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High flow nasal cannula for respiratory support in term infants (Review)

Dopper A, Steele M, Bogossian F, Hough J

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[Intervention Review]

High flow nasal cannula for respiratory support in term infants

Alex Dopper[1], Michael Steele[1,2], Fiona Bogossian[3,4,5], Judith Hough[1,6,7]

[1]School of Allied Health, Australian Catholic University, Brisbane, Australia. [2]Nursing Research and Practice Development Centre, The Prince Charles Hospital, Brisbane, Australia. [3]School of Nursing, Midwifery and Social Work, The University of Queensland, St Lucia, Australia. [4]Sunshine Coast Health Institute, Birtinya, Australia. [5]School of Health, University of the Sunshine Coast, Petrie, Australia. [6]Department of Physiotherapy, Mater Health, South Brisbane, Australia. [7]Centre for Children's Health Research, The University of Queensland, South Brisbane, Australia

Contact: Alex Dopper, adopper9@gmail.com.

ABSTRACT

Background

Respiratory failure or respiratory distress in infants is the most common reason for non-elective admission to hospitals and neonatal intensive care units. Non-invasive methods of respiratory support have become the preferred mode of treating respiratory problems as they avoid some of the complications associated with intubation and mechanical ventilation. High flow nasal cannula (HFNC) therapy is increasingly being used as a method of non-invasive respiratory support. However, the evidence pertaining to its use in term infants (defined as infants ≥ 37 weeks gestational age to the end of the neonatal period (up to one month postnatal age)) is limited and there is no consensus of opinion regarding the safety and efficacy HFNC in this population.

Objectives

To assess the safety and efficacy of high flow nasal cannula oxygen therapy for respiratory support in term infants when compared with other forms of non-invasive respiratory support.

Search methods

We searched the following databases in December 2022: Cochrane CENTRAL; PubMed; Embase; CINAHL; LILACS; Web of Science; Scopus. We also searched the reference lists of retrieved studies and performed a supplementary search of Google Scholar.

Selection criteria

We included randomised controlled trials (RCTs) that investigated the use of high flow nasal cannula oxygen therapy in infants ≥ 37 weeks gestational age up to one month postnatal age (the end of the neonatal period).

Data collection and analysis

Two review authors independently assessed trial eligibility, performed data extraction, and assessed risk of bias in the included studies. Where studies were sufficiently similar, we performed a meta-analysis using mean differences (MD) for continuous data and risk ratios (RR) for dichotomous data, with their respective 95% confidence intervals (CIs). For statistically significant RRs, we calculated the number needed to treat for an additional beneficial outcome (NNTB). We used the GRADE approach to evaluate the certainty of the evidence for clinically important outcomes.

Main results

We included eight studies (654 participants) in this review. Six of these studies (625 participants) contributed data to our primary analyses.

Four studies contributed to our comparison of high flow nasal cannula (HFNC) oxygen therapy versus continuous positive airway pressure (CPAP) for respiratory support in term infants. The outcome of death was reported in two studies (439 infants) but there were no events in either group. HFNC may have little to no effect on treatment failure, but the evidence is very uncertain (RR 0.98, 95% CI 0.47 to 2.04; 3 trials, 452 infants; very low-certainty evidence). The outcome of chronic lung disease (need for supplemental oxygen at 28 days of life) was reported in one study (375 participants) but there were no events in either group. HFNC may have little to no effect on the duration of respiratory support (any form of non-invasive respiratory support with or without supplemental oxygen), but the evidence is very uncertain (MD 0.17 days, 95% CI -0.28 to 0.61; 4 trials, 530 infants; very low-certainty evidence). HFNC likely results in little to no difference in the length of stay at the intensive care unit (ICU) (MD 0.90 days, 95% CI -0.31 to 2.12; 3 trials, 452 infants; moderate-certainty evidence). HFNC may reduce the incidence of nasal trauma (RR 0.16, 95% CI 0.04 to 0.66; 1 trial, 78 infants; very low-certainty evidence) and abdominal overdistension (RR 0.22, 95% CI 0.07 to 0.71; 1 trial, 78 infants; very low-certainty evidence), but the evidence is very uncertain.

Two studies contributed to our analysis of HFNC versus low flow nasal cannula oxygen therapy (LFNC) (supplemental oxygen up to a maximum flow rate of 2 L/min). The outcome of death was reported in both studies (95 infants) but there were no events in either group. The evidence suggests that HFNC may reduce treatment failure slightly (RR 0.44, 95% CI 0.21 to 0.92; 2 trials, 95 infants; low-certainty evidence). Neither study reported results for the outcome of chronic lung disease (need for supplemental oxygen at 28 days of life). HFNC may have little to no effect on the duration of respiratory support (MD -0.07 days, 95% CI -0.83 to 0.69; 1 trial, 74 infants; very low-certainty evidence), length of stay at the ICU (MD 0.49 days, 95% CI -0.83 to 1.81; 1 trial, 74 infants; very low-certainty evidence), or hospital length of stay (MD -0.60 days, 95% CI -2.07 to 0.86; 2 trials, 95 infants; very low-certainty evidence), but the evidence is very uncertain. Adverse events was an outcome reported in both studies (95 infants) but there were no events in either group.

The risk of bias across outcomes was generally low, although there were some concerns of bias. The certainty of evidence across outcomes ranged from moderate to very low, downgraded due to risk of bias, imprecision, indirectness, and inconsistency.

Authors' conclusions

When compared with CPAP, HFNC may result in little to no difference in treatment failure. HFNC may have little to no effect on the duration of respiratory support, but the evidence is very uncertain. HFNC likely results in little to no difference in the length of stay at the intensive care unit. HFNC may reduce the incidence of nasal trauma and abdominal overdistension, but the evidence is very uncertain.

When compared with LFNC, HFNC may reduce treatment failure slightly. HFNC may have little to no effect on the duration of respiratory support, length of stay at the ICU, or hospital length of stay, but the evidence is very uncertain.

There is insufficient evidence to enable the formulation of evidence-based guidelines on the use of HFNC for respiratory support in term infants. Larger, methodologically robust trials are required to further evaluate the possible health benefits or harms of HFNC in this patient population.

PLAIN LANGUAGE SUMMARY

High flow nasal cannula oxygen therapy for respiratory support in term infants

Review question

Does high flow nasal cannula oxygen therapy improve the health outcomes of critically ill newborn infants requiring support for their breathing?

Background

When newborn infants have difficulty breathing, they may need external support to help move air in and out of their lungs (ventilation). There are various methods used to provide this breathing support. Invasive ventilation delivers air via a breathing tube placed in the baby's windpipe. Non-invasive ventilation delivers air via a mask that can be applied over the mouth or face, or small tubes positioned just inside the nostrils. These methods are often preferred since they may help avoid some of the complications associated with invasive ventilation.

What is high flow nasal cannula (HFNC) oxygen therapy?

