; Corley 2014; Cuquemelle 2012; Maggiore 2014; Parke 2011; Parke 2013a; Rittayamai 2014; Schwabbauer 2014). Chanques 2013, Corley 2014, Parke 2011, Parke 2013a, and Rittayamai 2014 provided participant and outcome data and clarification on methodological issues; Cuquemelle 2012 provided information on methodological issues but was unable to provide data; Schwabbauer 2014 was unable to provide any additional details of this study. Following contact with Maggiore 2014, the full report was published, and we used data from this report, rather than information provided via email communication.

Excluded studies

We excluded 24 studies during full-text review and provided reasons for exclusion for nine key trials (Baneton 2014; Besch 2014; Braunlich 2013; Curley 2015; Parke 2013b; Pinto 2012; Simon 2014; Tiruvoipati 2010; Vourc'h 2015). Further investigation revealed that three trials were not RCTs (Baneton 2014; Besch 2014; Curley 2015); two trials did not include participants of interest (Braunlich 2013; Pinto 2012); one trial did not measure outcomes of interest (Parke 2013b); two trials assessed oxygen therapy for different procedures (during flexible bronchoscopy, Simon 2014; and with pre-oxygenation before intubation, Vourc'h 2015); and in one trial, the comparison intervention did not meet the review criteria (Tiruvoipati 2010). See Characteristics of excluded studies.

Studies awaiting classification

We were unable to assess eligibility for two studies, which were published as abstracts (Perbet 2014; Saeed 2015). We reran the search in December 2016 and identified four studies for potential inclusion (Futier 2016; Hernandez 2016a; Hernandez 2016b;

Lemiale 2016). We will incorporate these into formal review findings during the review update. See Characteristics of studies awaiting classification for additional details.

Ongoing studies

We identified nine ongoing studies (NCT01166256; NCT01820507; NCT01994928; NCT01702779; NCT01782430; NCT02123940; NCT02107183; UMIN000008778; NCT01617252). See Characteristics of ongoing studies for details.

Risk of bias in included studies

We detailed risks of bias for the included studies in the 'Risk of bias' tables in Characteristics of included studies, the 'Risk of bias' graph (Figure 2), and the 'Risk of bias' summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

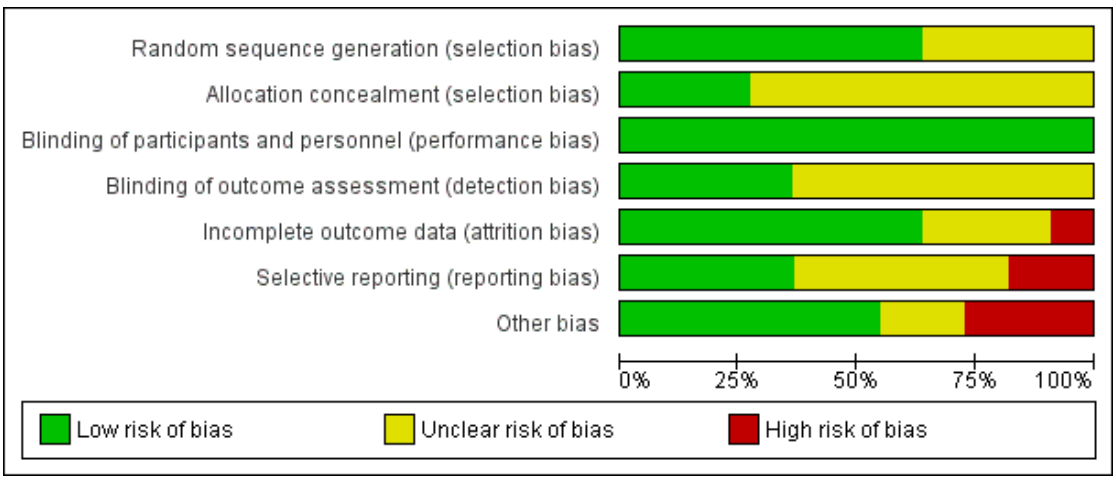
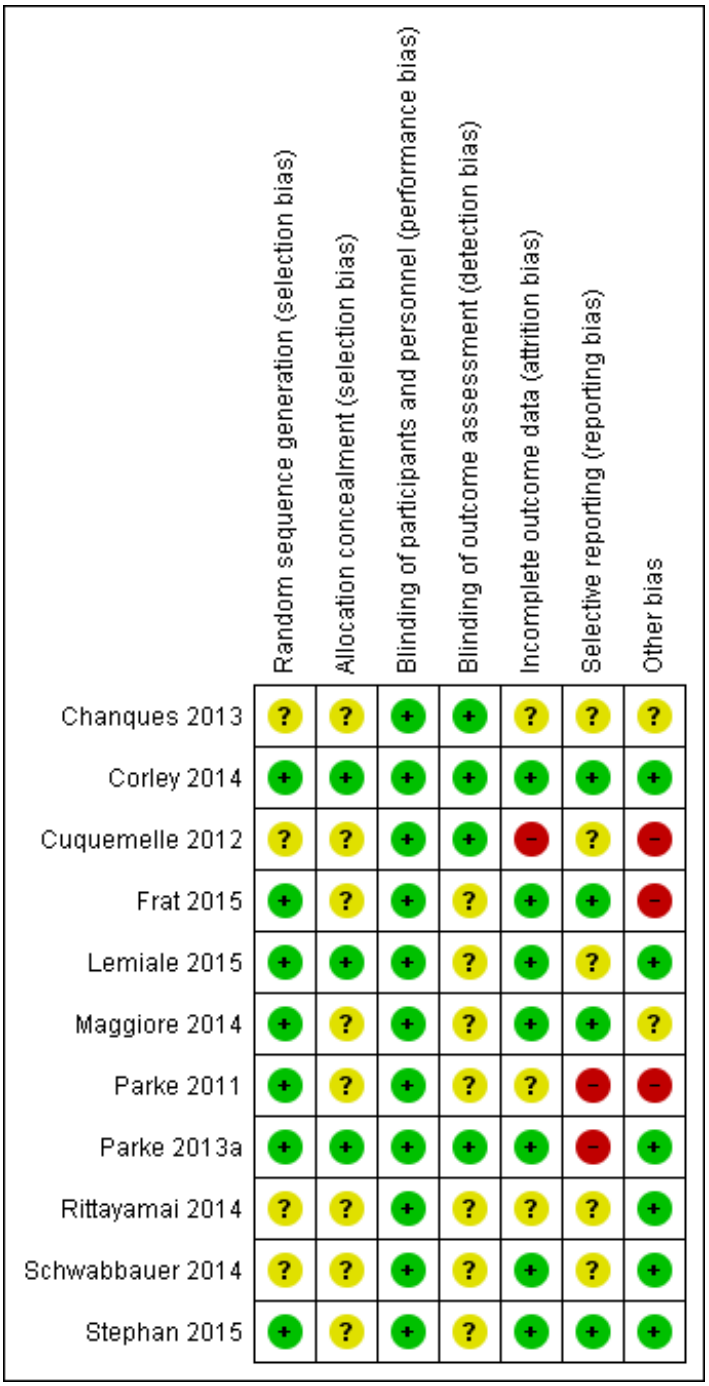


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We judged that seven studies used an appropriate method of randomization to allocate participants, for example, a block system, a computer-generated sequence, or an external randomization service (Corley 2014; Frat 2015; Lemiale 2015; Maggiore 2014; Parke 2011; Parke 2013a; Stephan 2015); three of these also reported adequate methods of concealing allocation (Corley 2014; Lemiale 2015; Parke 2013a). Other studies failed to provide sufficient information; therefore, it was unclear whether these studies were at risk of selection bias.

Blinding

Owing to the nature of the intervention and comparators, it is not possible to blind participants and their treating clinicians to treatment allocation. Subsequently, some of the included studies (Chanques 2013; Cuquemelle 2012; Maggiore 2014; Parke 2011; Parke 2013a; Rittayamai 2014) stated that participants and treating clinicians were not blinded to treatment allocation, and we assumed that no blinding occurred in the remaining studies. We believe that knowledge of treatment would not influence performance for the outcomes of interest for this review; we therefore judged all studies to have low risk of performance bias.

Participants were the outcome assessors in studies that examined patient-reported outcomes (Chanques 2013; Corley 2014; Cuquemelle 2012; Frat 2015; Lemiale 2015; Maggiore 2014; Parke 2013a; Rittayamai 2014; Stephan 2015). However, we believe that the inability to blind participants to treatment allocation would not affect outcome measurements because it would be unlikely that participants would have a particular bias towards one medical intervention over another. Cuquemelle 2012 measured only patient-reported outcomes; therefore we judged this study to have low risk of detection bias overall. For other studies, which included both patient-reported and clinician-reported outcomes, we considered the impact of clinician knowledge of participant group allocation. In Corley 2014 and Parke 2013a, outcome assessors for atelectasis were blinded to treatment allocation; therefore we judged these studies to have low risk of detection bias for these outcomes. However, for other outcomes and for other studies in which this information was not provided, it was unclear whether risk of detection bias was increased and what impact this may have had on the results.

Incomplete outcome data

We judged three studies to have low risk of attrition bias with outcome data fully reported for all participants (Corley 2014; Maggiore 2014; Stephan 2015). Schwabbauer 2014 used an intention-to-treat analysis, and we were satisfied that this represented low risk of bias. Frat 2015, Lemiale 2015, and Parke 2013a reported a small number of losses, and we judged these studies to have low risk of attrition bias. Chanques 2013 and Parke 2011 provided insufficient detail to allow judgement of whether losses had been adequately handled, and Rittayamai 2014 did not provide details on losses or numbers of participants analysed. Cuquemelle 2012 reported a high number of losses (seven losses out of 37 randomized participants), and we judged this study to have high risk of bias.

Selective reporting

Nine studies reported clinical trial registration (Chanques 2013; Corley 2014; Frat 2015; Lemiale 2015; Maggiore 2014; Parke 2011; Parke 2013a; Schwabbauer 2014; Stephan 2015). Five were prospectively registered, and we were able to compare a priori outcomes stated in clinical trials registration protocols, alongside outcomes measured and reported in completed published studies; three trials reported outcomes according to the study protocol (Corley 2014; Frat 2015; Stephan 2015), and we judged these studies to have low risk of reporting bias, but two studies reported additional outcomes (Parke 2011; Parke 2013a), and we therefore judged these studies to have high risk of bias for this domain.

Four studies were retrospectively registered (Chanques 2013; Lemiale 2015; Maggiore 2014; Schwabbauer 2014). Of these, Maggiore 2014 was registered shortly after the beginning of recruitment, and as a priori outcomes matched reported outcomes, we judged this study to have low risk of reporting bias. It was not feasible for us to compare protocols against completed studies for the remaining retrospectively registered studies; therefore, we could not judge bias for this domain. Two studies did not report trial registration; therefore, we also were not able to judge these studies (Cuquemelle 2012; Rittayamai 2014).

Other potential sources of bias

To date, one of the included studies (Maggiore 2014) has presented three abstracts, and this study is part of a larger ongoing clinical trial (see NCT02107183 in Characteristics of ongoing studies). Multiple interim analyses could introduce bias (Bland 1995).

One study (Cuquemelle 2012) reported potentially clinically relevant baseline imbalances between groups, with participants in the intervention group being older (median 66 years vs 51 years of age) and having a higher rate of infectious pneumonia (57% vs 33%).

For cross-over studies, we included data only from the first treatment period. Therefore, lack of a washout period or description of treatment during the washout period in Chanques 2013, Cuquemelle 2012, and Rittayamai 2014 did not introduce risk of bias for this review.

Participants in the NIPPV group in Frat 2015 used HFNC during breaks in delivery of oxygen. We judged this study to have high risk of bias as a result of this methodological decision.

Nine studies declared funding or provision of equipment from manufacturers of the HFNC system (Fisher & Paykel Healthcare) (Chanques 2013; Corley 2014; Cuquemelle 2012; Frat 2015; Lemiale 2015; Maggiore 2014; Parke 2011; Parke 2013a; Schwabbauer 2014). Six of these reported that the manufacturer had not been involved in study design, management, or data analyses, and we considered these studies to have low risk of bias (Corley 2014; Cuquemelle 2012; Frat 2015; Lemiale 2015; Parke 2013a; Schwabbauer 2014); two of these six did not report involvement of the manufacturer, and we were unclear whether this funding represented risk of bias (Chanques 2013; Maggiore 2014); one study reported that the manufacturer had been involved in the study design and had paid for statistical analysis; we judged this study to have high risk of bias (Parke 2011).

Effects of interventions

See: **Summary of findings for the main comparison** High-flow nasal cannulae versus low-flow oxygen for respiratory support in adult intensive care patients

See Summary of findings for the main comparison.

Primary outcomes

1. Failure of treatment as indicated by the need for NIPPV or invasive ventilation

Eight studies reported failure of treatment (Corley 2014; Cuquemelle 2012; Frat 2015; Lemiale 2015; Maggiore 2014; Parke 2011; Parke 2013a; Stephan 2015). Cuquemelle 2012 reported less treatment failure associated with HFNC, with one of 19 participants in the HFNC group failing treatment compared with four of 18 participants in the low-flow oxygen group. However, we were unable to include these data in the meta-analysis, as we could not confirm with study authors if these failures occurred during the initial 24-hour parallel period or during the final four-hour cross-over period. We did not combine Stephan 2015 in the meta-analysis, as the comparison group (BiPAP) was not comparable with the other low-flow oxygen groups; we presented the data in Table 1; study authors reported no differences between oxygen delivery devices (P = 0.99). As Frat 2015 included two comparison groups, we included data from both comparisons and halved the data in the intervention group. Among the 1066 participants (six studies) included in this analysis, we found no evidence of less treatment failure with HFNC than with low-flow oxygen (risk ratio (RR), Mantel-Haenszel (M-H), random-effects 0.79, 95% confidence interval (CI) 0.49 to 1.27; P = 0.33; risk difference (RD) -0.06, 95% CI - 0.15 to 0.03; P = 0.18; number needed to treat for an additional beneficial outcome (NNTB) 16, 95% CI 6 (NNTB) to 33 number needed to treat for an additional harmful outcome (NNTH)). See Analysis 1.1. We used GRADE to assess the quality of this evidence and considered a moderate level of statistical heterogeneity in the pooled estimate (I^2 = 58%); some studies had high or unclear risk of bias, and there was some indirectness in the effect estimate as pooled studies included some participants that required oxygen therapy for respiratory failure and others for post-extubation support. We therefore downgraded the quality of this evidence by two levels to low.

2. In-hospital mortality

Four studies with 1585 participants reported mortality. Time points were up to ICU discharge (Frat 2015; Maggiore 2014; Stephan 2015) and up to day 28 of hospital admission (Parke 2013a). We did not combine Stephan 2015 in the meta-analysis, as the comparison group (BiPAP) was not comparable with the other low-flow oxygen groups; we presented the data in Table 1; study authors reported no differences between oxygen delivery devices (P = 0.66). We included both comparison groups in Frat 2015 and halved data for the intervention group. When compared with low-flow oxygen, HFNC provided no significant benefit in terms of mortality (RR, M-H, random-effects 0.63, 95% CI 0.38 to 1.06; P = 0.08; RD -0.05, 95% CI -0.17 to 0.08; P value = 0.48; NNTB 1, 95% CI 1 (NNTB) to 12 (NNTH)).See Analysis 2.1. We downgraded the quality of this evidence by two levels to low; some studies had unclear risk of bias, and the effect estimate included participants requiring oxygen for different indications (i.e. for respiratory failure and for post-extubation support).

3. Adverse events

Study authors reported the following adverse events: incidence of nosocomial pneumonia (Frat 2015; Stephan 2015); visits to their general practitioner (GP) for respiratory complications up to day 28 (Parke 2013a); episodes of oxygen desaturation (Parke 2011); pneumothorax, and acute pseudo-obstruction (Stephan 2015); and cardiac dysrhythmia, septic shock, and cardiorespiratory arrest (Frat 2015). We could not combine data for nosocomial pneumonia, as the comparison groups were different, and meta-analysis was not possible because data were derived from single studies for all other adverse events. Subsequently, we graded the certainty of the evidence as low. Study authors reported no statistically significant differences between groups for each reported adverse event, except Parke 2011, which reported fewer episodes of oxygen desaturation in the HFNC group (P = 0.009). Parke 2013a did not provide P values for data; study authors reported the number of participants who had seen their GP since discharge for respiratory complications, and these data appeared comparable. We included in Table 2 data for each adverse event as reported by study authors.

Secondary outcomes

1. Duration in hours of any form of respiratory support (mechanical ventilation, NIPPV, HFNC, standard oxygen)

Parke 2013a reported duration of respiratory support, and study authors reported no differences in duration according to oxygen delivery device (P = 0.13). We included in Table 3 data as reported by study authors.

Stephan 2015 also reported duration of respiratory support. However, differences in method of use, with HFNC used continuously and BiPAP used for approximately one hour at four-hourly intervals, meant that inclusion of this information as outcome data was not feasible.

2. Length of stay in days (ICU and hospital)

Five studies with 1743 participants (Corley 2014; Frat 2015; Maggiore 2014; Parke 2013a; Stephan 2015) reported length of stay (LOS) in the ICU. Stephan 2015 reported LOS as median number of days; we included in Table 3 data as reported by study authors which show no differences between groups (P = 0.77). Frat 2015 reported LOS calculated at 90 days for both survivors and non-survivors, and for both face mask and NIPPV groups. In meta-analysis for Frat 2015, we included data for HFNC versus standard oxygen therapy (face mask) for survivors. We found no evidence of differences in LOS based on type of oxygen delivery device (mean difference (MD), inverse variance (IV) 0.15 days, 95% CI -0.03 to 0.34; P = 0.10; 770 participants). See Analysis 3.1. We used GRADE to assess the certainty of this evidence as low, as analysis included studies with participants requiring respiratory support for different indications, and some included studies had unclear or high risk of bias.

Stephan 2015 reported hospital LOS as a median number of days; we included in Table 3 data as reported by study authors, which show no differences between groups (P = 0.59).

3. Respiratory effects

None of the included studies reported positive end-expiratory pressure measured at the pharyngeal level nor work of breathing.

Degree of atelectasis on radiological examination

Corley 2014 reported atelectasis at days one and five, and Parke 2013a at days one and three. Both studies reported no differences between groups on either day (Corley 2014 day 1, P = 0.70; day 5, P = 0.15; Parke 2013a day 1, P = 0.63; day 3, P = 0.69). See Table 3.

Oxygenation

Included studies reported oxygenation data as PaO_2/FiO_2 ratio, PaO_2, and SpO_2.

Five studies with 1340 participants reported PaO_2/FiO_2 within the first 24 hours of treatment (Corley 2014; Frat 2015; Maggiore 2014; Parke 2011; Stephan 2015). We reported in Table 4 data as reported by study authors for the BiPAP comparison (Stephan 2015). To avoid a unit of analysis issue, we included data from Frat 2015 only for the standard oxygen therapy comparison group.Meta-analysis demonstrated no differences between oxygen delivery devices (MD, IV, random-effects 7.31, 95% CI -23.69 to 41.31; P = 0.67; 510 participants). See Analysis 4.1. We used GRADE to downgrade the quality of this evidence to very low; we were concerned about the substantial level of statistical heterogeneity evident in this estimate (I^2 = 86%), as well as the very wide confidence interval and differences among study participants requiring respiratory support for different purposes.

Three studies with 355 participants reported PaO_2 within the first 24 hours of treatment (Frat 2015; Maggiore 2014; Parke 2011). We combined data, including results for the standard oxygen therapy comparison only in Frat 2015. Results of meta-analysis showed no differences between HFNC and low-flow oxygen therapies (MD, IV, random-effects 2.79, 95% CI -5.47 to 11.05; P = 0.51). See Analysis 4.2.

Four studies with 512 participants reported SpO_2 within the first 24 hours of treatment (Maggiore 2014; Parke 2011; Parke 2013a; Rittayamai 2014), with no differences between oxygen delivery devices (MD, IV, random-effects 0.72, 95% CI -0.73 to 2.17; P = 0.33). See Analysis 4.3.

Two studies with 445 participants also reported SpO_2 at more than 24 hours of treatment (Maggiore 2014; Parke 2013a); although favouring use of HFNC, this result did not show clinically important differences in oxygen saturation according to oxygen delivery device (MD, IV, random-effects 1.28, 95% CI 0.02 to 2.55; P = 0.05). See Analysis 4.4.

Maggiore 2014 provided single study data for other longer-term oxygenation effects (PaO_2/FiO_2 and PaO_2). Study authors reported PaO_2/FiO_2 at 36 hours and 48 hours, both with a higher ratio in the HFNC group (P = 0.0003 and P = 0.01, respectively), as well as higher values for PaO_2 in the HFNC group (P = 0.04). See Table 3.

Carbon dioxide clearance

Four studies (Frat 2015; Parke 2011; Parke 2013a; Stephan 2015) reported carbon dioxide clearance ($PaCO_2$). We included data for the BiPAP comparison group (Stephan 2015) in Table 4. We included data from the standard oxygen therapy comparison in Frat 2015. Pooled data analysis revealed no differences in carbon dioxide clearance between groups (MD IV, random-effects -0.75, 95% CI -2.04 to -0.55; 590 participants). See Analysis 5.1.

Respiratory rate

Nine studies (Chanques 2013; Corley 2014; Frat 2015; Lemiale 2015, Maggiore 2014; Parke 2011; Parke 2013a; Rittayamai 2014; Stephan 2015), which included 1646 participants, reported short-term changes in respiratory rate up to 24 hours after commencement of treatment. We did not include study data for Lemiale 2015, which reported data as median values; we included in Table 3 data as reported by study authors. Meta-analysis of the six studies comparing low-flow oxygen (with data for the standard oxygen therapy comparison group in Frat 2015) (Corley 2014; Frat 2015; Maggiore 2014; Parke 2011; Parke 2013a; Rittayamai 2014) demonstrated no differences in respiratory rates between groups (MD, IV, random-effects -1.51, 95% CI -3.36 to 0.35; P = 0.11; 867 participants). See Analysis 6.1. Meta-analysis of the two studies comparing CPAP and BiPAP (Chanques 2013; Stephan 2015) revealed a difference, with an improved respiratory rate in the HFNC group, but this was not clinically important (MD, IV, random-effects -0.89, 95% CI -1.74 to -0.05; 834 participants).

Two studies (Maggiore 2014; Parke 2013a) examined longer-term changes in respiratory rate among 445 participants, with no differences between oxygen delivery devices (MD, IV, random-effects -2.71, 95% CI -7.12 to 1.70; P = 0.23). See Analysis 6.2.

4. Patient-reported outcomes

Dyspnoea

Six studies with 1431 participants reported patient dyspnoea (Corley 2014; Frat 2015; Lemiale 2015; Rittayamai 2014; Schwabbauer 2014; Stephan 2015). We could not perform a meta-analysis for this outcome, as studies had used different scales in reporting results.

Corley 2014 used a modified Borg scale (0 = no dyspnoea, 10 = maximal dyspnoea) and reported results for one hour and eight hours after intervention. Results at eight hours were statistically significant (P = 0.008), but study authors reported that this was not a clinically important difference. Frat 2015 used five categories for dyspnoea results (marked improvement, slight improvement, no change, slight deterioration, marked deterioration). Study authors reported improvement in the HFNC group, in which 19% of participants reported a marked improvement and 46% reported a slight improvement. In the standard oxygen group, percentages were 5% and 26%, respectively, and in the noninvasive ventilation group, percentages were 13% and 40%, respectively (P < 0.001). Among 17 participants, Rittayamai 2014 measured dyspnoea on a 0 to 10 scale, on which 0 = no dyspnoea and 10 = maximal dyspnoea. Study authors reported a higher dyspnoea score in the low-flow oxygen group (P = 0.04). Stephan 2015 used three categories for dyspnoea results (improvement, no improvement, and deterioration). Study authors reported no statistically significant differences between groups for each category. In the HFNC group, 58.6% of participants reported an improvement, 37.5% reported no improvement, and 4% reported deterioration; in the BiPAP group, percentages were 65.8%, 29.7%, and 4.5%, respectively. Lemiale 2015 used a scale of 0 to 10 (0 = absence of dyspnoea, 10 = worst possible dyspnoea) with no statistically significant differences between groups (median 3 (interquartile range 2 to 6) HFNC group; median 3 (interquartile range 5 to 9) low-flow group; P = 0.40).

We were unable to report data for Schwabbauer 2014, as study authors had not provided data from the first cross-over period.

Comfort

Seven studies with 1717 participants (Chanques 2013; Frat 2015; Lemiale 2015; Maggiore 2014; Parke 2013a; Rittayamai 2014; Stephan 2015) compared comfort or discomfort over the short term between HFNC and low-flow oxygen. Maggiore 2014 asked participants to rate their discomfort on a scale of 0 to 10, with 0 = no discomfort and 10 = maximal discomfort. Rittayamai 2014used a comfort scale on which 0 = maximal comfort and 10 = minimum comfort. Parke 2013a used a comfort scale on which 0 = no comfort and 10 = maximal comfort. Although the terminology of the scales differed between the three studies (Maggiore 2014; Parke 2013a; Rittayamai 2014), we were able to pool study data, as participants in Maggiore 2014 and Rittayamai 2014 essentially rated comfort on the same scale, and inverting mean scores for the data from Parke 2013a resulted in data on a comparable scale with Maggiore 2014 and Rittayamai 2014. In studies that reported different time points for measures of comfort, we selected the earliest time points (Maggiore 2014 at one hour; Parke 2013a at four hours; Rittayamai 2014 at 30 minutes). Meta-analysis of these three studies showed no differences in participants' level of comfort according to oxygen delivery device (MD, IV, random-effects 0.14, 95% CI -0.65 to 0.93; 462 participants). See Analysis 8.1. We used GRADE to assess the quality of this evidence as low, as analysis included studies with participants requiring respiratory support for different purposes, and some included studies had unclear or high risk of bias. We downgraded the quality of this evidence to moderate owing to heterogeneity and unclear risk of bias in two of the included studies; therefore, confidence in the effect estimates may change with further research.

Lemiale 2015 used a scale of 0 to 10 (0 = absence of discomfort, 10 = worst possible discomfort) with no statistically significant differences between groups measured at 120 minutes (P = 0.88). In Stephan 2015, participants rated their comfort on a five-point scale, which was categorised as 'poor', 'acceptable', or 'good'. Study authors reported no statistically significant differences between groups at one hour (P = 0.32). We included in Table 3 data as reported by study authors.

Two studies (Maggiore 2014; Parke 2013a) reported longer-term measures of patient comfort (i.e. after 24 hours), which demonstrated no improvement in comfort when HFNC were used (MD,

IV, random-effects -0.36, 95% CI -3.70 to 2.98; 445 participants). See Analysis 8.2. We downgraded the quality of this evidence to very low; there were only two studies with unclear risk of bias across some domains and a substantial level of statistical heterogeneity (I^2 = 97%), which we were unable to explain through subgroup analysis.

Mouth dryness

Maggiore 2014 reported data on subjective mouth dryness, with more participants in the low-flow oxygen group than in the HFNC group reporting mouth dryness (P = 0.016). We included in Table 3 data as reported by study authors.
Cuquemelle 2012 included mouth dryness as one a study outcome, but we were unable to obtain data from study authors for this outcome. Study authors reported no significant differences between groups in relation to mouth dryness.

Patient refusal to continue with treatment

Parke 2013a reported participants who were unable to continue with treatment owing to discomfort or excessive heat. Study authors reported 20 participants in the HFNC group and no participants in the low-flow oxygen group who were unable to continue with treatment. We also reported data in Table 2.

5. Cost comparison of treatment

None of the included studies reported this outcome.

Subgroup analysis

We performed subgroup analysis on our primary analysis for studies that included participants requiring oxygen therapy for respiratory failure and studies that included participants requiring oxygen therapy following extubation. Analysis showed no differences in treatment failure based on the reason for oxygen therapy (Chi^2 = 0.01, df = 1; P = 0.94; I^2 = 0%) and no differences in failure rates in both groups (respiratory failure: RR, MH, random-effects 0.79, 95% CI 0.56 to 1.11; and post extubation: RR, MH, random-effects 0.84; 95% CI 0.17 to 4.21). See Analysis 9.1.

Sensitivity analysis

Risk of bias

Among the studies included in our primary analyses of treatment failure and mortality (Analysis 1.1 and Analysis 2.1), we judged Frat 2015, Parke 2011, and Parke 2013a to have high risk of bias. We removed these studies from analyses and noted no changes in the significance of findings. Other studies that we judged to have unclear risk of selection bias had not reported data for these outcomes.

Effects model

We had selected a random-effects model for analysis of each outcome, as included studies were few. We re-calculated our primary analysis using a fixed-effect model. This altered the result to a statistically significant effect, with fewer treatment failures when HFNC was used (RR, MH, fixed-effect 0.77, 95% CI 0.60 to 0.98). However, data with a fixed-effect model should be interpreted cautiously, as there remain unexplained moderate levels of statistically heterogeneity (I^2 = 58%) and differences between included participants that would support use and interpretation of a random-effects model for this outcome.

DISCUSSION

Summary of main results

We identified eight randomized controlled trials (Corley 2014; Cuquemelle 2012; Frat 2015; Lemiale 2015; Maggiore 2014; Parke 2011; Parke 2013a; Stephan 2015) and three randomized cross-over trials (Chanques 2013; Rittayamai 2014; Schwabbauer 2014) comparing high-flow nasal cannulae (HFNC) with low-flow oxygen in participants admitted to the intensive care unit (ICU). Data comparing HFNC with continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) were very limited and were provided only in two studies (Chanques 2013 and Stephan 2015, respectively). These eight studies included a total of 1972 adult participants.
For primary outcomes of failure of treatment, mortality, and adverse events, low-quality evidence showed that no differences between HFNC and low-flow oxygen were evident. ICU length of stay did not differ between HFNC and low-flow oxygen groups, nor did the duration of any form of respiratory support. Atelectasis did not differ between HFNC and low-flow oxygen in two studies. Oxygenation, carbon dioxide clearance, and respiratory rate data were analysed as short-term effects (i.e. up to 24 hours after initiation of therapy) and as long-term effects (i.e. longer than 24 hours after initiation of therapy). Analysis showed no differences in oxygenation and carbon dioxide clearance between HFNC and low-flow oxygen over the short term; only two studies provided evidence that HFNC improved oxygenation saturation after 24 hours of use, but these differences were small and were not clinically important. Analysis showed no significant differences between HFNC and low-flow oxygen in short- or long-term effects on respiratory rate. In the only comparison in the review with CPAP and BiPAP; the difference in short-term effects of these

therapies on respiratory rate was small and was not clinically important, nor could it be interpreted with any certainty owing to the very small sample size.

In terms of patient-reported outcomes, six studies had reported dyspnoea but on scales that were not compatible and could not be combined. Authors of three studies reported statistically significant improvement in dyspnoea for participants using HFNC. Patient comfort data were analysed and showed no differences between HFNC and low-flow oxygen. One study provided data for short-term and long-term patient-reported mouth dryness, which was significantly less with HFNC than with low-flow oxygen. One study reported that participants randomized to low-flow oxygen were more likely than those randomized to HFNC to continue with their treatment owing to reports of discomfort caused by excessive heat.

Study authors reported no data for positive end-expiratory pressure measured at the pharyngeal level; work of breathing; or cost comparison of treatment.