HFNC oxygen therapy is one form of non-invasive respiratory support. It delivers heated, humidified oxygen gas at flow rates greater than 2 litres per minute via tubes positioned just inside the nostrils and is proposed to provide advantages over alternative oxygen therapies. However, in term infants (babies born after 37 weeks of pregnancy are completed) during their first month of life (the neonatal period) the evidence regarding the safety and effectiveness of HFNC is limited, and there is no consensus of opinion regarding its use in this population.

What did we want to find out?

We wanted to find out if high flow nasal cannula oxygen therapy improves the health outcomes of critically ill, term infants requiring respiratory support in their first month of life, when compared with other methods of non-invasive support. We also wanted to find out if it was associated with any unwanted effects.

What did we do?

In a search conducted to December 2022, we identified eight studies that investigated HFNC therapy across a total of 654 term infants. Six of these studies (625 participants) contributed data to our primary analysis. This involved comparing and summarising the results of the studies, and rating our confidence in the evidence based on factors such as study size and any limitations in the methods they used. Four of the studies compared HFNC with an alternative method of non-invasive support known as continuous positive airway pressure (CPAP) (where air is pressurised by a machine to a constant pressure and delivered into the airway via a mask placed over the face/mouth or tubes positioned just inside the nostrils). Two studies compared HFNC with low flow nasal cannula (LFNC) (oxygen therapy up to a maximum gas flow rate of 2 L/min).

Key results

The first results are from the comparison of HFNC and CPAP. Zero deaths were recorded by the studies. HFNC may have little to no effect on treatment failure, but the evidence is very uncertain. One study investigated chronic lung disease (the need for oxygen support at 28 days of life) but no infants in the study met these criteria. HFNC may have little to no effect on the duration of respiratory support (length of time infants receive any form of extra breathing support with or without the addition of oxygen), but the evidence is very uncertain. HFNC likely results in little to no difference in the length of stay at the intensive care unit (ICU). HFNC may reduce the incidence of nasal trauma (damage to the nasal tissue) and abdominal overdistension (where air accumulates in the abdomen and causes excessive expansion), but the evidence is very uncertain.

Our second results are from the comparison of HFNC and LFNC. Zero deaths were recorded by the studies. The evidence suggests HFNC may reduce treatment failure slightly. Neither study investigated chronic lung disease. HFNC may have little to no effect on the duration of respiratory support, length of stay at the ICU, or hospital length of stay, but the evidence is very uncertain. Both studies recorded zero adverse events.

What are the limitations of the evidence?

Our confidence in the evidence is moderate to very low. Three main factors reduced our confidence in the evidence. Firstly, some studies used methods likely to introduce errors in their results. Secondly, the results across the different studies were moderately inconsistent. Finally, some studies were very small.

Conclusions

When compared with CPAP, HFNC may result in little to no difference in treatment failure. HFNC may have little to no effect on the duration of respiratory support, but the evidence is very uncertain. HFNC likely results in little to no difference in the length of stay at the intensive care unit. HFNC may reduce the incidence of nasal trauma and abdominal overdistension, but the evidence is very uncertain.

When compared with LFNC, HFNC may reduce treatment failure slightly. HFNC may have little to no effect on the duration of respiratory support, length of stay at the ICU, or hospital length of stay, but the evidence is very uncertain.

There is insufficient evidence to enable the formulation of evidence-based guidelines on the use of HFNC for respiratory support in term infants. Larger, methodologically robust trials are required to further evaluate the possible health benefits or harms of HFNC in this patient population.

SUMMARY OF FINDINGS

Summary of findings 1.   Summary of findings table - High flow nasal cannula (HFNC) compared to continuous positive airway pressure (CPAP) for respiratory support in term infants (infants ≥ 37 weeks gestational age to the end of the neonatal period (up to 1 month postnatal age))

High flow nasal cannula (HFNC) compared to continuous positive airway pressure (CPAP) for respiratory support in term infants (infants ≥ 37 weeks gestational age to the end of the neonatal period (up to 1 month postnatal age))

Patient or population: respiratory support in term infants (infants ≥ 37 weeks gestational age to the end of the neonatal period (up to 1 month postnatal age))
Setting: hospital neonatal intensive care units (NICU) and neonatal units
Intervention: high flow nasal cannula (HFNC)
Comparison: continuous positive airway pressure (CPAP)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with continuous positive airway pressure (CPAP)	**Risk with high flow nasal cannula (HFNC)**				
Death				439 (2 RCTs)	-	The outcome was reported in 2 studies (439 infants) but there were no events in either group.
Treatment failure assessed with: as defined by trial authors, but typically indicated by the need for intubation or reintubation within 72 hours of initial extubation	172 per 1000	**169 per 1000** (81 to 351)	**RR 0.98** (0.47 to 2.04)	452 (3 RCTs)	⊕⊝⊝⊝ Very low[a,b]	HFNC may have little to no effect on treatment failure, but the evidence is very uncertain.
Chronic lung disease assessed with: need for supplemental oxygen at 28 days of life follow-up: 28 days				375 (1 RCT)	-	The outcome was reported in 1 study (375 participants) but there were no events in either group.
Duration of any form of respiratory support (any form of non-invasive respiratory support with or without supplemental oxygen) assessed with: measured in hours/days at the time of ceasing respiratory support	The mean duration of any form of respiratory support (any form of non-invasive respiratory support with or without supplemental oxygen)	MD **0.17 days higher** (0.28 lower to 0.61 higher)	-	530 (4 RCTs)	⊕⊝⊝⊝ Very low[a,c,d]	HFNC may have little to no effect on the duration of respiratory support, but the evidence is very uncertain.

	ranged from **0.83 to 4.17** days					
Length of stay at intensive care unit assessed with: measured in hours at the time of transfer/discharge from the ICU	The mean length of stay at intensive care unit ranged from **6 to 8.3** days	MD **0.9 days higher** (0.31 lower to 2.12 higher)	-	452 (3 RCTs)	⊕⊕⊕⊖ Moderate[d]	HFNC likely results in little to no difference in the length of stay at the intensive care unit.
Adverse events - nasal trauma assessed with: observation from treating team	316 per 1000	**51 per 1000** (13 to 208)	RR 0.16 (0.04 to 0.66)	78 (1 RCT)	⊕⊖⊖⊖ Very low[e,f]	HFNC may reduce the incidence of nasal trauma, but the evidence is very uncertain.
Adverse events - abdominal overdistention assessed with: observation from treating team	342 per 1000	**75 per 1000** (24 to 243)	RR 0.22 (0.07 to 0.71)	78 (1 RCT)	⊕⊖⊖⊖ Very low[e,f]	HFNC may reduce the incidence of abdominal overdistention, but the evidence is very uncertain.

*__The risk in the intervention group__ (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; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_432563670426595669.