Overall completeness and applicability of evidence

We identified 11 trials of HFNC in adult participants in the ICU. Six trials included participants who required oxygen therapy for respiratory failure, and five included participants who required oxygen therapy post extubation. Data for this review were therefore applicable to these two indications. Studies included data on most outcomes of interest for this review, although studies addressing each outcome were often few, or did not report data comparably and could not be combined in a meta-analysis. This also limited the potential for subgroup analyses, which could have explored heterogeneity between studies.

Quality of the evidence

The included studies enrolled small numbers of participants; four studies each included no more than 30 participants. Whether they were adequately powered to detect differences between groups was uncertain, especially the smaller studies. Indeed, two studies (Cuquemelle 2012; Parke 2011) stated that they were not sufficiently powered to detect differences between groups for the primary review outcome of failure of treatment. We used GRADE to assess the quality of the evidence for seven of our outcomes. Not all studies had adequately described methods of randomization or allocation concealment, and blinding of outcome assessment was inconsistent between studies. Differences between study participants in indications for oxygen therapy may have influenced the results as well. Few studies were available for each of our outcomes. We were not able to explain substantial levels of statistical heterogeneity for some results. We considered each of these factors and graded evidence of most outcomes as low or very low quality.

This GRADE assessment meant that we were not certain of the effect estimates that we had presented for each outcome.

Potential biases in the review process

Through adhering to the processes set out in the review protocol, the review authors believe that the review was conducted in a way that minimized bias in the review process. Review methods used were set a priori, which is a robust way of ensuring transparency and reproducibility. Study selection, data extraction, and risk of bias assessment were conducted independently by two review authors, who achieved complete agreement without contention. Two review authors (AC and JF) have declared potential conflicts of interest due to a prior relationship with manufacturers of the HFNC system (see Declarations of interest) but believe that these relationships did not affect their ability to impartially conduct this review.

We identified two studies for which we were able to obtain only abstracts. We reran the search in December 2016 and identified four studies of potential interest. This review did not include data from these studies, and we will incorporate these data during the formal review update.

Agreements and disagreements with other studies or reviews

Most of the evidence around HFNC use is derived from observational studies, and this is the first systematic review and meta-analysis that limits included studies to randomized or quasi-randomized controlled trials. Kernick 2010 performed the first systematic review of the literature on adult participants, which included eight studies, but the review authors were unable to perform a meta-analysis owing to the paucity of data. Nevertheless, review authors found preliminary evidence to support the use of HFNC for improving oxygenation among adults in intensive care.

Since that time, several comprehensive literature reviews (El-Khatib 2012; Gotera 2013; Lee 2013; Ricard 2012; Scala 2014; Ward 2013) have examined available evidence. These concluded that HFNC has a place in providing respiratory support for patients with hypoxic respiratory failure by improving short-term respiratory parameters such as oxygenation, respiratory rate, and positive airway pressure. These review authors noted some support for HFNC use among patients with hypoxic respiratory failure but concluded that its role in providing respiratory support for patients with other aetiologies has yet to be determined. Through our review, we were not able to establish any certainties about HFNC use, particularly for those who require respiratory support for respiratory failure or post extubation.

AUTHORS' CONCLUSIONS

Implications for practice

We found insufficient evidence to determine effects of HFNC in the delivery of respiratory support to adult intensive care patients. In addition, the included trials have some potentially problematic limitations, particularly in the area of lack of blinding of outcome assessors or limited detail on study methods for adequate assessment of bias.

Implications for research

The small number of studies included in this review highlights the need for further research. This is an emerging field of interest, and larger-scale randomized controlled trials conducted to address clinically important outcomes are currently under way (see Characteristics of ongoing studies). Further research should help to clarify the level of safety and efficacy of HFNC in providing respiratory support for adult ICU patients.

Upcoming trials must be of sufficient size and must be methodologically rigorous; they should place particular emphasis on determining the role of HFNC in respiratory failure of different aetiologies and on comparing use of HFNC versus other forms of respiratory support such as non-invasive ventilation, while focusing more on clinically important long-term outcome measures such as impact on invasive and non-invasive ventilation rates and mortality, rather than on surrogate outcomes. Trials should examine rates and severities of adverse events associated with HFNC use. In addition, the introduction of new therapies requires effective economic evaluations to determine their economic cost or benefit. As no current evidence confirms detriment or harm associated with HFNC, continued investigation appears warranted.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chanques 2013

Methods	Randomized cross-over study, single-centre study
Participants	Total number of participants = 10 Setting: medical-surgical ICU; Montpelier, France Inclusion criteria: ≥ 18 years old hospitalized in a medical-surgical ICU, planned for tracheostomy tube removal which was placed in the ICU for weaning from mechanical ventilation Exclusion criteria: pregnancy, adult under tutelage, contraindications for NIV Baseline characteristics (all patients) Age: 54 to 66 years Respiratory rate (breaths/min) median (25th-75th percentiles): 18 (22 to 20) $PaCO_2$: not reported PaO_2/FiO_2: not reported
Interventions	1. High-flow face mask with a reservoir bag 2. Optiflow high-flow nasal cannulae 3. Boussignac oxygen therapy system Flow rates of 15, 30, and 45 litres per minute were tested in a randomized order for each device. For each device and flow rate, participants were asked to have their mouth open and mouth closed in a randomized order. Each device was used for 5 minutes, with 15-minute washout between treatments
Outcomes	Tracheal pressure, FiO_2 delivered, respiratory discomfort, respiratory rate (at end of each treatment period), noise intensity
Notes	Funding sources/declarations of interest: Study authors disclose funding of EURO3000 from Fisher & Paykel Healthcare, France, which was used to acquire technical equipment and clinical research insurance, and to present results at scientific meetings Study dates: not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomization not stated
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants and personnel to treatment allocation

Chanques 2013 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were outcome assessors for respiratory and auditory discomfort on a standardized scale. Investigators were outcome assessors for other outcomes, but standardized tools were used for measurement, reducing risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One participant was excluded owing to major intolerance to the device but possibly should have been regarded as a treatment failure. In such a small study, this is likely to have had an effect Owing to inability of 4 participants in the Boussignac group to adhere to the protocol, it is likely that data are incomplete; however it is not mentioned how this was handled in the analysis
Selective reporting (reporting bias)	Unclear risk	ISRCTN15995925. Retrospectively registered in August 2012. Not possible to establish any reporting bias through comparison with the trial register protocol
Other bias	Unclear risk	Fifteen-minute washout between devices but no mention of respiratory support received by the participant during this period. No washout period between changes in flow rate, so carry-over effect may skew data Funding from manufacturer: paper does not state whether manufacturer was involved in study design or management

Corley 2014

Methods	Randomized controlled trial, single-centre study
Participants	Total number of participants = 155 Setting: ICU; Brisbane, Australia Inclusion criteria: ≥ 18 years, BMI ≥ 30 kg/m^2, scheduled to undergo cardiac surgery on cardiopulmonary bypass Exclusion criteria: ventilation time > 36 hours, extubation onto NIPPV, requirement for tracheostomy, extubation as part of end-of-life treatment Baseline characteristics 1. HFNC Age mean (SD): 63 (± 11.4) years Respiratory rate (breaths/min): not reported $PaCO_2$: not reported

Corley 2014 (*Continued*)

	PaO_2/FiO_2: not reported 2. Standard oxygen therapy Age mean (SD): 65 (± 11.1) years Respiratory rate (breaths/min): not reported $PaCO_2$: not reported PaO_2/FiO_2: not reported
Interventions	1. HFNC (Optiflow; Fisher & Paykel Healthcare); n = 81 Humidifed to 37°C, flow rate commenced at 35 L/min, then titrated to a maximum of 50 L/min; FiO_2 titrated to maintain $SpO_2 \geq 95\%$ for 8 hours, with short breaks for nasal care or mobilisation 2. Standard oxygen therapy; n = 74 Oxygen delivered at 2 to 4 L/min via nasal cannulae or 6 L/min via simple face mask titrated to maintain $SpO_2 \geq 95\%$ Both applied after extubation
Outcomes	Atelectasis on chest X-ray, oxygenation, respiratory rate, subjective dyspnoea, failure of allocated treatment
Notes	Funding/declarations of interest: unrestricted grant from Fisher & Paykel Healthcare; two study authors received travel and accommodation support from Fisher & Paykel Healthcare; manufacturer had no part in study design, data collection, data analysis, or creation of the manuscript Study dates: February 2011 to March 2012

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised random numbers table in blocks of 8
Allocation concealment (selection bias)	Low risk	Use of numbered, opaque envelopes to maintain allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants and personnel but unlikely to influence performance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome assessment (atelectasis) blinded, but other outcome assessment not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses
Selective reporting (reporting bias)	Low risk	ACTRN12610000942055. Prospective trial registration. All outcomes reported as stated in trial registry

Corley 2014 (*Continued*)

Other bias	Low risk	Baseline characteristics largely comparable. Funding provided by manufacturer, who was not involved in study design and management

Cuquemelle 2012

Methods	Parallel randomized controlled trial (for 24 hours) with a final cross-over period (for 4 hours); single-centre study
Participants	Total number of participants = 30 Setting: medical ICU; Paris, France Inclusion criteria: acute hypoxaemic respiratory failure requiring at least 4 L/min oxygen to maintain SpO_2 above 95% Exclusion criteria: use of NIV or invasive mechanical ventilation; presence of delirium that impaired the ability of the participant to rate dryness; preference for 1 of the 2 oxygen delivery systems Baseline characteristics Age: 39 to 77 years Respiratory rate (breaths/min): not reported $PaCO_2$: not reported PaO_2/FiO_2: not reported
Interventions	1. HFNC Optiflow; Fisher & Paykel Healthcare; humidified to 37°C, flow rate at 40 L/min 2. Standard oxygen therapy Use of a flow meter from wall oxygen without humidification Randomized to receive therapy during first 24 hours, then crossed-over to alternative therapy for 4 hours to reduce drop-outs
Outcomes	Nasal airway calibre was measured by acoustic rhinometry at baseline, after 4 and 24 hours, and 4 hours after cross-over. Dryness of the nose, mouth, and throat was auto-evaluated and was assessed blindly by an otorhinolaryngologist. After cross-over, participants were asked which system they preferred
Notes	Funding/declarations of interest: relationship with Fisher & Paykel Healthcare disclosed, but manufacturers had no part in the study Study dates: not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated in the paper
Allocation concealment (selection bias)	Unclear risk	Not stated in the paper

Cuquemelle 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants to treatment allocation but unlikely to affect outcome. No mention of blinding of personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were outcome assessors for dryness scores - unblinded but unlikely to affect the result
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 37 participants randomized, 7 were excluded from analysis, as they were unable to complete the study (5 owing to deterioration and 2 because of rapid improvement in respiratory status)
Selective reporting (reporting bias)	Unclear risk	Trial registration not reported in the paper. Unable to establish whether outcomes were reported according to prepublished protocol or trial registration documents
Other bias	High risk	Although they did not reach statistical significance, potentially clinically important differences in baseline characteristics were noted. Specifically, participants in the intervention group were older and had higher rates of infectious pneumonia. Reasons for exclusion potentially related to treatment

Frat 2015

Methods	Randomized controlled trial, multi-centre 23 ICUs
Participants	Total number of participants = 313 Setting: ICUs; France and Belgium Inclusion criteria: consecutive patients, aged ≥ 18 years, respiratory rate > 25 breaths per minute, $PaO_2/FiO_2 \leq 300$ mmHg while patient was breathing oxygen at flow rate ≥ 10 L/min for at least 15 minutes, $PaCO_2$ not higher than 45 mmHg, absence of clinical history of underlying chronic respiratory failure Exclusion criteria: $PaCO_2 > 45$ mmHg, exacerbation of asthma or chronic respiratory failure, cardiogenic pulmonary oedema, severe neutropenia, haemodynamic instability, use of vasopressors, GCS ≤ 12, contraindications to NIV, urgent need for tracheal intubation, a do-not-resuscitate order, or decision to not participate Baseline characteristics 1. HFNC Age mean (SD): 61 (± 16) years Respiratory rate (breaths/min) mean (SD): 33 (± 6) $PaCO_2$ (mmHg) mean (SD): 36 (± 6) PaO_2/FiO_2(mmHg) mean (SD): 157 (± 89)

Frat 2015 (*Continued*)

	2. Standard oxygen Age mean (SD): 59 (± 17) years Respiratory rate (breaths/min) mean (SD): 32 (± 6) $PaCO_2$ (mmHg) mean (SD): 35 (± 5) PaO_2/FiO_2 (mmHg) mean (SD): 161 (± 73) 3. Non-invasive ventilation Age mean (SD): 61 (± 17) years Respiratory rate (breaths/min) mean (SD): 33 (± 7) $PaCO_2$ (mmHg) mean (SD): 34 (± 6) PaO_2/FiO_2 (mmHg) mean (SD): 149 (± 72)
Interventions	1. HFNC; n = 106 Oxygen passed through heated humidifier, applied continuously through large-bore nasal prongs; gas flow rate 50 L/min, FiO_2 1.0 at initiation (Optiflow); adjusted to maintain $SpO_2 \geq 92\%$; for at least 2 calendar days, then this could be stopped or participant switched to standard oxygen therapy 2. Standard-oxygen; n = 94 Continously through nonrebreather face mask; flow rate ≥ 10L/min; adjusted to maintain $SpO_2 \geq 92\%$; until participant recovered or was intubated 3. Non-invasive ventilation; n = 110 Through a face mask connected to an ICU ventilator with pressure support applied in NIV mode; adjusted to obtain expired tidal volume of 7 to 10 mL/kg of predicted body weight, with initial PEEP between 2 and 10 cm of water; adjusted to maintain $SpO_2 \geq 92\%$; minimum of 8 hours per day for at least 2 calendar days; applied during sessions of at least 1 hour, could be resumed if respiratory rate > 25 breaths per minute or SpO_2 less than 92%; between noninvasive-ventilation sessions, participants received high-flow oxygen
Outcomes	Participants requiring endotracheal intubation within 28 days of randomization, mortality in ICU, mortality at 90 days, number of ventilator-free days between day 1 and day 28, duration of ICU stay, complications during ICU stay, dyspnoea, comfort
Notes	Funding/declarations of interest: equipment provided by Fisher & Paykel Healthcare, but manufacturer had no involvement in the study Study dates: February 2011 to April 2013

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of centralized Web-based management system, blocks of 6, stratified by centre and history or no history of cardiac insufficiency
Allocation concealment (selection bias)	Unclear risk	No details

Frat 2015 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lack of blinding unlikely to affect performance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 losses (2 in standard oxygen group and 1 in NIV group) due to withdrawal of consent. Small number of losses unlikely to influence outcome data
Selective reporting (reporting bias)	Low risk	NCT01320384. Study prospectively registered. Outcomes reported as stated in protocol with some data reported in supplementary index
Other bias	High risk	Participants in NIV monitoring group given HFNC between ventilation sessions Unequal numbers of participants in each group, not explained, but baseline characteristics comparable Equipment provided by manufacturer, but no involvement in study design and management

Lemiale 2015

Methods	Randomized controlled trial, multi-centre 4 ICUs
Participants	Total number of participants = 102 Setting: ICUs; France Inclusion criteria: consecutive immunocompromised patients admitted to ICU for acute respiratory failure, aged > 18 years Exclusion criteria: hypercapnia (> 45 mmHg), mechanical ventilation before ICU admission, need for immediate NIV or invasive mechanical ventilation, and patient refusal to participate in study Baseline characteristics 1. HFNC: Age median (25th to 75th percentile): 59.3 (43 to 70) years Respiratory rate (breaths/min) median (25th to 75th percentile): 26 (21.7 to 31.2) $PaCO_2$: not reported PaO_2/FiO_2 mmHg: median (25th to 75th percentile): 128 (48 to 178) 2. Venturi mask Age median (25th to 75th percentile): 64.5 (53.25 to 72) years Respiratory rate (breaths/min) median (25th to 75th percentile): 27 (22 to 32.2)

Lemiale 2015 (*Continued*)