[a] Downgraded by one level due to moderate inconsistency (due to the I2 value of 64% indicating moderate heterogeneity between studies).
[b] Downgraded by two levels due to imprecision in the result. Firstly, sample sizes were not sufficiently large and did not meet the optimal information size criteria (OIS) (the OIS is calculated on the basis of the number of participants required for an adequately powered individual study, equating to approximately 2000 patients assuming α of 0.05, and β of 0.2). Secondly, the 95% CI does not exclude a RR of 1.0 (i.e. does not exclude no effect) and therefore fails to exclude appreciable benefit or harm. Furthermore, the ratio of the upper and lower 95% CIs for RR is > 3 (2.04/0.47), and when calculated the 95% CIs for risk differences (RD) ranged from -0.25 to 0.16.
[c] Downgraded by one level for serious study limitations (due to two studies that were determined to have 'some concerns' for risk of bias, Gao 2017 provided 45% weighting in the meta-analysis with 'some concerns' of bias in the randomisation process; Milesi 2017 provided 3.5% weighting with 'some concerns' in the selection of the reported result).
[d] Downgraded by one level due to imprecision in the result (sample sizes were not sufficiently large).
[e] Downgraded by one level for serious study limitations (due to 'some concerns' for risk of bias, Gao 2017 - 'some concerns' of bias in the randomisation process).
[f] Downgraded by two levels for imprecision because only one study contributed evidence to this outcome and we noted a wide CI in the effect.

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Summary of findings 2.   Summary of findings table - High flow nasal cannula (HFNC) compared to low flow nasal cannula (LFNC) for respiratory support in term infants (infants ≥ 37 weeks gestational age to the end of the neonatal period (up to 1 month postnatal age))

High flow nasal cannula (HFNC) compared to low flow nasal cannula (LFNC) for respiratory support in term infants (infants ≥ 37 weeks gestational age to the end of the neonatal period (up to 1 month postnatal age))

Patient or population: respiratory support in term infants (infants ≥ 37 weeks gestational age to the end of the neonatal period (up to 1 month postnatal age))
Setting: hospital emergency departments and neonatal units
Intervention: high flow nasal cannula (HFNC)
Comparison: low flow nasal cannula (LFNC)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low flow nasal cannula (LFNC)	**Risk with high flow nasal cannula (HFNC)**				
Death				95 (2 RCTs)	-	The outcome of death was reported in both studies (95 participants) but there were no events in either group.
Treatment failure assessed with: as defined by trial authors, but typically indicated by the need for intubation or reintubation within 72 hours of initial extubation)	368 per 1000	**162 per 1000** (77 to 339)	**RR 0.44** (0.21 to 0.92)	95 (2 RCTs)	⊕⊕⊖⊖ Low[a,b]	HFNC may reduce treatment failure slightly.
Chronic lung disease (need for supplemental oxygen at 28 days of life) - not measured			-	-		No study reported this outcome.
Duration of any form of respiratory support (any form of non-invasive respiratory support with or without supplemental oxygen) assessed with: measured in hours/days at the time of ceasing respiratory support	The mean duration of any form of respiratory support (any form of non-invasive respiratory support with or without supplemental oxygen) was **2.45** days	MD **0.07 days lower** (0.83 lower to 0.69 higher)	-	74 (1 RCT)	⊕⊖⊖⊖ Very low[b,c]	HFNC may have little to no effect on the duration of respiratory support, but the evidence is very uncertain.
Length of stay at intensive care unit (ICU)	The mean length of stay at intensive	MD **0.49 days higher**	-	74 (1 RCT)	⊕⊖⊖⊖ Very low[b,c]	HFNC may have little to no effect on the length of stay at the

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
assessed with: measured in hours/days at the time of transfer/discharge from the ICU	care unit (ICU) was **3.82** days	(0.83 lower to 1.81 higher)				ICU, but the evidence is very uncertain.
Hospital length of stay assessed with: measured in hours/days at the time of discharge from the hospital	The mean hospital length of stay ranged from **3.6 to 3.78** days	MD **0.6 days lower** (2.07 lower to 0.86 higher)	-	95 (2 RCTs)	⊕⊖⊖⊖ Very low[b,d,e]	HFNC may have little to no effect on hospital length of stay, but the evidence is very uncertain.
Adverse events				95 (2 studies)	-	Adverse events was an outcome reported in both studies (95 infants) but there were no events in either group.

***The risk in the intervention group** (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; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_432566524860183380.

[a] We downgraded by one level due to imprecision in the result (sample sizes were not sufficiently large and did not meet the criteria for optimal information size (OIS). The OIS is calculated on the basis of the number of participants required for an adequately powered individual study, equating to approximately 2000 patients assuming α of 0.05, and β of 0.2.
[b] We downgraded by one level due to indirectness (the evidence may be regarded as indirect in relation to the broader question of interest because the population is primarily related to term infants with bronchiolitis).
[c] We downgraded by two levels due to imprecision because only one study contributed evidence to this outcome and we noted a wide CI in the effect.
[d] We downgraded by one level due to moderate inconsistency (due to the I2 value 63% indicating moderate heterogeneity between studies).
[e] We downgraded by one level due to imprecision in the result (sample sizes were not sufficiently large).

BACKGROUND

Description of the condition

Respiratory failure or respiratory distress in infants is the most common reason for non-elective admission to hospitals and neonatal intensive care units. Central to the care of these critically ill infants is the support of breathing and ventilation. In term infants (defined as infants ≥ 37 weeks gestational age to the end of the neonatal period (up to one month postnatal age)), support may be needed due to respiratory infections such bronchiolitis or pneumonia, congestive heart failure, parenchymal lung disease, trauma, or post-surgical interventions. Those with significant hypoxaemia or respiratory insufficiency often require invasive respiratory support via endotracheal tubes and mechanical ventilation. However, invasive methods are associated with various complications, such as ventilator-induced lung injury and ventilator-associated pneumonia (ARDS Network 2000; Dahlem 2003).

Non-invasive methods of respiratory support may avoid some of the complications associated with intubation and mechanical ventilation, and for many clinicians have become the preferred mode of treating respiratory problems in neonates (Hough 2012). These methods can include the provision of supplemental oxygen therapy or the delivery of positive airway pressure via a mask/nasal interface to help stabilise airways, reduce an infant's work of breathing, increase functional residual capacity, and improve oxygenation (Frey 2001). However, there are disadvantages with non-invasive methods. They are often cumbersome, and the interface can be poorly tolerated by infants (Yong 2005). This can make the delivery of oxygen and positive airway pressure variable and may result in ineffective ventilation. Therefore, an important consideration for providing effective non-invasive support is deciding which system will best support the infant's work of breathing, yet remain well tolerated throughout treatment.

Description of the intervention

Heated, humidified, high flow nasal cannula (HFNC) therapy is increasingly being used as a form of non-invasive respiratory support. High flow rates of oxygen gas are delivered (typically 2 to 8 L/min) via thin tapered tubes positioned inside the nostrils (Hough 2012; Manley 2019). The inspired oxygen concentration of the gas mixture can be manipulated from 21% to 100% (de Klerk 2008). Heating and humidification also provide advantages over standard oxygen delivery, reducing upper airway mucosal damage, preventing inflammatory interactions, decreasing mucus production and viscosity, and reducing naso-pulmonary bronchoconstrictor reflexes (Cingi 2015; Dysart 2009). HFNC can be used as an initial form of respiratory support or as a 'step-down' modality after intubation/mechanical ventilation. HFNC has also been reported to be better tolerated than other forms of non-invasive ventilation, and easier to care for and apply (Roca 2010; Saslow 2006; Spentzas 2009). This reduces the need for the sedation that is often required to help tolerate more uncomfortable forms of respiratory support. Retrospective studies have shown that the use of HFNC reduced overall ventilator days in infants and that reintubation rates were also greatly reduced (McKiernan 2010; Schibler 2011; Wing 2012).

How the intervention might work

The proposed mechanisms of action of HFNC include:

- High flow rates of gas flush the anatomical dead space of the nasopharyngeal cavity resulting in improved alveolar ventilation. This may also wash out carbon dioxide and reduce apnoea caused from hypercapnia, thereby improving overall ventilation (Dysart 2009; Spence 2007).
- High flow rates can generate continuous positive airway pressure, helping to stent open and stabilise airways, improve functional residual capacity, and increase alveolar recruitment (McKiernan 2010; Schibler 2011; Wilkinson 2011). The amount of pressure generated depends on the flow delivered relative to the size of the infant, the size of the nasal cannula, and the leak around the nares (Lampland 2009; Screenan 2001).
- Improved ability to meet the respiratory needs of patients with high inspiratory demands and deliver a more accurate fraction of inspired oxygen (FiO_2) with less entrainment of room air (Dysart 2009).
- Heating and humidification of gas mixtures reduces upper airway mucosal damage, preventing inflammatory interactions, decreasing mucus production and viscosity, enhancing mucociliary transport, and reducing naso-pulmonary bronchoconstrictor reflexes (Cingi 2015; Dysart 2009).

Why it is important to do this review

Given the known associated risks of intubation and mechanical ventilation and the increasing use and clinician preference for non-invasive respiratory support methods, it is important that HFNC therapy is appropriately evaluated. To date, there is no review that examines the use of HFNC in the term infant population (aged ≥ 37 weeks gestational age to one month postnatal age). This notable gap in the literature for term infants may suggest that clinical decisions surrounding HFNC in neonatal wards and intensive care units (ICUs) are based on rituals and clinician preference rather than physiological rationale and reliable evidence. Hence, this review may help standardise care and promote evidence-based practice.

There is a published Cochrane Review on the use of HFNC therapy in preterm infants (Wilkinson 2016). This review concluded HFNC has similar rates of efficacy to other forms of non-invasive respiratory support and may be associated with less nasal trauma and reduced pneumothorax rates when compared with nasal continuous positive airway pressure (CPAP). There are also Cochrane Reviews investigating HFNC in adults (Lewis 2021), children (Mayfield 2014a), and infants with bronchiolitis (Beggs 2014). In the latter populations, there was insufficient evidence to determine the safety or effectiveness of HFNC, while in adults there was low-quality evidence suggesting that HFNC may lead to fewer treatment failures when compared to standard oxygen therapy.

OBJECTIVES

To assess the safety and efficacy of high flow nasal cannula oxygen therapy for respiratory support in term infants when compared with other forms of non-invasive respiratory support.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We included prospective randomised controlled trials (RCTs) investigating the use of high flow nasal cannula oxygen therapy in infants ≥ 37 weeks gestational age to one month postnatal age. We also accepted RCT data available only in conference abstract form. We did not include quasi-RCTs (since their methods of allocating participants to groups are not truly random) or other RCT designs.

Types of participants

We defined term infants as infants ≥ 37 weeks gestational age to the end of the neonatal period (up to one month postnatal age). We excluded preterm infants below 37 completed gestational weeks, and infants older than one month postnatal age. There was no exclusion based on diagnosis of disease or condition.

Two populations of term infants were considered:

1. those infants requiring HFNC as an initial mode of respiratory support, regardless of length of therapy and without a prior period of intermittent positive pressure ventilation;
2. those infants requiring HFNC as respiratory support following a period of intermittent positive pressure ventilation, i.e. post extubation.

Types of interventions

For the purpose of this review, HFNC oxygen therapy is defined as flow rates greater than 2 L/min with a blended air/oxygen system delivered via nasal cannula.

Comparator interventions included:

- continuous positive airway pressure;
- low flow nasal cannula oxygen therapy (supplemental oxygen up at flow rates less than or equal to 2 L/min).

Other comparator interventions we intended to investigate included head box oxygen, non-invasive positive pressure ventilation, and HFNC using an alternative technique (e.g. non-humidified). However, we identified no studies comparing HFNC and these comparator interventions in term neonates.

Types of outcome measures

In clarifying the role of outcomes, we are aware that outcome measures should not always form part of the criteria for including studies in a review (as per the MECIR standard C8 in *Cochrane Handbook for Systematic Reviews of Interventions Section 3, 3.2.4.1.* (Higgins 2022)). However, some reviews do legitimately restrict eligibility to specific outcomes. For example, the same intervention may be studied in the same population for different purposes. We believe this is the case for high flow nasal cannula oxygen therapy. Some studies investigate high flow nasal cannula oxygen therapy with regard to specific treatment monitoring outcomes such as work of breathing and respiratory rate. Our review sought to investigate endpoint outcomes such as treatment failure or duration of respiratory support (any form of non-invasive respiratory support with or without supplemental oxygen). Furthermore, for any studies that were excluded on the basis

of outcomes, our review authors took care in ascertaining that the relevant outcomes were not available because they had not been measured rather than simply not reported. This was done by examining the relevant trial registrations and protocols to confirm that our review outcomes were not measured or reported.

Primary outcomes

- Death (before hospital discharge)
- Treatment failure (as defined by trial authors, but typically indicated by the need for intubation or reintubation within 72 hours of initial extubation)
- Chronic lung disease (defined as the need for supplemental oxygen at 28 days of life (Wilkinson 2016))

Secondary outcomes

- Duration of any form of respiratory support (defined as any form of non-invasive respiratory support with or without supplemental oxygen, measured in hours/days at the time of ceasing respiratory support)
- Length of stay at intensive care unit (ICU) (measured in hours/days at the time of transfer/discharge from the ICU)
- Hospital length of stay (measured in hours/days at the time of discharge from the hospital)
- Adverse effects
  - Air leak syndrome (such as pneumothorax, pneumomediastinum, pneumopericardium or pulmonary interstitial emphysema (PIE) reported either individually or as a composite outcome)
  - Nasal trauma (defined as damage to the nasal tissue, such as erosion of the nasal mucosa, nares or septum, reported individually as a discrete outcome)
  - Abdominal overdistension (where air escapes from the lungs into surrounding areas where air is not normally present, reported as individually as a discrete outcome)
  - Nosocomial pneumonia (or hospital-acquired pneumonia, that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission, reported individually as a discrete outcome)

Search methods for identification of studies

Electronic searches

We searched the following databases in December 2022:

- Cochrane Central Register of Controlled Trials (Cochrane Library) (earliest to 13 December 2022);
- CINAHL via EBSCO Host (1982 to 12 December 2022);
- Embase via Ovid (1947 to 12 December 2022);
- LILACS (1982 to 13 December 2022);
- Web of Science (1985 to 12 December 2022);
- PubMed (1966 to 13 December 2022); and
- Scopus (1966 to 12 December 2022).