	$PaCO_2$: not reported PaO_2/FiO_2 mmHg median (25th to 75th percentile): 100 (40 to 156)
Interventions	Participants were randomly allocated to oxygen therapy groups for a 2-hour period 1. HFNC; n = 52 Heated, humidified circuit, with initial flow of 40 to 50 L/min; FiO_2 100%, which was then adjusted to maintain $SpO_2 \geq 95\%$ 2. Venturi mask; n = 48 FiO_2 initially 60%, 15 L/min, then adjusted to maintain $SpO_2 \geq 95\%$
Outcomes	Need for invasive mechanical ventilation or NIV during or at the end of the 2-hour study period; VAS scores for comfort, thirst, and dyspnoea (all at 120 minutes); respiratory rate (at 120 minutes); heart rate
Notes	Funding/declarations of interest: Fisher & Paykel Healthcare provided oxygen delivery devices and funds for study insurance and presentation of results. The sponsors had no role in designing or conducting the study Study dates: November 2012 to April 2014

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients described as randomly allocated, with stratification on study centre by permuted block method
Allocation concealment (selection bias)	Low risk	Use of opaque, sealed envelopes to ensure identity concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lack of blinding unlikely to influence performance for review outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of two participants after randomization due to withdrawal of consent. Low number, unlikely to influence results
Selective reporting (reporting bias)	Unclear risk	NCT02424773. Retrospective registration in April 2015. Therefore not feasible to judge if any reporting bias. All outcomes reported from methods section

Lemiale 2015 (*Continued*)

Other bias	Low risk	Some funding supplied by manufacturer but no involvement in study design or management Some differences in baseline characteristics but not clinically significant

Maggiore 2014

Methods	Randomized controlled trial, multi-centre study 2 ICUs
Participants	Total number of participants = 105 Setting: ICUs; Rome and Novara, Italy Inclusion criteria: patients who were mechanically ventilated for longer than 24 hours, passed a spontaneous breathing trial, PaO_2/FiO_2 ratio < 300 at the end of the trial Exclusion criteria: tracheostomy, age < 18 years, pregnancy, anticipated need for non-invasive ventilation after extubation Baseline characteristics 1. HFNC Age mean (SD): 65 (± 18) years Respiratory rate (breaths/min) mean (SD): 23 (± 5) $PaCO_2$ mmHg mean (SD): 34.7 (± 7.6) PaO_2/FiO_2mmHg mean (SD): 239.4 (± 42.4) 2. Venturi mask Age mean (SD): 64 (± 17) years Respiratory rate (breaths/min) mean (SD): 23 (6) $PaCO_2$ mmHg mean (SD): 36 (± 7.1) PaO_2/FiO_2 mmHg mean (SD): 241.7 (± 51.1)
Interventions	1. HFNC; n = 53 50 L/min 2. Venturi mask; n = 52 Both used after extubation. FiO_2 was set to obtain SpO_2 92% to 98% (88% to 95% in chronic obstructive pulmonary disease). Applied for 48 hours or until ICU discharge
Outcomes	Arterial blood gas, SaO_2, FiO_2, PaO_2/FiO_2 ratio, respiratory rate, mean arterial pressure, heart rate, and discomfort (recorded at 1, 3, 6, 12, 24, 36, and 48 hours). Adverse events (displacement of oxygenation device, oxygen desaturation post extubation requiring NIV or endotracheal intubation). Length of stay and mortality
Notes	Funding/declarations of interest: supported by an unrestricted research grant from Fisher & Paykel Healthcare and by an independent research grant Study dates: November 2010 to April 2011 3 secondary references to this study (conference reports)

Risk of bias		***Risk of bias***

Maggiore 2014 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A unique random number sequence that was computer generated
Allocation concealment (selection bias)	Unclear risk	Participants were randomly assigned, using a block size of 30, to Optiflow or Venturi mask in a blinded fashion with opaque envelopes - no specific mention as to whether the envelopes were consecutively numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel not possible but unlikely to affect outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Database monitored by independent third parties, analysis performed as agreed before commencement of the study However, assumed that outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Low risk	NCT01575353. Retrospectively registered in December 2010 (but only shortly before start of recruitment). All outcomes reported as stated in protocol. Length of stay and mortality rates reported but not previously stated in protocol
Other bias	Unclear risk	Multiple interim analyses performed (3 abstracts presented from same study) Unrestricted grant from manufacturer. Does not state whether manufacturer was involved in study design and management

Parke 2011

Methods	Randomized controlled trial, single-centre study
Participants	Total number of participants = 56 Setting: cardiothoracic and vascular ICU; Auckland, New Zealand Inclusion criteria: Patients in a cardiothoracic and vascular ICU with mild to moderate hypoxaemic respiratory failure defined by study authors as follows: receiving $\geq$ 4 L/min of oxygen via nasal cannula for longer than 4 hours and/or respiratory rate $\geq$ 25 breaths per minute and/or increased work of breathing, evidenced by clinical signs such

	as dyspnoea, in-drawing, accessory muscle use, and diaphoresis; or receiving ≥ 6 L/min of oxygen via face mask for longer than 2 hours, or respiratory rate ≥ 25 breaths per minute, or both, or increased work of breathing, as evidenced by clinical signs such as dyspnoea, in-drawing, accessory-muscle use, and diaphoresis, or both Exclusion criteria: patients requiring imminent mechanical ventilation and those under orders to not receive mechanical ventilation Baseline characteristics 1. HFNC Age mean (range): 64 (39 to 83) years Respiratory rate (breaths/min) mean (SD): 21 (± 7) $PaCO_2$ mmHg mean (SD): 43 (± 7) PaO_2/FiO_2: not reported 2. Standard oxygen therapy Age mean (range): 64 (26 to 85) years Respiratory rate (breaths/min) mean (SD): 18 (± 8) $PaCO_2$ mmHg mean (SD): 42 (± 7) PaO_2/FiO_2: not reported
Interventions	1. HFNC; n = 29 Optiflow, Fisher & Paykel Healthcare, with MR880 humidifier, RT241 heated delivery tube, and RT033 large/RT034 small, wide-bore nasal cannula; therapy commenced at an initial flow of 35 L/min; flow and FiO_2 titrated to SpO_2 or SaO_2 of 95%. Duration of oxygen therapy not reported 2. Standard oxygen therapy; n = 27 HFFM (standard face mask, MR850 humidifier, RT308 heated delivery tube and air entrainer, Fisher & Paykel Healthcare) with an aerosol mask (HudsonRCI, TFX Medical, High Wycombe, UK); flow rate ≤ 15 L/min; humidified oxygen delivered at 31°C and 32 mg H_2O/L; titrated to an SpO_2 or SaO_2 95%. Duration of oxygen therapy not reported
Outcomes	Assessment score, arterial blood gas values, SpO_2, respiratory rate, and heart rate at baseline, 30 minutes, 1 hour, 2 hours, and 4 hours after randomization, then as per unit protocol. Continuous SpO_2 data and instances of desaturation (SpO_2 93% for longer than 5 seconds) were collected. Episodes were discounted if the SpO_2 trace indicated signal interference or signal loss. Allocated therapy was considered successful if participants were maintained on or were weaned from their assigned oxygen therapy within 24 hours of enrolment. Failure of therapy was defined as worsening respiratory failure that required a change in the respiratory support device within 24 hours of study enrolment
Notes	Funding/declarations of interest: Fisher & Paykel Healthcare consulted regarding study design and data analysis, and paid for statistical analysis Study dates: not reported Note: some additional outcome data retrieved through email contact with study authors

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Parke 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Opaque sealed envelopes but no mention of whether numbered or not
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants or personnel to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of 60 enrolled in the study, 4 participants (1 from the HFNC group, and 3 from the HFFM group) were excluded: 2 refused consent for all data collection, and 2 failed the screening. Five of 27 participants in the high-flow face mask group were switched to nasal high flow - no mention of how these data were treated
Selective reporting (reporting bias)	High risk	ACTRN012606000139572. Prospective registration in April 2006. Reported additional outcomes that were not stated in trial registration records (outcomes in protocol were arterial blood gas, heart rate, blood pressure, and respiratory rate)
Other bias	High risk	Underpowered for outcome of failure of treatment. Risk of bias introduced with involvement of manufacturer in study design and analysis

Parke 2013a

Methods	Randomized controlled trial, single-centre study
Participants	Total number of participants = 340 Setting: ICU; Auckland, New Zealand Inclusion criteria: All patients undergoing elective cardiac surgery utilizing cardiopulmonary bypass were eligible for inclusion in this study if aged ≥ 18 years and undergoing surgery involving full median sternotomy Exclusion criteria: contraindication to HFNC, e.g. presence of a nasal septal defect, and previous recruitment Baseline characteristics 1. HFNC

Parke 2013a (*Continued*)

	Age median (range): 65 (19 to 88) years Respiratory rate (breaths/min) mean (SD): 16.6 (± 1.9) $PaCO_2$: not reported PaO_2/FiO_2: not reported 2. Simple face mask Age median (range): 66 (21 - 87) years Respiratory rate (breaths/min) mean (SD): 16.5 (± 1.7) $PaCO_2$: not reported PaO_2/FiO_2: not reported
Interventions	1. HFNC; n = 169 Optiflow system; flow rate 45 L/min 2. Simple face mask; n = 171 Oxygen at 2 to 4 L/min via simple face mask or nasal prongs; FiO_2 in both groups was titrated to maintain SpO_2 > 93% Oxygen therapy started after extubation. Duration of therapy not reported
Outcomes	Primary outcome: number of participants with SpO_2/FiO_2 ratio ≥ 445 on day 3 after cardiac surgery Secondary outcomes: atelectasis score of chest X-rays, spirometry, re-admission to ICU for respiratory causes, ICU and hospital length of stay, mortality, incidence of respiratory complications on day 28, respiratory rate, oxygenation, use of adjunctive respiratory support therapies, escalation of respiratory support, adverse events, patient comfort
Notes	Funding/declarations of interest: Study authors declared that research was supported by an unrestricted grant from Fisher & Paykel Healthcare, but that the sponsors had no part in the study design and no access to trial data Study dates: not reported, Conducted over a 14-month period Note: some additional outcome data retrieved through email contact with study authors

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers in blocks of 12
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque envelopes prepared by non-study staff
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants or personnel to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors for atelectasis scoring blinded to treatment allocation

Parke 2013a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition fully reported. Small number of losses
Selective reporting (reporting bias)	High risk	ACTRN12610000973011. Prospective registration in November 2010. Reported additional outcomes that were not stated in trial registration records (outcomes in protocol were SpO_2/FiO_2 ratio, atelectasis, spirometry, adjunctive respiratory support therapies, mortality, respiratory complications in hospital and that required visit to general practitioner in 28 days, patient comfort)
Other bias	Low risk	Fisher & Paykel Healthcare provided consumables for intervention arm but had no part in study design, conduct, analysis, reporting, or publication

Rittayamai 2014

Methods	Randomized cross-over study, single-centre study
Participants	Total number of participants = 17 Setting: respiratory ICU; Bangkok, Thailand Inclusion criteria: mechanically ventilated patients who were 18 years of age, successfully weaned by spontaneous breathing, trial with oxygen T-piece or low level of pressure support for 120 minutes, and ready for endotracheal extubation Exclusion criteria: haemodynamic instability or decreased level of consciousness; patients who lacked cooperation, tracheostomized patients, and pregnant women Baseline characteristics Age mean (SD): 66.8 (± 13.8) years Respiratory rate (breaths/min) mean (SD): recorded before each cross-over period: baseline 1: 20.3 (± 4.5); baseline 2: 21.7 (± 3.8) $PaCO_2$: not reported PaO_2/FiO_2: not reported
Interventions	After endotracheal extubation, participants were randomized into either: 1. HFNC Optiflow system, Fisher & Paykel Healthcare; initial inspiratory flow of 35 L/min, and FiO_2 adjusted to achieve $SpO_2 \geq 94\%$ within the first 5 minutes and to maintain this setting for 30 minutes 2. Non-rebreather face mask 6 to 10 L/min to achieve SpO_2 94% for another 30 minutes
Outcomes	Dyspnoea, patient comfort, breathing frequency, heart rate blood pressure, SpO_2

Rittayamai 2014 (*Continued*)

Notes	Funding/declarations of interest: Study authors did not report funding sources. They disclosed no conflicts of interest Study dates: August to December 2011

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Methods used to generate group allocation not stated
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants or study staff owing to nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to blind outcome assessors owing to nature of the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement of how many reported. No participant numbers in tables or graphs
Selective reporting (reporting bias)	Unclear risk	Trial registration not reported in paper. Unable to establish whether outcomes were reported according to pre-published protocol or trial registration documents SpO_2 and mean arterial pressure not reported for all time points set out in methods
Other bias	Low risk	No washout period between treatments, but not a relevant risk of bias for our review methods. No other sources of bias identified

Schwabbauer 2014

Methods	Randomized cross-over study
Participants	Total number of participants = 14 Setting: medical ICU; Germany Inclusion criteria: patients with hypoxic respiratory failure (PaO_2 < 55 mmHg under room air) Exclusion criteria: ventilatory failure, haemodynamic instability, cardiogenic pulmonary oedema, non-invasive ventilation contraindications, inability to co-operate

Schwabbauer 2014 (*Continued*)

	Baseline characteristics (recorded before each cross-over period) Age mean: 55.9 years Respiratory rate (breaths/min) mean (SD): baseline 1: 28 (± 9); baseline 2: 28 (± 9); baseline 3: 26 (± 7) $PaCO_2$ mean (SD): baseline 1: 36 (± 5); baseline 2: 38 (± 5); baseline 3: 37 (± 5) PaO_2/FiO_2: not reported
Interventions	Participants were treated in randomized order for 30 minutes 1. HFNC Optiflow system, Fisher & Paykel Healthcare; oxygen flow 55 L/min; FiO_2 0.6, using active respiratory gas humidifier 2. Venturi mask Oxygen flow 15 L/min; FiO_2 0.6 3. Non-invasive ventilation Intensive care ventilators in pressure support mode; PEEP set to 5 cm H_2O; pressure support above PEEP adjusted individually to achieve tidal volume of 6 to 8 mL/kg ideal body weight; FiO_2 0.6 Each treatment phase was preceded by a 15-minute baseline phase during which participants received oxygen via a standard nasal prong (oxygen flow 4 to 12 L/min, SaO_2 goal ≥ 88%)
Outcomes	PaO_2, respiratory rate, dyspnoea (Borg scale), discomfort (10-point scale), $PaCO_2$, heart rate, blood pressure, SpO_2, global rating, patient preference
Notes	Funding/declarations of interest: Fisher & Paykel Healthcare provided 2 Optiflow devices at no charge for the study. Investigators received no financial support and manufacturer had no part in study design, conduct, analysis, reporting, or publication Study dates: March 2009 to March 2011

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Order of experimental protocol was randomly assigned, and assignments of participants to the sequence of the 3 oxygen applicators was randomized. However, no details on how this randomization was conducted
Allocation concealment (selection bias)	Unclear risk	No detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants to treatment allocation. No mention of blinding of personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding of outcome assessors.