Search terms and subject headings were database-specific and included: infant* OR neonat* OR neo-nat* OR newborn* OR new-born* OR "new born*" OR "newly born*" OR baby* OR babies AND "nasal cannula*" OR "nasal prong*" OR "high-flow nasal" OR "high flow nasal" OR HFNC OR "respiratory support*" OR "artificial respiration". Database-specific filters for RCTs were also used. We

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did not apply any language or publication restrictions to our searches. See Appendix 1 for the full search strategies.

Searching other resources

We manually handsearched the reference lists of retrieved studies, along with grey literature to locate any additional relevant studies. We also conducted a supplementary search of Google Scholar. We screened results in Google Scholar, and the screening approach was to stop when five pages of Google Scholar search results (or 50 results) yielded nothing relevant. Since Google Scholar results are relevancy ranked, the probability of another relevant article then drops to less than 1 in 50 (Griffith University 2017).

Data collection and analysis

We used the standard methods of Cochrane Neonatal, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

Selection of studies

We exported the results of the electronic database searches to Covidence (Covidence 2021). Two review authors (AD, JH) independently reviewed the search results by title and abstract, excluding studies that clearly did not meet the inclusion criteria. We then performed full-text assessment on the potentially relevant studies, and those deemed ineligible are listed in the Characteristics of excluded studies table with reasons for exclusion. We resolved disagreements by consulting a third author (MS). When further information was required for a study's inclusion, we attempted to contact the authors directly.

Data extraction and management

Two review authors (AD, JH) independently performed data extraction using the standardised Cochrane data extraction form. We resolved any discrepancies by discussion and consensus with a third author (MS). We used Review Manager Web software for data entry and construction of comparison tables and graphs (RevMan Web 2020)

Assessment of risk of bias in included studies

We used the Cochrane RoB 2 tool to assess the risk of bias in the included studies (Sterne 2019). The outcomes that we assessed for each study are specified in Summary of findings 1 and Summary of findings 2. Of interest was the effect of the assignment to the intervention (the intention-to-treat (ITT) effect), thus we performed all assessments with RoB 2 on this effect.

Two review authors (AD, JH) independently assessed the risk of bias (low, high, or some concerns) for each outcome. In case of discrepancies amongst their judgements and inability to reach consensus, we consulted the third review author to reach a final decision. We assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

To address these types of bias, we used the signalling questions recommended in RoB 2 and made a judgement using the following options.

- 'Yes': if there is firm evidence that the question was fulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'Probably yes': a judgement was made that the question was fulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'No': if there was firm evidence that the question was unfulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'Probably no': a judgement was made that the question was unfulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'No information': if the study report provided insufficient information to allow any judgement.

We then used the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias:

- Low risk of bias.
- Some concerns.
- High risk of bias.

This allowed the review authors to derive an overall risk of bias rating for each outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judged the trial at low risk of bias for all domains for this result.
- 'Some concerns': we judged the trial to raise some concerns in at least one domain for this result, but not at high risk of bias for any domain.
- 'High risk of bias': we judged the trial at high risk of bias in at least one domain for the result, or we judged the trial to have some concerns for multiple domains in a way that substantially lowered confidence in the results.

We used the RoB 2 Excel tool to implement RoB 2 (accessed on 28 February 2022 and available at riskofbias.info). See the RoB 2 full guidance document for a detailed view of each domain, its signalling questions, and algorithms (available at riskofbias.info).

Measures of treatment effect

We analysed the results of the included studies using the statistical package in RevMan Web (RevMan Web 2020). We collected the means and standard deviations for continuous data (such as duration of respiratory support) and analysed the data using mean differences with 95% confidence intervals (CIs). For dichotomous data (such as treatment failure) we presented risk ratios with 95% confidence intervals (CIs). For statistically significant risk ratios, we calculated the number needed to treat for an additional beneficial outcome (NNTB). We used the methods described in Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022), to calculate the NNTB from the risk ratio, using the risk in the comparator group from Summary of findings 1 and Summary of findings 2 as the 'assumed comparator risk' (ACR).

Unit of analysis issues

The aim of this review was to summarise trials that analysed data at the level of the individual. We would have accepted cluster-randomised trials for inclusion had any been identified, and analysed these according to the methods in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2022). Data from cluster-randomised trials would have been included in meta-analyses only if the following information could be extracted:

- the number of clusters (or groups) randomised to each intervention group and the total number of participants in the study; or the average (mean) size of each cluster;
- the outcome data ignoring the cluster design for the total number of individuals (e.g. the number or proportion of individuals with events, or means and standard deviations for continuous data); and
- an estimate of the intracluster (or intraclass) correlation coefficient (ICC).

Dealing with missing data

Our review has narrowly defined inclusion criteria (infants aged ≥ 37 weeks gestational age to the end of the neonatal period (up to one month postnatal age)). Most RCTs included large cohorts of infants with ages up to 24 months and could include preterm infants. As a result, we contacted the corresponding author for all potentially eligible studies to request further information to determine study inclusion or exclusion, and to obtain the data and results of all participants that met our inclusion criteria. Where authors did not respond, we were unable to include their study in our review and the details of these studies can be found in Characteristics of studies awaiting classification. The remaining authors kindly provided additional data, and we would like to acknowledge their contribution to this review (see Acknowledgements).

Assessment of heterogeneity

Three review authors (AD, JH, MS) analysed methodological and clinical heterogeneity across the studies. This involved a consideration of their participants, interventions, comparators, and outcomes to determine whether there were differences between the studies that might have affected results. Where groups of studies seemed similar enough to pool in a meta-analysis, we then considered statistical heterogeneity. We quantified this using a Chi^2 test on the N-1 degrees of freedom, with an alpha value of 0.1 used for statistical significance, and the I^2 statistic (Higgins 2022). We used the following I^2 values for interpreting the degree of heterogeneity:

- < 25%: no heterogeneity
- 25% to 49%: low heterogeneity
- 50% to 74%: moderate heterogeneity
- ≥ 75%: high heterogeneity

In the presence of heterogeneity > 50%, we planned to examine the sources of heterogeneity through a sensitivity and/or subgroup analysis providing there were sufficient data for the analyses to be meaningful. Where we found no or low heterogeneity amongst trials, we used a fixed-effect model for meta-analysis. Conversely, where we found evidence of moderate or high heterogeneity amongst trials, we combined the data in a meta-analysis using a random-effects model.