Schwabbauer 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses. Treatment stopped early in 3 participants in the NIV group, but data still collected
Selective reporting (reporting bias)	Unclear risk	DRKS00005132. Retrospectively registered with German clinical trials register in July 2013. Not feasible to assess presence of any risk of selective reporting bias
Other bias	Low risk	Funding from manufacturer, which had no involvement in study design and management

Stephan 2015

Methods	Randomized controlled trial, multi-centre study 6 ICUs
Participants	Total number of participants = 830 *Setting*: ICUs; France Inclusion criteria: patients who had undergone cardiothoracic surgery and had failed a spontaneous breathing trial, or had preexisting risk factors for post extubation acute respiratory failure, or had failed extubation Exclusion criteria: obstructive sleep apnoea, tracheostomy, do-not-intubate status, delirium, nausea and vomiting, bradypnoea, impaired consciousness, haemodynamic instability Baseline characteristics 1. HFNC Age mean (95% CI): 63.8 (62.5 to 65.2) years Respiratory rate (breaths/min) mean (95% CI): 22.8 (22.1 to 23.5) $PaCO_2$ mmHg mean (95% CI): 38.7 (38.1 to 39.4): PaO_2/FiO_2 mmHg mean (95% CI): 196 (187 to 204) 2. BiPAP Age mean (95% CI): 63.9 (62.6 to 65.2) years Respiratory rate (breaths/min) mean (95% CI): 23.3 (22.6 to 24.0) $PaCO_2$ mmHg mean (95% CI): 39.1 (38.4 to 39.8) PaO_2/FiO_2 mmHg mean (95% CI): 203 (195 to 212)
Interventions	1. HFNC; n = 414 Optiflow system at initial flow rate of 50 L/min 2. BiPAP; n = 416 Pressure support started at 8 cm H_2O to achieve exhaled tidal volume of 8 mL/kg and respiratory rate < 25 breaths per minute, via full face mask and ventilatory specifically designed for BiPAP or ICU ventilator Initial FiO_2 in both groups was 50%, adjusted to maintain SaO_2 at 92% to 98% HFNC was delivered continuously. BiPAP was delivered for 2 hours initially, then for approximately 1 hour every 4 hours, or more if needed
Outcomes	Treatment failure (defined as reintubation for mechanical ventilation, switch to other study treatment, or premature study treatment discontinuation), respiratory variables, dyspnoea, comfort, skin breakdown, respiratory and extrapulmonary complications,

Stephan 2015 (*Continued*)

	number of bronchoscopies, mortality in ICU
Notes	Funding/declarations of interest: Study authors did not report any funding sources. They disclosed no conflicts of interest Study dates: June 2011 to January 2014 Respiratory variables and respiratory rate reported at baseline, 1 hour, and 6 to 12 hours. For meta-analysis in the review, data were taken at 6 to 12 hours

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence in blocks of 2 or 4
Allocation concealment (selection bias)	Unclear risk	Use of opaque envelopes but no further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind participants or personnel to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses
Selective reporting (reporting bias)	Low risk	NCT01458444. Study registered retrospectively in October 2011 (although early in study period). All relevant outcomes were reported as stated in protocol
Other bias	Low risk	No other sources of bias identified

BiPAP: bilevel positive airway pressure
BMI: body mass index
FiO_2: fraction of inspired oxygen
GCS: Glasgow coma score
HFFM: high-flow face mask
HFNC: high-flow nasal cannulae
ICU: intensive care unit
n: number of participants
NIPPV: non-invasive positive-pressure ventilation
NIV: non-invasive ventilation
$PaCO_2$: carbon dioxide clearance
PaO_2: partial pressure of arterial oxygen

PEEP: positive end-expiratory pressure
SaO_2: oxygen saturation of arterial blood
SD: standard deviation
SpO_2: oxygen saturation
VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baneton 2014	Not a randomized controlled trial
Besch 2014	Ancillary study of Stephan 2015, but observational study - not a randomized controlled trial
Braunlich 2013	Not participants of interest
Curley 2015	Not a randomized controlled trial
Parke 2013b	No review outcomes of interest
Pinto 2012	Not participants of interest
Simon 2014	Randomized controlled trial with appropriate intervention and comparison but used for oxygenation during bronchoscopy
Tiruvoipati 2010	Flow rate for comparison intervention was 30 L/min, which is outside the review criteria
Vourc'h 2015	Study of pre-oxygenation methods before intubation

Characteristics of studies awaiting assessment *[ordered by study ID]*

Futier 2016

Methods	RCT. Multi-centre study. France
Participants	220 participants
Interventions	HFNC or standard oxygen therapy (low-flow oxygen delivered via nasal prongs or face mask) directly after extubation
Outcomes	Hypoxaemia, postoperative pulmonary complications within 7 days after surgery, duration of hospital stay, in-hospital mortality
Notes	

Hernandez 2016a

Methods	RCT. Multi-centre study. Three ICUs in Spain
Participants	604 participants at high risk for reintubation
Interventions	HFNC or NIV after extubation
Outcomes	Reintubation and postextubation respiratory failure within 72 hours, respiratory infection, sepsis, multiple organ failure, length of stay and mortality; adverse events; time to reintubation
Notes	

Hernandez 2016b

Methods	RCT. Multi-centre study. Seven ICUs in Spain
Participants	527 participants at low risk for re-intubation
Interventions	HFNC or standard oxygen therapy after extubation
Outcomes	Re-intubation within 72 hours, postextubation respiratory failure, respiratory infection, sepsis and multi-organ failure, ICU and hospital length of stay, mortality, adverse events, time to reintubation
Notes	

Lemiale 2016

Methods	RCT. Multi-centre. France and Belgium
Participants	353 immunocompromised participants
Interventions	HFNC or NIV
Outcomes	Mortality at day 28, intubation rate, duration of mechanical ventilation, ICU-acquired infection, ICU and hospital length of stay
Notes	Post hoc analysis of larger study.

Perbet 2014

Methods	RCT. Multi-centre study. Four intensive care units at 2 hospitals
Participants	80 participants
Interventions	HFNC or standard oxygenation for 48 hours post extubation
Outcomes	Lung ultrasound score, dyspnoea, postextubation distress incidence

Perbet 2014 (*Continued*)

Notes	Abstract only. Insufficient information on standard oxygenation

Saeed 2015

Methods	Not stated if this is RCT. Single-centre
Participants	85 participants with chronic obstructive pulmonary disease
Interventions	HFNC or Venturi face mask
Outcomes	Arterial blood gas variables, successful weaning, treatment failure
Notes	Abstract only. Need to establish if this is an RCT

HFNC: high-flow nasal cannulae
ICU: intensive care unit
NIV: non-invasive ventilation
RCT: randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT01166256

Trial name or title	Comparison between high-flow nasal cannula system and non-invasive ventilation in acute hypoxaemic respiratory failure
Methods	Randomized controlled trial
Participants	Total number of participants = 74 Inclusion criteria: age ≥ 18 years, acute hypoxaemic respiratory failure Exclusion criteria: age < 18 years; hypercapnoea (arterial carbon dioxide tension ($PaCO_2$ > 45 mmHg) at admission); need for emergency intubation, including cardiopulmonary resuscitation; recent oesophageal, facial, or cranial trauma or surgery; severely decreased consciousness (GCS < 11); cardiogenic shock or severe haemodynamic instability; systolic blood pressure < 90 mmHg associated with decreased urinary output (< 20 mL per hour) despite fluid repletion and use of vasoactive agents; lack of co-operation; altered mental status with decreased consciousness and/or evidence of inability to understand or lack of willingness to co-operate with procedures; tracheotomy or other upper airway disorders; severe ventricular arrhythmia or active myocardial ischaemia; active upper gastrointestinal bleeding; inability to clear respiratory secretions; more than 1 severe organ dysfunction in addition to respiratory failure
Interventions	Experimental: high-flow nasal cannula. In this arm, acute hypoxaemic respiratory failure treated with high-flow nasal cannula system (Optiflow, Fisher & Paykel, Auckland, New Zealand) to achieve SpO_2 > 92% or PaO_2 > 65 mmHg Active comparator: non-invasive ventilation. In this arm, participants with acute hypoxaemic respiratory

NCT01166256 (*Continued*)

	failure are treated with the bilevel positive airway pressure mode (BiPAP Vision, Respironics Inc., Murrysville, PA) and with S/T mode to achieve SpO_2 > 92% or PaO_2 > 65 mmHg
Outcomes	Primary outcome measures: success rate of treatment in 2 groups (successful treatment is to avoid intubation and achieve PaO_2 > 75 mmHg without respiratory distress for 24 hours while spontaneously breathing oxygen provided by a Venturi device at FiO_2 0.50) Secondary outcome measures: compliance with treatment, withdrawal of non-invasive ventilation or high-flow nasal cannula system without intubation because of intolerance, adverse event, hospital length of stay, hospital mortality
Starting date	July 2010
Contact information	Chae-Man Lim, MD, Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
Notes	ClinicalTrials.gov Identifier: NCT01166256

NCT01617252

Trial name or title	High flow nasal oxygen therapy for hypoxaemia after cardiac surgery (Optiflow)
Methods	Randomized controlled trial
Participants	Total number of participants = 98 Inclusion criteria: indication of coronary artery bypass, absence of preoperative respiratory failure, hypoxia after extubation defined as SpO2 < 96% with Venturi mask, FiO_2 50% 8 L/min, age > 18 years, signed informed consent Exclusion criteria: requiring imminent intubation, coma or respiratory exhaustion, state of shock or severe rhythm disorders, pneumothorax, ventricular arrhythmia, pregnancy, non-controlled hyperalgia
Interventions	Experimental: Optiflow Experimental: facial mask
Outcomes	Primary outcome measures: measure of PaO_2/FiO_2 ratio Secondary outcome measures: scale of satisfaction completed by participant; measure of pH, SaO_2, PaO_2/FiO_2 ratio; number of days of hospitalization; measure of PCO_2 and respiratory frequency
Starting date	June 2011
Contact information	Dr Johanna Nicolet, Nantes University Hospital
Notes	ClinicalTrials.gov identifier: NCT01617252

NCT01702779

Trial name or title	Nasal humidified high flow oxygen during weaning from mechanical ventilation: ultrasonography study (HiFloLUS)
Methods	Randomized controlled trial
Participants	Total number of participants = 80 Inclusion criteria: adult patients ventilated longer than 48 hours, stable respiratory and haemodynamic conditions for spontaneous breathing trial, consent of participants, arterial line Exclusion criteria: COPD, laryngeal dyspnoea, tracheostomy, arrhythmia, no echogenicity, paraplegia > T8
Interventions	Optiflow vs standard oxygen
Outcomes	Primary outcome measures: variations in lung ultrasound score Secondary outcome measures: lung ultrasound score, rates of postextubation distress, electrical Impedance tomography, epithelial and endothelial biomarkers
Starting date	August 2011
Contact information	Patrick Lacarin, University Hospital, Clermont-Ferrand, placarin@chu-clermonetferrand.fr
Notes	ClinicalTrials.gov identifier: NCT01702779

NCT01782430

Trial name or title	PREoxygenation for the intubation of hypoxaemic patients: comparison of standard oxygenation, high flow nasal oxygen therapy, and nonInvasive ventilation (PREONIV)
Methods	Randomized controlled trial, open label
Participants	Total number of participants = 144 Inclusion criteria: adults requiring intubation and hypoxaemia (defined by PaO_2/FiO_2 < 200), covered by French healthcare system Exclusion criteria: patient refusal, intubation for other causes (excluding hypoxaemia), impossibility of measuring pulse oxymetry value, contraindication for NIV, vomiting, NIV intolerance, cardiac arrest during intubation
Interventions	Standard oxygenation vs high-flow nasal oxygen therapy vs non-invasive ventilation (NIV)
Outcomes	Primary outcome measures: least pulse oximetry value Secondary outcome measures: pulse oximetry value (at end of pre-oxygenation), PaO_2, respiratory rate, oxyhaemoglobin desaturation < 80%
Starting date	April 2013
Contact information	Patrick Lacarin, placarin@chu-clermonetferrand.fr
Notes	ClinicalTrials.gov Identifier:NCT01782430

NCT01820507

Trial name or title	Extubation failure prevention in high risk patients by high-flow conditioned oxygen therapy vs standard oxygen therapy
Methods	Double-blind randomized controlled trial
Participants	Total number of participants = 400 Inclusion criteria: mechanically ventilated for > 48 hours and at least 1 of the following: aged > 65 years, cardiac failure as primary indication of mechanical ventilation, COPD, severity score (APACHE II > 12 points) extubation day, BMI > 30, inability to manage respiratory secretions, 1 failed spontaneous breathing trial, 1 comorbidity, 7 days under mechanical ventilation Exclusion criteria: aged < 18 years, tracheotomized patients, recent facial or cervical trauma/surgery, active gastrointestinal bleeding, lack of co-operation, any failed spontaneous breathing trial because of hypercapnia development
Interventions	Experimental: high-flow conditioned oxygen therapy intervention: Optiflow(R) device supplies oxygen in controlled concentrations and at high flow (from 10 to 70 L/min) through special nasal cannulae. The device also humidifies the gas mixture up to 100% relative humidity. Active comparator: standard oxygen therapy: standard way of oxygen supply after extubation is by nasal cannulae at flow between 1 and 5 L/min or by mask with controlled oxygen concentration from 24% to 50%
Outcomes	Primary outcome measures: respiratory failure after extubation, severe hypoxaemia (PaO_2/FiO_2 < 200), hypercapnia ($PaCO_2$ > 50), respiratory acidosis (arterial pH < 7.30), severe tachypnoea (> 40 beats per minute) Secondary outcome measures: survival
Starting date	March 2013
Contact information	Rafael Fernandez, rfernandezf@althais.cat
Notes	ClinicalTrials.gov Identifier: NCT01820507

NCT01994928

Trial name or title	Preoxygenation in the intensive care unit using a nose-mouth mask versus high-flow nasal cannula oxygen
Methods	Randomized controlled trial, open label
Participants	Total number of participants = 50 Inclusion criteria: aged ≥ 18 years, patients treated in an ICU, indication for intubation, presence of hypoxaemia (SaO_2/FiO_2: ≤ 300), respiratory failure, informed consent Exclusion criteria: blocked nasopharynx, contraindications for nose-mouth mask or high-flow nasal cannula oxygen, expected difficult airway
Interventions	Active comparator: nose-mouth mask; performance of intubation after pre-oxygenation using a nose-mouth mask Experimental: high-flow nasal cannula oxygen; performance of intubation after pre-oxygenation using high-flow nasal cannula oxygen

NCT01994928 (*Continued*)

Outcomes	Primary outcome measures: mean decrease in SpO_2 during intubation Secondary outcome measures: changes in blood gases after intubation, changes in haemodynamics
Starting date	November 2013
Contact information	Stefan Kluge, skluge@uke.de
Notes	ClinicalTrials.gov Identifier: NCT01994928

NCT02107183

Trial name or title	Impact of nasal high-flow vs Venturi mask oxygen therapy on weaning outcome: a multicenter, randomized, controlled trial (RINO)
Methods	Randomized controlled trial, open label
Participants	Total number of participants = 500 Inclusion criteria: age $\geq$ 18 years, mechanical ventilation > 24 hours, signed informed consent, successful spontaneous breathing trial, PaO_2/FiO_2 ratio $\leq$ 300 (or SpO_2/FiO_2 ratio $\leq$ 300 if SpO_2 < 98%) within 30 minutes after extubation while breathing through a Venturi mask with a delivered FiO_2 of 30% Exclusion criteria: pregnancy, presence of tracheostomy, need for immediate postextubation non-invasive ventilation (> 3 consecutive failures of the spontaneous breathing trial and/or $PaCO_2$ > 45 mmHg before spontaneous breathing trial, with respiratory rate $\geq$ 25/min)
Interventions	Experimental: nasal high-flow oxygen therapy; high-flow, fully humidified oxygen delivered through nasal cannula (Optiflow, Fisher & Paykel Healthcare) after extubation up to ICU discharge Active comparator: Venturi mask oxygen therapy; oxygen delivered through standard Venturi mask after extubation up to ICU discharge
Outcomes	Primary outcome measure: reintubation Secondary outcome measures: need for NIV, ICU length of stay, hospital length of stay, ICU re-admission, ICU mortality, hospital mortality
Starting date	June 2014
Contact information	Salvatore Maurizio Maggiore, smmaggiore@rm.unicatt.it
Notes	ClinicalTrials.gov Identifier: NCT02107183

NCT02123940

Trial name or title	Treatment strategy in patients with high-risk of postextubation distress in ICU based on a lung ultrasound score versus standard strategy (WIN IN WEAN)
Methods	Randomized controlled trial

NCT02123940 (*Continued*)

Participants	Total number of participants = 640 Inclusion criteria: adult patients ventilated > 48 hours, stable respiratory and haemodynamic conditions for SBT, consent of patients, arterial line Exclusion criteria: severe COPD, laryngeal dyspnoea, tracheostomy, arrhythmia, no echogenicity, paraplegia > T8
Interventions	Comparing a treatment strategy (nasal humidified high-flow therapy and non-invasive ventilation) in patients with high risk of postextubation distress in ICU based on a lung ultrasound score vs standard strategy
Outcomes	Primary outcome measures: incidence of postextubation distress, postextubation period requiring ventilatory support (reintubation or curative non-invasive ventilation) Secondary outcome measures: number of ventilator-free-days, length of stay in ICU, mortality in ICU
Starting date	February 2014
Contact information	Patrick Lacarin, placarin@chu-clermonetferrand.fr
Notes	ClinicalTrials.gov Identifier: NCT02123940

UMIN000008778

Trial name or title	Evaluation of nasal high flow oxygen therapy for severe acute hypoxaemic respiratory failure
Methods	Randomized controlled trial
Participants	Total number of randomized participants = 40 Inclusion criteria: admitted to respiratory department of our hospital for severe AHRF other than cardiogenic pulmonary edema, met the standard clinical and/or blood gas criteria for use of non-invasive ventilation to treat severe AHRF, received NIV for < 12 hours Exclusion criteria: hypercapnoea ($PaCO_2$ > 45 mmHg), unstable clinical conditions (i.e. need for vasopressors, metabolic acidosis, life-threatening arrhythmias, need for $FiO \geq 0.8$, agitation and anxiety), inability to obtain consent, face or neck deformities, use of NIV before admission, need for continuous sedation
Interventions	Nasal high-flow oxygen therapy Non-invasive ventilation
Outcomes	Primary outcome: interface discomfort Secondary outcomes: dyspnoea, easy to speak, sleep perception, easy to eat and drink, arterial blood gas analysis, vital signs, early failure, length of ICU stay, length of hospital stay, in-hospital mortality, 90-day survival, complications
Starting date	September 2012
Contact information	Kazuma Nagata, Kobe City Medical Center General Hospital, kazuma_n1101@yahoo.co.jp
Notes	Clinical trials register ID: UMIN000008778

AHRF: acute hypoxic respiratory failure
APACHE: Acute Physiology and Chronic Health Evaluation
BiPAP: bilevel positive airway pressure
BMI: body mass index
COPD: chronic obstructive pulmonary disease
FiO_2: fraction of inspired oxygen
GCS: Glasgow coma score
ICU: intensive care unit
NIV: non-invasive ventilation
$PaCO_2$: carbon dioxide clearance
PaO_2: partial pressure of arterial oxygen
PCO_2: partial pressure of carbon dioxide
SaO2: oxygen saturation
SBT: spontaneous breathing trial
SpO_2: oxygen saturation
S/T: spontaneous/timed

DATA AND ANALYSES

Comparison 1. High-flow nasal cannulae versus low-flow oxygen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of treatment as indicated by the need for NIPPV or invasive ventilation	6	1066	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.27]

Comparison 2. High-flow nasal cannulae versus low-flow oxygen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 In-hospital mortality	3	755	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.38, 1.06]

Comparison 3. High-flow nasal cannulae versus low-flow oxygen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of ICU stay	4	770	Mean Difference (IV, Random, 95% CI)	0.15 [-0.03, 0.34]

Comparison 4. High-flow nasal cannulae versus low-flow oxygen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PaO_2/FiO_2 ratio up to 24 hours after initiation of therapy	4	510	Mean Difference (IV, Random, 95% CI)	7.31 [-26.69, 41.31]
2 PaO_2 up to 24 hours after initiation of therapy	3	355	Mean Difference (IV, Random, 95% CI)	2.79 [-5.47, 11.05]
3 SpO_2 up to 24 hours after initiation of therapy	4	512	Mean Difference (IV, Random, 95% CI)	0.72 [-0.73, 2.17]
4 SpO_2 at > 24 hours after initiation of therapy	2	445	Mean Difference (IV, Random, 95% CI)	1.28 [0.02, 2.55]

Comparison 5. High-flow nasal cannulae versus low-flow oxygen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 $PaCO_2$ up to 24 hours	3	590	Mean Difference (IV, Random, 95% CI)	-0.75 [-2.04, 0.55]

Comparison 6. High-flow nasal cannulae versus low-flow oxygen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory rate up to 24 hours after initiation of therapy (short-term effects)	6	867	Mean Difference (IV, Random, 95% CI)	-1.51 [-3.36, 0.35]
2 Respiratory rate > 24 hours after initiation of therapy (longer-term effects)	2	445	Mean Difference (IV, Random, 95% CI)	-2.71 [-7.12, 1.70]

Comparison 7. High-flow nasal cannulae versus CPAP/BiPAP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory rate up to 24 hours	2	834	Mean Difference (IV, Random, 95% CI)	-0.89 [-1.74, -0.05]

Comparison 8. High-flow nasal cannulae versus low-flow oxygen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comfort (short-term effect)	3	462	Mean Difference (IV, Random, 95% CI)	0.14 [-0.65, 0.93]
2 Comfort (long-term effect)	2	445	Mean Difference (IV, Random, 95% CI)	-0.36 [-3.70, 2.98]

Comparison 9. High-flow nasal cannulae versus low-flow oxygen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure of treatment: subgroup by reason for respiratory support	6	1066	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.27]
1.1 Respiratory failure	3	466	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.56, 1.11]
1.2 Post extubation	3	600	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.17, 4.21]

Analysis 1.1. Comparison 1 High-flow nasal cannulae versus low-flow oxygen, Outcome 1 Failure of treatment as indicated by the need for NIPPV or invasive ventilation.

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 1 High-flow nasal cannulae versus low-flow oxygen

Outcome: 1 Failure of treatment as indicated by the need for NIPPV or invasive ventilation

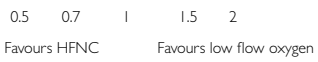
Study or subgroup	High flow nasal cannulae n/N	Low flow oxygen n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Corley 2014	3/81	2/74		5.8 %	1.37 [0.24, 7.97]
Frat 2015 (1)	20/53	55/110		24.5 %	0.75 [0.51, 1.12]
Frat 2015 (2)	20/53	44/94		24.2 %	0.81 [0.54, 1.21]
Lemiale 2015 (3)	8/52	4/48		10.9 %	1.85 [0.59, 5.74]
Maggiore 2014	4/53	18/52		12.5 %	0.22 [0.08, 0.60]
Parke 2011	3/29	8/27		9.9 %	0.35 [0.10, 1.18]
Parke 2013a	11/169	5/171		12.2 %	2.23 [0.79, 6.27]
Total (95% CI)	**490**	**576**		**100.0 %**	**0.79 [0.49, 1.27]**

Total events: 69 (High flow nasal cannulae), 136 (Low flow oxygen)

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 14.36$, df = 6 (P = 0.03); $I^2 = 58\%$

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable



(1) HFNC vs noninvasive ventilation (data in HFNC group has been halved)

(2) HFNC vs standard (data in HFNC group has been halved)

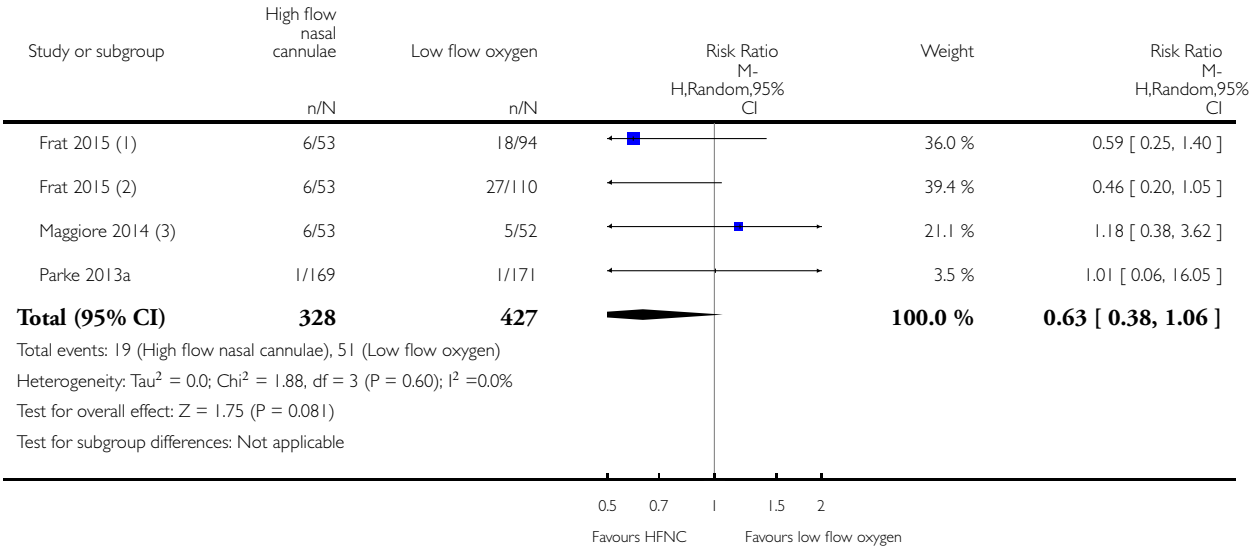
(3) within 2 hours

Analysis 2.1. Comparison 2 High-flow nasal cannulae versus low-flow oxygen, Outcome 1 In-hospital mortality.

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 2 High-flow nasal cannulae versus low-flow oxygen

Outcome: 1 In-hospital mortality



(1) HFNC vs standard oxygen (data in HFNC has been halved). In ICU

(2) HFNC vs noninvasive ventilation (data in HFNC group has been halved). In ICU

(3) At ICU discharge

Analysis 3.1. Comparison 3 High-flow nasal cannulae versus low-flow oxygen, Outcome 1 Length of ICU stay.

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 3 High-flow nasal cannulae versus low-flow oxygen

Outcome: 1 Length of ICU stay

Study or subgroup	High flow nasal cannulae N	Mean(SD)	Low flow oxygen N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Frat 2015 (1)	94	10.7 (15.8)	76	9.1 (11.7)		0.2 %	1.60 [-2.54, 5.74]
Maggiore 2014	53	11.7 (10.2)	52	10.4 (8.5)		0.3 %	1.30 [-2.29, 4.89]
Corley 2014	81	1.61 (1.47)	74	1.61 (1)		21.7 %	0.0 [-0.39, 0.39]
Parke 2013a	169	1.39 (0.95)	171	1.2 (1)		77.9 %	0.19 [-0.02, 0.40]
Total (95% CI)	**397**		**373**			**100.0 %**	**0.15 [-0.03, 0.34]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.57$, df = 3 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 1.65 (P = 0.098)

Test for subgroup differences: Not applicable

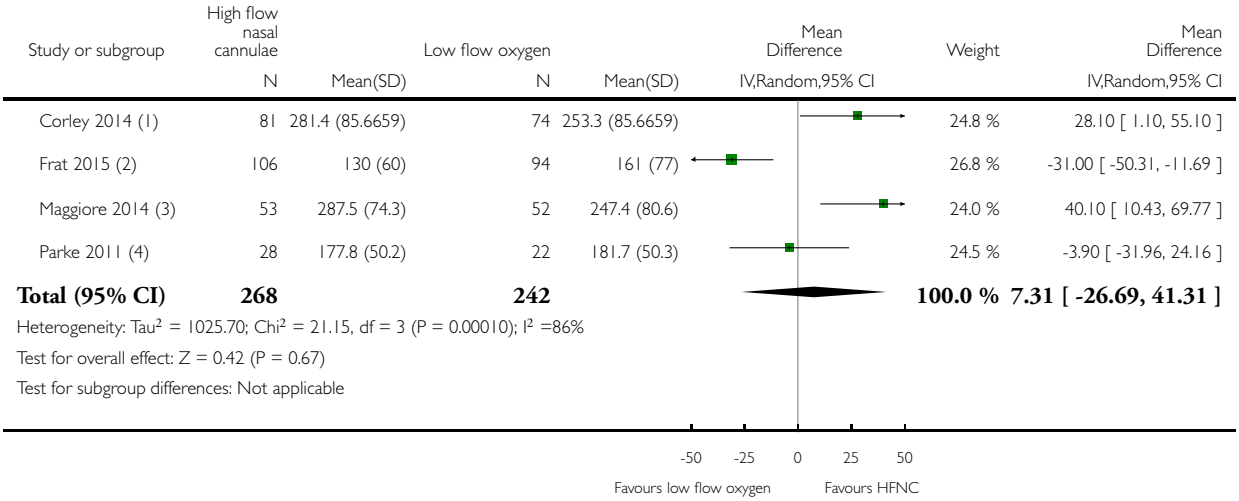
(1) survivors at 90 days (standard oxygen therapy)

Analysis 4.1. Comparison 4 High-flow nasal cannulae versus low-flow oxygen, Outcome 1 PaO2/FiO2 ratio up to 24 hours after initiation of therapy.

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 4 High-flow nasal cannulae versus low-flow oxygen

Outcome: 1 PaO_2/FiO_2 ratio up to 24 hours after initiation of therapy



(1) first 24 hours

(2) HFNC vs standard oxygen therapy (at 6 hours)

(3) At 24 hours

(4) At four hours

Analysis 4.2. Comparison 4 High-flow nasal cannulae versus low-flow oxygen, Outcome 2 PaO2 up to 24 hours after initiation of therapy.

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 4 High-flow nasal cannulae versus low-flow oxygen

Outcome: 2 PaO_2 up to 24 hours after initiation of therapy

Study or subgroup	High flow nasal cannulae		Low flow oxygen		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Frat 2015 (1)	106	90 (35)	94	93 (36)		35.0 %	-3.00 [-12.87, 6.87]
Maggiore 2014 (2)	53	95 (28)	52	84.6 (22.6)		35.5 %	10.40 [0.68, 20.12]
Parke 2011 (3)	28	80.2 (11.8)	22	79.7 (25.6)		29.5 %	0.50 [-11.06, 12.06]
Total (95% CI)	**187**		**168**			**100.0 %**	**2.79 [-5.47, 11.05]**

Heterogeneity: $Tau^2 = 25.42$; $Chi^2 = 3.82$, df = 2 (P = 0.15); $I^2 = 48\%$

Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Not applicable

(1) HFNC vs standard oxygen (at 6 hours)

(2) At 24 hours

(3) At four hours

Analysis 4.3. Comparison 4 High-flow nasal cannulae versus low-flow oxygen, Outcome 3 SpO2 up to 24 hours after initiation of therapy.

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 4 High-flow nasal cannulae versus low-flow oxygen

Outcome: 3 SpO_2 up to 24 hours after initiation of therapy

Study or subgroup	High flow nasal cannulae		Low flow oxygen		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Maggiore 2014 (1)	53	97 (2)	52	95 (2)		27.6 %	2.00 [1.23, 2.77]
Parke 2011 (2)	28	95 (2)	22	95.4 (2.9)		23.3 %	-0.40 [-1.82, 1.02]
Parke 2013a (3)	169	96.6 (2.1)	171	96.9 (1.9)		29.2 %	-0.30 [-0.73, 0.13]
Rittayamai 2014 (4)	9	99.11 (1.45)	8	97.38 (2.34)		19.9 %	1.73 [-0.15, 3.61]
Total (95% CI)	**259**		**253**			**100.0 %**	**0.72 [-0.73, 2.17]**

Heterogeneity: Tau^2 = 1.83; Chi^2 = 29.69, df = 3 (P<0.00001); I^2 =90%

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable

(1) At 24 hours

(2) At four hours

(3) At day 1

(4) At 30 minutes

Analysis 4.4. Comparison 4 High-flow nasal cannulae versus low-flow oxygen, Outcome 4 SpO2 at > 24 hours after initiation of therapy.