Assessment of reporting biases

We planned to calculate funnel plot symmetry to detect any publication bias, however there were not at least 10 trials included in each meta-analysis.

Data synthesis

We reviewed the Characteristics of included studies to identify clinical heterogeneity amongst trials. We employed the following approaches for data synthesis.

- For continuous data, we used an inverse-variance approach.
- For dichotomous data, we used a Mantel-Haenszel approach.

The primary analysis included only the studies with either a low risk of bias or some concerns of bias.

Subgroup analysis and investigation of heterogeneity

We intended to perform subgroup analysis to explore possible sources of heterogeneity, with the planned analyses to be stratified by:

- pneumonia/pneumonitis (aspiration, bacterial, or viral);
- congestive heart failure.

However, this was not performed given there were insufficient data for the analyses to be meaningful.

Sensitivity analysis

There were insufficient data for a meaningful sensitivity analysis to take place. If there had been an adequate number of studies, we had planned to perform a sensitivity analysis for methodological quality and robustness of results. This would have been performed by using the overall risk of bias from RoB 2 for each outcome.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence of the following clinically relevant outcomes: death, treatment failure, chronic lung disease, duration of respiratory support, length of stay at intensive care unit (ICU), hospital length of stay, and adverse events.

Two review authors (AD, JH) independently assessed the certainty of the evidence for each outcome. We arrived at these conclusions by starting with a default of high certainty based on study design (RCT) and then downgraded based on any limitations relating to the RoB 2 overall risk of bias judgements and other GRADE considerations such as imprecision, indirectness, inconsistency, and publication bias. The GRADE Handbook guidance for downgrades based on the RoB 2 judgements are as follows:

- Low risk of bias would indicate "no serious limitations".
- Some concerns of risk of bias would indicate either "no serious limitations" or "serious limitations".
- If the identified risk of bias is considered serious, the quality of evidence for the outcome is downgraded by one level.
- If the identified risk of bias is considered very serious, the quality of evidence for the outcome is downgraded by two levels.

We downgraded the certainty of evidence by one level where the risk of bias judgement was 'some concern'. Bias judgements of 'some concern' do not always indicate serious limitations in design. However, given that our bias judgements were due to some concerns in the randomisation process, we felt this represented a potentially serious limitation and downgraded accordingly.

We used the GRADEpro GDT Guideline Development Tool to create Summary of findings 1 and Summary of findings 2 to report the certainty of the evidence. The GRADE approach results in an assessment of the certainty of a body of evidence as one of four grades.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

- Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

R E S U L T S

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

Searches identified 7265 references; after removing 2937 duplicates, 4328 records were available for title/abstract screening. We excluded 4234 based on title/abstract, reviewed 94 full texts, included 8 studies (18 references), excluded 59 studies, classified 10 studies as awaiting classification (14 references), and identified 3 ongoing studies. For details see Figure 1.

Figure 1. Study flow diagram.

Figure 1. (Continued)

6 studies included in quantitative synthesis (meta-analysis)
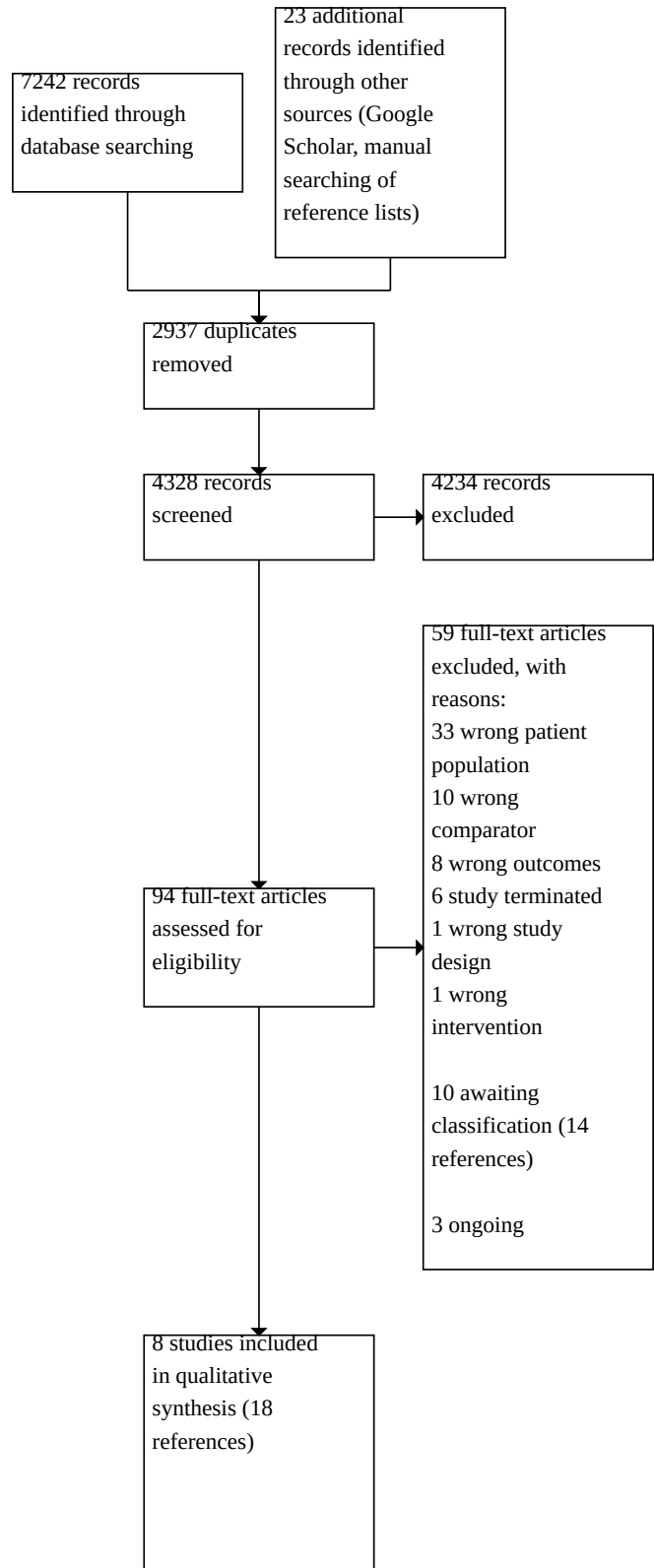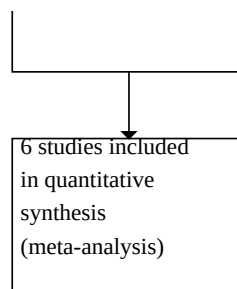
Included studies

We included eight RCTs (18 references), with a total of 654 term infants in the review (see Characteristics of included studies table). There were five RCTs investigating high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) (546 participants), and three RCTs investigating HFNC versus low flow nasal cannula (LFNC) (108 participants). We deemed two of the eight included studies to have high overall risk of bias (Abboud 2015; Vahlkvist 2020), so we excluded them from our primary analysis. Therefore, our primary analysis included six studies (625 term infants).

High flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP)

Milesi 2017 performed a multi-centre RCT across five paediatric intensive care units (PICU) from French university hospital centres. The study enrolled 142 participants (aged one day to six months) with moderate to severe respiratory distress. Inclusion criteria were a modified Wood's Clinical Asthma Score (mWCAS) > 3, no underlying cardiac or neuromuscular disease and no pneumothorax on chest radiograph, absence of indication for imminent intubation, and authorisation to perform the study signed by both parents. The total number of term infants that met the inclusion criteria of this review was 64 (35 nCPAP, 29 HFNC). Infants allocated to the CPAP group received positive continuous pressure set at + 7 cmH_2O. Infants allocated to the HFNC group received flow delivered at 2 L/kg/min, equipped with a pressure release valve set at + 45 cmH_2O. For both experimental groups, FiO_2 was titrated to achieve a normoxic SpO_2 of 94% to 97%. The protocol lasted a minimum of 24 hours after the allocated treatment had begun, and occurrence of at least one treatment failure criterion justified a switch to the alternative respiratory support. Patients that switched supports were maintained on the second support for 24 hours. The primary outcome was treatment failure within 24 hours after randomisation. Secondary outcomes included predictors of failure, success rate after cross-over, intubation rate, occurrence of skin lesions, length of stay, and serious adverse events.

Manley 2019 performed a multicentre RCT across nine Australian non-tertiary centres. The study enrolled 768 patients (aged less than 24 hours) born at a gestational age of 31 weeks or later. The total number of term infants that met the inclusion criteria of this review was 375 (179 CPAP, 196 HFNC). Infants assigned to the CPAP group received + 7 to 8 cmH_2O delivered through short binasal prongs or a nasal mask. Infants who met the criteria for treatment failure while receiving CPAP received endotracheal intubation as appropriate. Infants assigned to the high-flow group received 6 to 8 L/min delivered via an Optiflow Junior device (Fisher and Paykel Healthcare). If the criteria for treatment failure were met, the infants could receive CPAP as rescue therapy initiated at a pressure of 8 cmH_2O. The primary outcome was treatment failure within 72 hours after randomisation. The study had a similar threshold for failure to Milesi 2017, classified by occurrence of one or more of their prespecified criteria: (1) FiO_2 of 0.4 or higher for more than one hour to maintain target SpO_2 levels of 91% to 95%, (2) a pH of less than 7.2 plus a pCO_2 greater than 60 mmHg in two samples of arterial or capillary blood obtained at least one hour after commencement and obtained one hour apart, (3) two or more episodes of apnoea for which positive-pressure ventilation was indicated within a 24-hour period, (4) need for endotracheal intubation and mechanical ventilation or required transfer to a neonatal intensive care unit (NICU), (5) respiratory management escalated at the discretion of the clinician. Secondary outcomes included reasons for treatment failure, endotracheal intubation, transfer to the NICU, duration of respiratory support, supplemental oxygen, and length of hospitalisation.

Cesar 2020 performed a single-centre, two-arm, parallel-group RCT in the PICU of the Hospital Infantil Sabará, in São Paulo, Brazil. The study enrolled 63 children (up to nine months of age) with a primary diagnosis of critical bronchiolitis. Exclusion criteria included any congenital or acquired heart disease, neuromuscular disease, chronic lung disease, pulmonary malformations, or the presence of a tracheostomy. The total number of term infants that met the inclusion criteria of this review was 13 (7 CPAP, 6 HFNC). Infants allocated to the CPAP group were fitted with nasal prongs with pressure set at 6 cmH_2O for all patients. Infants allocated to the HFNC received flow rates titrated up to a maximum of 1.5 L/kg/min. In both experimental groups, FiO_2 was adjusted to achieve a SpO_2 > 93%. Unlike Milesi 2017 and Manley 2019, the study protocol did not allow for a switch to the alternative intervention. The primary outcome was the rate of treatment failure (the need to escalate support to non-invasive bilevel pressure ventilation, or endotracheal intubation). Secondary outcomes included the duration of the primary treatment, PICU and hospital length of stay, and development of apnoea.

Vahlkvist 2020 performed a multicentre RCT in the paediatric department at the Hospital of South West Jutland, Denmark, and the department of paediatrics at Kolding Hospital, Denmark.

The study enrolled 50 participants (up to two years of age) with bronchiolitis and need for respiratory support. Exclusion criteria included previous chronic disease or severe respiratory insufficiency with decreased consciousness, need for urgent treatment, and a capillary $pCO_2 > 9.0$. The total number of term infants that met the inclusion criteria of this review was 16 (10 CPAP, 6 HFNC). Children allocated to the CPAP group were fitted with nasal prongs connected to Fisher & Paykel Healthcare® Auckland, New Zealand, at an initial flow rate of 12 to 14 L/min. Children allocated to the HFNC group received initial flow rates of 2 L/kg/min. For both experimental groups, flow could be increased to a maximum of 15 L/min and oxygen supply was delivered as needed to maintain a SpO_2 above 92%. Secondary outcomes included differences in pain scores, treatment duration, and frequency of system failure.

Gao 2017 conducted a single-centre RCT in the Department of Neonatology of the Maternal and Child Health Hospital of Guangxi Zhuang Region. The study enrolled 78 term infants (aged 37 to 42 weeks gestational age). Exclusion criteria included severe asphyxia, hypoxic ischaemic encephalopathy, congenital malformations, and inherited metabolic diseases. Infants in the CPAP group received an initial gas flow of 8 to 10 L/min, positive end-expiratory pressure (PEEP) of 4 to 6 cmH_2O, and an FiO_2 of 0.3 to 0.45. The HFNC group received heated and humidified inhaled gas at 37 °C, flow rates of 2 to 8 L/min and an FiO_2 of 0.3 to 0.4. The primary outcome was weaning failure. Secondary outcomes included time of non-invasive respiratory support, establishment of total enteral feeding, hospital length of stay, incidence of nasal injury, abdominal muscle overdistension, air leak, and intraventricular haemorrhage.