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 4 High-flow nasal cannulae versus low-flow oxygen

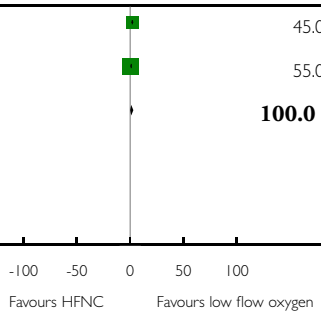
Outcome: 4 SpO_2 at > 24 hours after initiation of therapy

Study or subgroup	High flow nasal cannulae		Low flow oxygen		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Maggiore 2014 (1)	53	97 (2)	52	95 (3)		45.0 %	2.00 [1.02, 2.98]
Parke 2013a (2)	169	95.6 (2.6)	171	94.9 (2.6)		55.0 %	0.70 [0.15, 1.25]
Total (95% CI)	**222**		**223**			**100.0 %**	**1.28 [0.02, 2.55]**

Heterogeneity: $Tau^2 = 0.68$; $Chi^2 = 5.15$, df = 1 (P = 0.02); $I^2 = 81\%$

Test for overall effect: Z = 1.99 (P = 0.047)

Test for subgroup differences: Not applicable



(1) At 48 hours

(2) At day 2

Analysis 5.1. Comparison 5 High-flow nasal cannulae versus low-flow oxygen, Outcome 1 PaCO2 up to 24 hours.

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 5 High-flow nasal cannulae versus low-flow oxygen

Outcome: 1 $PaCO_2$ up to 24 hours

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Frat 2015 (1)	106	36 (7)	94	36 (6)		31.6 %	0.0 [-1.80, 1.80]
Parke 2011	28	40.6 (6)	22	39.8 (6.3)		12.0 %	0.80 [-2.65, 4.25]
Parke 2013a (2)	169	38.2 (4.95)	171	39.7 (4)		56.4 %	-1.50 [-2.46, -0.54]
Total (95% CI)	**303**		**287**			**100.0 %**	**-0.75 [-2.04, 0.55]**

Heterogeneity: $Tau^2 = 0.54$; $Chi^2 = 3.26$, df = 2 (P = 0.20); $I^2 = 39\%$

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable

(1) HFNC versus standard oxygen

(2) At day 1

Analysis 6.1. Comparison 6 High-flow nasal cannulae versus low-flow oxygen, Outcome 1 Respiratory rate up to 24 hours after initiation of therapy (short-term effects).

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 6 High-flow nasal cannulae versus low-flow oxygen

Outcome: 1 Respiratory rate up to 24 hours after initiation of therapy (short-term effects)

Study or subgroup	High flow nasal cannulae N	Mean(SD)	Low flow oxygen N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Corley 2014 (1)	81	17.24 (2.38)	74	16.7 (2.38)		21.4 %	0.54 [-0.21, 1.29]
Frat 2015 (2)	106	27 (7)	94	29 (8)		17.3 %	-2.00 [-4.10, 0.10]
Maggiore 2014 (3)	53	21 (4)	52	26 (5)		18.6 %	-5.00 [-6.73, -3.27]
Parke 2011 (4)	28	17 (7)	22	16 (8)		10.3 %	1.00 [-3.23, 5.23]
Parke 2013a (5)	169	16.6 (4.9)	171	16.9 (5.1)		20.7 %	-0.30 [-1.36, 0.76]
Rittayamai 2014 (6)	9	19.8 (3.2)	8	23.1 (4.4)		11.8 %	-3.30 [-7.00, 0.40]
Total (95% CI)	**446**		**421**			**100.0 %**	**-1.51 [-3.36, 0.35]**

Heterogeneity: $Tau^2 = 4.05$; $Chi^2 = 38.04$, df = 5 ($P<0.00001$); $I^2 = 87\%$

Test for overall effect: Z = 1.59 (P = 0.11)

Test for subgroup differences: Not applicable

(1) first 24 hours

(2) HFNC versus standard oxygen (at 6 hours)

(3) At 24 hours

(4) at four hours

(5) At day 1

(6) at 30 minutes

Analysis 6.2. Comparison 6 High-flow nasal cannulae versus low-flow oxygen, Outcome 2 Respiratory rate > 24 hours after initiation of therapy (longer-term effects).

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 6 High-flow nasal cannulae versus low-flow oxygen

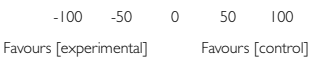
Outcome: 2 Respiratory rate > 24 hours after initiation of therapy (longer-term effects)

Study or subgroup	High flow nasal cannulae N	Mean(SD)	Low flow oxygen N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Maggiore 2014 (1)	53	21 (3)	52	26 (4)		49.0 %	-5.00 [-6.35, -3.65]
Parke 2013a (2)	169	16.9 (2.7)	171	17.4 (2.6)		51.0 %	-0.50 [-1.06, 0.06]
Total (95% CI)	**222**		**223**			**100.0 %**	**-2.71 [-7.12, 1.70]**

Heterogeneity: Tau^2 = 9.84; Chi^2 = 36.15, df = 1 (P<0.00001); I^2 =97%

Test for overall effect: Z = 1.20 (P = 0.23)

Test for subgroup differences: Not applicable



(1) At 48 hours

(2) At day 2

Analysis 7.1. Comparison 7 High-flow nasal cannulae versus CPAP/BiPAP, Outcome 1 Respiratory rate up to 24 hours.

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 7 High-flow nasal cannulae versus CPAP/BiPAP

Outcome: 1 Respiratory rate up to 24 hours

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chanques 2013 (1)	1	20 (6.3)	3	19 (9)		0.3 %	1.00 [-15.01, 17.01]
Stephan 2015 (2)	414	21.6 (6.2105)	416	22.5 (6.2256)		99.7 %	-0.90 [-1.75, -0.05]
Total (95% CI)	**415**		**419**			**100.0 %**	**-0.89 [-1.74, -0.05]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 2.08 (P = 0.038)

Test for subgroup differences: Not applicable

(1) Measured at end of treatment

(2) at 6-12 hours

Analysis 8.1. Comparison 8 High-flow nasal cannulae versus low-flow oxygen, Outcome 1 Comfort (short-term effect).

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 8 High-flow nasal cannulae versus low-flow oxygen

Outcome: 1 Comfort (short-term effect)

Study or subgroup	HFNC N	Mean(SD)	Low flow oxygen N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Maggiore 2014 (1)	53	5.2 (3.4)	52	5.6 (3.5)		23.7 %	-0.40 [-1.72, 0.92]
Parke 2013a (2)	169	2.5 (2.6)	171	1.9 (1.8)		56.3 %	0.60 [0.12, 1.08]
Rittayamai 2014 (3)	9	1.11 (1.37)	8	1.63 (1.73)		20.0 %	-0.52 [-2.02, 0.98]
Total (95% CI)	**231**		**231**			**100.0 %**	**0.14 [-0.65, 0.93]**

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 3.54$, df = 2 (P = 0.17); $I^2 = 44\%$

Test for overall effect: Z = 0.34 (P = 0.73)

Test for subgroup differences: Not applicable

(1) at 1 hour

(2) at 4 hours

(3) at 30 minutes

Analysis 8.2. Comparison 8 High-flow nasal cannulae versus low-flow oxygen, Outcome 2 Comfort (long-term effect).

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 8 High-flow nasal cannulae versus low-flow oxygen

Outcome: 2 Comfort (long-term effect)

Study or subgroup	HFNC N	Mean(SD)	Low flow oxygen N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Maggiore 2014 (1)	53	1.5 (1.9)	52	3.6 (3.4)		49.0 %	-2.10 [-3.16, -1.04]
Parke 2013a (2)	169	3.06 (2.5)	171	1.75 (1.9)		51.0 %	1.31 [0.84, 1.78]
Total (95% CI)	**222**		**223**			**100.0 %**	**-0.36 [-3.70, 2.98]**

Heterogeneity: $Tau^2 = 5.64$; $Chi^2 = 33.36$, df = 1 (P<0.00001); $I^2 = 97\%$

Test for overall effect: Z = 0.21 (P = 0.83)

Test for subgroup differences: Not applicable

(1) At 48 hours

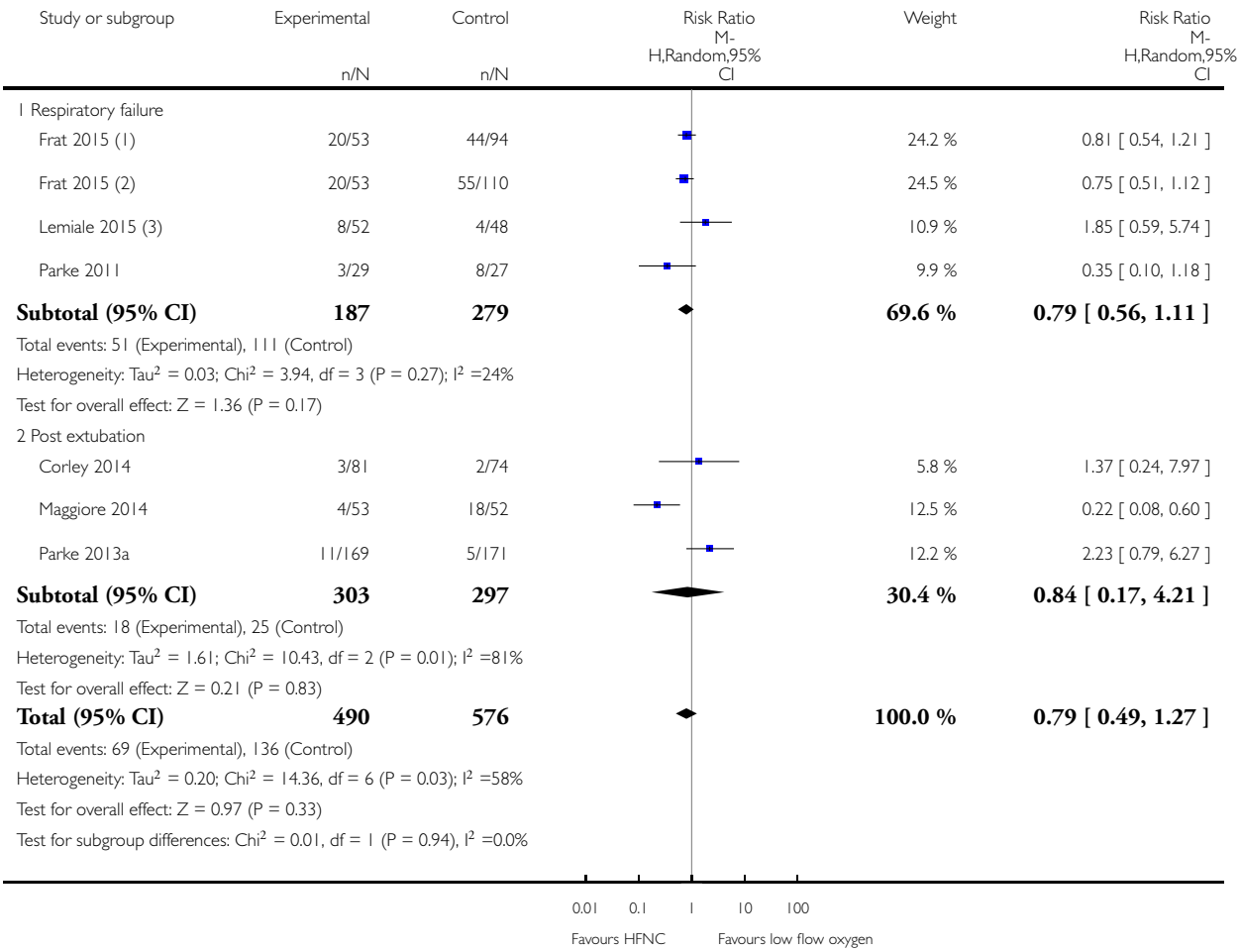
(2) At day 2

Analysis 9.1. Comparison 9 High-flow nasal cannulae versus low-flow oxygen, Outcome 1 Failure of treatment: subgroup by reason for respiratory support.

Review: High-flow nasal cannulae for respiratory support in adult intensive care patients

Comparison: 9 High-flow nasal cannulae versus low-flow oxygen

Outcome: 1 Failure of treatment: subgroup by reason for respiratory support



(1) HFNC vs standard (data in HFNC group has been halved)

(2) HFNC vs noninvasive ventilation (data in HFNC group has been halved)

(3) within 2 hours

ADDITIONAL TABLES

Table 1. Dichotomous outcomes from single studies (HFNC vs BiPAP)

Outcome	Total N	Intervention n/N	Control n/N	P value *(as reported by study authors)*	Study
Failure of treatment	830	58/414	57/416	0.99	Stephan 2015
Mortality	830	28/414	23/416	0.66	Stephan 2015
Adverse events - nosocomial pneumonia	830	83/414	98/516	0.57	Stephan 2015
Adverse events - pneumothorax	830	8/414	7/416	0.86	Stephan 2015
Adverse events - acute colonic pseudo-obstruction	830	9/414	8/416	0.86	Stephan 2015

N: total number of participants
n: number of participants who had an event
P: significance level

Table 2. Dichotomous outcomes from single studies (HFNC vs low-flow oxygen)

Outcome	Total N	Intervention n/N	Control n/N	P value *(as reported by study authors)*	Study
Adverse events - nosocomial pneumonia	310	4/106	Standard: 8/94 NIV: 9/110	0.32	Frat 2015
Adverse events - septic shock	310	19/106	Standard: 26/94 NIV: 34/110	0.08	Frat 2015
Adverse events - cardiac dysrhythmia	310	11/106	Standard: 16/94 NIV: 17/110	0.35	Frat 2015
Adverse events - cardiorespiratory arrest	310	5/106	Standard: 7/94 NIV: 6/110	0.70	Frat 2015
Adverse events - at least 1 episode of oxygen desaturation	35*	8/19	10/14	0.009	Parke 2011

Table 2. Dichotomous outcomes from single studies (HFNC vs low-flow oxygen) *(Continued)*

Adverse events - incidence of respiratory complications up to day 28 (GP visits)	340	13	15	Not reported	Parke 2013a
Patient-reported outcome - refusal to continue with treatment - excess heat/ discomfort	340	20/171	0/169	Not reported	Parke 2013a

* Data available for only 35 participants
GP: general practitioner
HFNC: high-flow nasal cannulae
N: total number of participants
n: number of participants who had an event
NIV: non-invasive ventilation group
P: significance level

Table 3. Continuous outcomes from single studies (HFNC vs low-flow oxygen)

Outcome	Total N	Intervention	Control	P values *(as reported by study authors)*	Study
Duration of respiratory support (hours)	340	Mean (SD) 59.0 (30.8)	Mean (SD) 65.0 (41.6)	0.13	Parke 2013a
Atelectasis (radiological atelectasis score)	155	Day 1: median (IQR) 2 (1.5 to 2.5) Day 5: median (IQR) 2 (1.5 to 2.5)	Day 1: median (IQR) 2 (1.5 to 3) Day 5: median (IQR) 2 (1 to 2.5)	Day 1: 0.70 Day 5: 0.15	Corley 2014
Atelectasis (chest X-ray)	340	Day 1: mean (SD) 4.8 (1.9) Day 3: mean (SD) 4.8 (1.9)	Day 1: mean (SD) 4.9 (1.8) Day 3 mean (SD) 4.7 (2.1)	Day 1: 0.63 Day 3: 0.69	Parke 2013a
PaO_2/FiO_2 at 36 hours (mmHg)	105	Mean (SD) 310.8 (80.6)	Mean (SD) 233.2 (75.8)	0.0003	Maggiore 2014
PaO_2/FiO_2 at 48 hours (mmHg)	105	Mean (SD) 313.3 (83.8)	Mean (SD) 250.2 (110.1)	0.01	Maggiore 2014
PaO_2 at 36 hours (mmHg)	105	Mean (SD) 97.5 (29.2)	Mean (SD) 85.4 (16.3)	0.04	Maggiore 2014

Table 3. Continuous outcomes from single studies (HFNC vs low-flow oxygen) (*Continued*)

Respiratory rate at 120 minutes (breaths per minute)	100	Median (IQR) 25 (22 to 29)	Median (IQR) 25 (21 to 31)	Not reported	Lemiale 2015
Patient comfort at 120 minutes. Scale of 0 to 10 (0 = absence of discomfort, 10 = worst possible discomfort)	100	Median (IQR) 3 (1 to 5)	Median (IQR) 3 (0 to 5)	0.88	Lemiale 2015
Patient-reported mouth dryness (on a scale of 0 to 10; 0 = no dryness, 10 = maximum dryness)	105	Mean (SD) 3.6 (2.5)	Mean (SD) 5 (3.1)	0.016	Maggiore 2014

HFNC: high-flow nasal cannulae
IQR: interquartile range
N: Total number of participants
P: significance level
PaO_2/FiO_2: ratio of partial pressure of arterial oxygen to fraction of inspired oxygen
SD: standard deviation

Table 4. Continuous outcomes for single studies (HFNC vs BiPAP)

Outcome	Total N	Intervention	Control	P value	Study
Length of stay in ICU (days)	830	Median (IQR) 6 (4 to 10)	Median (IQR) 6 (4 to 10)	0.77	Stephan 2015
Length of stay in hospital (days)	830	Median (IQR) 13 (9 to 22)	Median (IQR) 14 (9 to 20)	0.59	Stephan 2015
PaO_2/FiO_2 (6 to 12 hours)	830	Mean (95% CI) 198 (187 to 208)	Mean (95% CI) 261 (248 to 274)	< 0.001	Stephan 2015
$PaCO_2$ mmHg (6 to 12 hours)	830	Mean (95% CI) 38.2 (37.6 to 38.9)	Mean (95% CI) 39.3 (38.6 to 40.0)	0.19	Stephan 2015
Patient comfort at 1 hour. Five-point scale of 'poor', 'acceptable', or 'good'	830	Poor: 16.7% Acceptable: 31.0% Good: 51.0%	Poor: 17.8% Acceptable: 29.3% Good: 53.0%	0.32	Stephan 2015

CI: confidence interval
ICU: intensive care unit

IQR: interquartile range
N: total number of participants
P: significance level
$PaCO_2$: carbon dioxide clearance
PaO_2/FiO_2: ratio of partial pressure of arterial oxygen to fraction of inspired oxygen

APPENDICES

Appendix 1. CENTRAL (the Cochrane Library) search strategy

#1 (((high flow or highflow or nasal*) near can?ul*) or HFNC or (nasal near (high flow highflow or prong)) or Vapotherm or Optiflow)

Appendix 2. Search strategy for MEDLINE (OvidSP)

1 (((high flow or highflow or nasal*) adj6 can?ul*) or HFNC or (nasal adj6 (high flow or highflow or prong)) or Vapotherm or Optiflow).af.
2 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
3 1 and 2

Appendix 3. CINAHL (EBSCO host) search strategy

S1 (((high flow or highflow or nasal*) N3 can?ul*) or HFNC or (nasal N3 (high flow or highflow or prong)) or Vapotherm or Optiflow)
S2 ((random* or (trial* N3 (controlled or clinical)) or placebo* or prospective or multicenter) or ((blind* or mask*) N3 (single or double or triple or treble)))
S3 S1 and S2

Appendix 4. Embase (OvidSP) search strategy

1. (((high flow or highflow or nasal*) adj6 can?ul*) or HFNC or (nasal adj6 (high flow or highflow or prong)) or Vapotherm or Optiflow).af.
2. (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross?over* or multicenter* or factorial* or placebo* or volunteer*).mp. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab. or (latin adj square).mp.) not (animals not (humans and animals)).sh.
3. 1 and 2

Appendix 5. ISI Web of Science search strategy

#1 TS=(((high flow or highflow or nasal*) SAME can?ul*) or HFNC or (nasal SAME (high flow or highflow or prong)) or Vapotherm or Optiflow)
#2 TS=(random* or (trial* SAME (controlled or clinical)) or placebo* or prospective or multicenter) or TS=((blind* or mask*) SAME (single or double or triple or treble))
#3 #1 and #2

Appendix 6. Study selection form

Study Details		
First Author		
Journal / Place of publication		
Year		
Study Eligibility		***Comments***
Study Type - RCT - Randomized crossover	Yes / No / Unclear	
Relevant participants - Age $\geq$ 16 years - Admitted to intensive care unit	Yes / No / Unclear	
Relevant interventions - HFNC compared with comparison interventions (LFNC, face mask, CPAP, BiPAP)	Yes / No / Unclear	
Relevant outcomes Failure of treatment as indicated by the need for NIPPV or invasive ventilation (up to 28 days) In hospital mortality (up to 90 days) Adverse events Duration in hours of any form of respiratory support (mechanical ventilation, NIPPV, HFNC, standard oxygen) Length of stay in days (ICU and hospital) Respiratory effects as indicated by any of the following: • Degree of atelectasis on	Yes / No / Unclear	

radiological examination • Positive end expiratory pressure measured at the pharyngeal level (cmH_2O) • Oxygenation (PaO_2/FiO_2 ratio, PaO_2, SaO_2 and SpO_2) • Carbon dioxide clearance ($PaCO_2$ and pCO_2) • Respiratory rate • Work of breathing (joules per litre) Patient reported outcomes as indicated by any of the following: • Dyspnoea • Comfort • Mouth dryness • Patient refusal to continue with treatment Cost comparison of treatment (in Australian dollars)		

Appendix 7. Data extraction form

Data extraction form

Review title or ID
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*
Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*

1. General Information

Date form completed *(dd/mm/yyyy)*	
Name of person extracting data	
Report title *(title of paper/ abstract/ report that data are extracted from)*	
Report ID *(ID for this paper/ abstract/ report)*	
Reference details	
Report author contact details	
Publication type *(full report, abstract, letter)*	
Study funding sources *(including role of funders)*	
Possible conflicts of interest *(for study authors)*	
Notes:	**Notes:**

2. Population and setting

	Description *Include comparative information for each group (i.e. intervention and controls) if available*	**Location in text** *(pg & fig/table)*
Population description *(from which study participants are drawn)*		
Setting *Including:* *· Country of study* *· Level of Hospital (Tertiary, Metropolitan, Regional, Rural)* *· Number of beds*		
Inclusion criteria		

(*Continued*)

Exclusion criteria		
Method/s of recruitment of participants		
Informed consent obtained	Yes/No/Unclear	

Notes: **Notes:**

3. Methods

	Descriptions as stated in report/paper	**Location in text** *(pg & fig/table)*
Aim/s of study		
Design *(e.g. parallel, cross-over)*		
Start date		
End date		
Total study duration		
Ethical approval needed/obtained for study	Yes/No/Unclear	

Notes: **Notes:**

4. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	**Location in text** (pg & fig/table)
Total no. randomized		
Baseline imbalances		

(*Continued*)

Withdrawals and exclusions *(if not provided below in results section)*		
Age range		
Sex		
Severity of illness *(ARDS/ALI criteria, APACHE score, SOFA score)*		
Co-morbidities *(if detailed)*		
Other treatment received *(additional to study intervention)*		
Subgroups measured		
Subgroups reported		
Notes:		**Notes:**

5. Intervention groups

Copy and paste table for each intervention and comparison group.
Intervention Group

	Description as stated in report/paper	**Location in text** *(pg & fig/table)*
Group name		
No. randomized to group		
Description of therapy · *Type of delivery device [Vapotherm/Optiflow/other]* · *Size of nasal cannula* · *Litres/ minute delivered*		
Duration of treatment period		
Co-interventions		

(*Continued*)

Notes:	Notes:

Comparison Group 1

	Description as stated in report/paper	Location in text *(pg & fig/table)*
Group name		
No. randomized to group		
Description of therapy · *Type of delivery device [Vapotherm/Optiflow/other]* · *Size of nasal cannula* · *Litres/ minute delivered*		
Duration of treatment period		
Co-interventions		

Notes:	Notes:

Add another table if more than one comparison group

6. Outcomes

Outcomes measures reported in paper (circle)		Outcomes meas
Failure of treatment as indicated by the need for NIPPV or invasive ventilation (up to 28 days)	Yes / No	
In hospital mortality (up to 90 days)	Yes / No	
Adverse events	Yes / No	
Duration in hours of any form of respiratory support (mechanical ventilation, NIPPV, HFNC, standard oxygen)	Yes / No	

(*Continued*)

Length of stay (ICU and hospital)	Yes / No
Degree of atelectasis on radiological examination	Yes / No
Positive end expiratory pressure measured at the pharyngeal level (cmH_2O)	Yes / No
Oxygenation (PaO_2/FiO_2 ratio, PaO_2, SaO_2 and SpO_2)	Yes / No
Carbon dioxide clearance ($PaCO_2$ and pCO_2)	Yes / No
Respiratory rate	Yes / No
Work of breathing (joules per litre)	Yes / No
Patient reported dyspnoea	Yes / No
Patient reported comfort	Yes / No
Patient reported mouth dryness	Yes / No
Patient refusal to continue with treatment	Yes / No
Cost comparison of treatment (in Australian dollars)	Yes / No

DETAILS OF OUTCOMES INCLUDED IN PAPER
Cut and paste for each included outcome
(Insert outcome name here)

	Description as stated in report/paper	**Location in text**
Outcome name as stated in paper		
Unit of measurement		
Time points measured		
Time points reported		
Person measuring/reporting		
Is outcome/tool validated?	Yes/No/Unclear	
Missing data		

(*Continued*)

Power		
Notes:		**Notes:**

7. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.
Dichotomous outcome

	Description as stated in report/paper				**Location in text** *(pg & fig/table)*
Comparison group/s					
Outcome					
Subgroup					
Time point measured					
Results (add more comparison groups here if necessary)	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
No. missing participants and reasons					
No. participants moved from other group/s and reasons					
Any other results reported					
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*					

(*Continued*)

Reanalysis required? *(specify)*	Yes/No/Unclear	
Reanalysis possible?	Yes/No/Unclear	
Reanalysed results		
Notes:		**Notes:**

Continuous outcome

	Description as stated in report/paper						**Location in text** *(pg & fig/table)*
Comparison group/s							
Outcome							
Subgroup							
Time point measured							
Post-intervention or change from baseline?							
Results	**Intervention**			**Comparison**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							

(*Continued*)

Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*		
Reanalysis required? *(specify)*	Yes/No/Unclear	
Reanalysis possible?	Yes/No/Unclear	
Reanalysed results		
Notes:		**Notes:**

8. Other information

	Description as stated in report/paper	**Location in text** *(pg & fig/table)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what, and when)*		
Notes:		**Notes:**

Appendix 8. Quality assessment form

Allocation of Intervention		Comments
Method used to generate group allocation		
Quality of group allocation	Yes/No/Unclear	

(*Continued*)

Allocation Concealment		
Method used to conceal allocation		
Quality of allocation concealment	Yes/No/ Unclear	
Blinding		
Participant	Yes/No /Unclear	
Outcome assessor	Yes /No/Unclear	
Other - Specify:	Yes/No/Unclear	
Intention-to-treat		
Intention-to-treat analysis was applied to all participants entering study		
15% or fewer excluded		
Not analysed as intention-to-treat		
Unclear		
Incomplete outcome data		Comments
Was outcome data complete?		
Primary Outcome	Yes/No/Unclear	
Secondary Outcome 1	Yes/No/Unclear	
Secondary Outcome 2 (add more rows if necessary)	Yes/No/Unclear	
Reporting bias		
Have all stated outcomes been fully reported?		

(*Continued*)

Primary Outcome	Yes/No/Unclear	
Secondary Outcome 1	Yes/No/Unclear	
Secondary Outcome 2 (add more rows if necessary)	Yes/No/Unclear	
Other potential sources of bias		
Are there any other potential threats to validity?		
Imbalances of participants characteristics at baseline	Yes/No/Unclear	
Crossover studies (Refer 16.4.3 in *Cochrane Handbook* (Higgins 2011))	Yes/No/Unclear	
Other (Refer 8.15.1.5 in *Cochrane Handbook* (Higgins 2011))	Yes/No/Unclear	

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Amanda Corley (AC), Claire M Rickard (CMR), Leanne M Aitken (LMA), Amy Johnston (AJ), Adrian Barnett (AB), John F Fraser (JFF), Sharon R Lewis (SRL), Andrew F Smith (AFS).

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Providing additional data about papers: AC.

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Conducting other statistical analysis not using RevMan: AB, AC.

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Performing previous work that was the foundation of the present study: AC, JFF, AB.

Serving as guarantor for the review (one review author): AC.

Taking responsibility for reading and checking the review before submission: AC, AFS.

DECLARATIONS OF INTEREST

Amanda Corley (AC), Claire M Rickard (CMR), Leanne M Aitken (LMA), Amy Johnston (AJ), Adrian Barnett (AB), John F Fraser (JFF), Sharon R Lewis (SRL), Andrew F Smith (AFS).

JFF's employer, The Prince Charles Hospital, received an unrestricted grant from Fisher and Paykel Healthcare Ltd, the makers of Optiflow, an HFNC delivery system. The recipient of this grant was the institution of The Prince Charles Hospital, not JFF personally. The grant period was from April 2010 to March 2013. This unrestricted grant assisted in partially funding employment of a research nurse (Taressa Bull) to complete the study titled 'Oxygen delivery through high-flow nasal cannulae increases end expiratory lung volume and reduces respiratory rate in post-cardiac surgical patients when compared to standard low flow oxygen' (Corley 2011). This study is not eligible for inclusion in the current review. Fisher and Paykel Healthcare Ltd had no part in study design, data collection, data analysis, or manuscript preparation for that study (Corley 2011).

Fisher and Paykel Healthcare Ltd paid for AC to attend the American Thoracic Society meeting in New Orleans, in May 2010 (airfare), and a Fisher and Paykel research meeting in Auckland, New Zealand, in August 2009 (airfare and accommodation). JFF received travel funding from Fisher and Paykel to speak at research meetings in Paris (2009) and London (2010) on the Critical Care Research Group respiratory research programme, which included the study mentioned above (Corley 2011).

AC, AB, and JFF are investigators for an included study (Corley 2014), which was supported by a grant from The Prince Charles Hospital Foundation, and by the unrestricted grant from Fisher and Paykel Healthcare mentioned above. Again, the recipient of that grant was the institution of The Prince Charles Hospital, not JFF, AB, or AC. Any ongoing relationship between AC, AB, and AC and Fisher and Paykel Healthcare involves the research grants received by their institution, The Prince Charles Hospital, not by them personally. Fisher and Paykel Healthcare Ltd had no part in study design, data collection, data analysis, or manuscript preparation of the ongoing study (Corley, in progress).

Review authors CMR, LMA, AJ, SRL, and AFS have no conflicts of interest to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We included all three primary outcomes in the 'Summary of findings' table. In the protocol, we had previously stated that we would include the following outcomes in the 'Summary of findings' table: failure of treatment, as indicated by the need for NIPPV or invasive ventilation; duration in hours of any form of respiratory support; length of ICU stay; degree of atelectasis on radiological examination; oxygenation; carbon dioxide clearance; and patient-reported outcomes. In this review, we included the following outcomes in the 'Summary of findings' table: failure of treatment, as indicated by the need for NIPPV or invasive ventilation; in-hospital mortality; adverse events; length of ICU stay in days; oxygenation; and the patient-reported outcome - comfort.

- We did not perform a sequential meta-analysis for the primary outcome of failure of treatment.

- We did not perform subgroup analyses for age, BMI, aetiology of acute respiratory failure, obstructive sleep apnoea, or flow rates of HFNC owing to lack of studies with required detail.

- We did not perform sensitivity analysis on study design (randomized vs quasi-randomized studies) nor on missing data owing to lack of detail or insufficient studies.

NOTES

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