HFNC versus LFNC

Franklin 2018 performed a multicentre RCT across emergency departments and general paediatric inpatient units in 17 tertiary and regional hospitals in Australia and New Zealand. The study enrolled 1472 participants (up to 12 months of age) with clinical signs of bronchiolitis and a need for supplemental oxygen therapy to keep oxygen saturation levels in the range of 92% to 98%. Exclusion criteria included critically ill infants who had an immediate need for respiratory support and ICU admission, infants with cyanotic heart disease, basal skull fracture, upper airway obstruction, or craniofacial malformation, and infants who were receiving oxygen therapy at home. The total number of term infants that met the inclusion criteria of this review was 74 (28 "standard therapy" group, 46 high flow group). Franklin 2018 defined standard therapy as supplemental oxygen through a nasal cannula up to a maximum of 2 L/min to maintain an oxygen saturation level in the range of 92% to 98%. Infants in the high flow group received heated and humidified high flow oxygen at a rate of 2 L/kg/min. FiO_2 was adjusted to obtain oxygen saturation levels in the range of 92% to 98%. The primary outcome was escalation of care due to treatment failure (defined as meeting ≥ 3 of 4 clinical criteria: persistent tachycardia, tachypnoea, hypoxaemia, and medical review triggered by a hospital early-warning tool). Secondary outcomes included duration of hospital stay, duration of oxygen therapy, rates of transfer to a tertiary hospital, ICU admission, intubation, and adverse events.

Kepreotes 2017 conducted a single-centre RCT in the emergency department and medical unit of the John Hunter Children's Hospital, Australia. The study enrolled 202 participants (up to 24

months of age) with clinical signs of bronchiolitis and a need for supplemental oxygen therapy. Exclusion criteria included infants with mild bronchiolitis not requiring oxygen, infants admitted to the ward after ICU management, infants transferred from other facilities if they had received supplemental oxygen prior to arrival, a known diagnosis of asthma, the presence of pneumothorax or nasal trauma, and severe or life-threatening bronchiolitis. The total number of term infants that met the inclusion criteria of this review was 21 (10 "standard therapy" group, 11 HFNC group). Kepreotes 2017 defined standard therapy as infants fitted with nasal cannulae receiving cold wall oxygen 100% at low flow to a maximum of 2 L/min. The intervention group received high flow warm humidified oxygen (HFWHO) via age-appropriate Optiflow Junior nasal cannulae and the MR850 humidifier (Fisher and Paykel Healthcare, Auckland, New Zealand) up to a limit of 20 L/min using 1:1 air-oxygen ratio, resulting in a maximum FiO_2 of 0.6. The primary outcome was time to weaning off oxygen. Treatment failure was a secondary outcome defined as critically abnormal observations that fell within the red zone on an age-appropriate standard paediatric observation chart for heart rate, respiratory rate, SpO_2 (< 90%), or respiratory distress score (severe) while on maximum therapy, along with a clinical decision by the treating physician that the current treatment was insufficient to reverse the deterioration. Other outcomes included proportion of serious adverse events, transfer to ICU, length of hospital stay, baseline-adjusted heart rate and respiratory rate, and parent-reported outcomes via phone follow-up.

Abboud 2015 presented the findings of their RCT via a conference poster and study abstract. Their study enrolled 51 participants (up to 13 months of age) with clinical signs and symptoms of viral bronchiolitis or confirmed laboratory evidence of viral infection. Exclusion criteria were one of the following conditions: cyanotic heart disease, neuromuscular disease, multiple congenital abnormalities, immunocompromised, or the presence of a tracheostomy or intubation. The total number of term infants that met the inclusion criteria of this review was 13 (1 CPAP, 12 HFNC). Participants were randomised to either the standard nasal cannula (NC) oxygen group or the high flow high humidity (HFHH) NC group. The details and settings of the interventions were omitted from the conference poster. Treatment failure was defined as progression to HFHH (NC group only), CPAP or intubation. Secondary outcomes included PICU length of stay, respiratory rate, work of breathing, capillary pH and pCO_2, desaturations, and grunting pre and one hour post therapy initiation.

Excluded studies

We excluded 59 studies following full-text assessment: 33 were excluded due to wrong patient populations, 10 due to wrong comparator, 8 due to wrong outcomes, 6 due to study termination, 1 due to wrong study design, and 1 due to wrong intervention. Refer to the Characteristics of excluded studies for additional information.

Risk of bias in included studies

Overall and domain level risk of bias assessments for each outcome are included alongside the forest plots for each outcome located in Data and analyses. Domain level risk of bias judgements and support for judgements are included in the Risk of bias (tables). To access detailed risk of bias assessment data (with consensus responses to the signalling questions) use the following link.

Risk of bias for the randomisation process is a study-level judgement. We deemed two studies to have 'some concerns' of bias arising from the randomisation process (Abboud 2015; Gao 2017). These studies failed to provide information on the concealment of their allocation sequence. The remaining studies achieved adequate allocation concealment via sequentially numbered, sealed, opaque envelopes (low risk of bias). All studies reported that participants were randomly assigned to groups, however the methods of random sequence generation were not described in four studies (Abboud 2015, Cesar 2020; Kepreotes 2017; Vahlkvist 2020). For all studies, any baseline differences observed between intervention groups appeared to be compatible with chance and did not lead to a risk of bias.

Overview of risk of bias assessments by outcome

Treatment failure

HFNC versus CPAP (Risk of bias table for Analysis 1.2)

We deemed one of the four studies to have a high overall risk of bias for treatment failure ('some concerns' with measurement of the outcome, 'high risk' for deviations from the intended intervention, 'high risk' for missing outcome data) (Vahlkvist 2020). As a result, we excluded this study from the primary analysis, since only studies with 'low risk' or 'some concerns' of bias were included. The remaining three studies were at low risk of bias for this outcome (Cesar 2020; Manley 2019; Milesi 2017).

HFNC versus LFNC (Risk of bias table for Analysis 2.2)

We deemed one of the three studies to have a high risk of bias for treatment failure ('some concerns' with the randomisation process and selection of the reported result, 'high risk' for deviations from the intended intervention and measurement of the outcome) (Abboud 2015). We excluded this study from the primary analysis. The remaining two studies were at low risk of bias for this outcome (Franklin 2018; Kepreotes 2017).

Duration of any form of respiratory support

HFNC versus CPAP (Risk of bias table for Analysis 1.4)

We deemed one of the five studies to have a high overall risk of bias for this outcome ('some concerns' with measurement of the outcome, 'high risk' for deviations from the intended intervention, 'high risk' for missing outcome data) (Vahlkvist 2020). We excluded this study from the primary analysis. Two studies received a judgement of 'some concerns' (due to 'some concerns' with the randomisation process (Gao 2017), and selection of the reported result (Milesi 2017)). The remaining two studies were at low risk of bias for this outcome (Cesar 2020; Manley 2019).

HFNC verus LFNC (Risk of bias table for Analysis 2.4)

One study investigated the duration of respiratory support and was found to be at low risk of bias (Franklin 2018).

Length of stay at ICU (days)

HFNC versus CPAP (Risk of bias table for Analysis 1.5)

All three studies investigating ICU length of stay were at low risk of bias for this outcome (Cesar 2020; Manley 2019; Milesi 2017).

HFNC versus LFNC (Risk of bias table for Analysis 2.5)

We deemed one study to have a high risk of bias for this outcome ('some concerns' with the randomisation process and selection of the reported result, 'high risk' for deviations from the intended intervention and measurement of the outcome) (Abboud 2015). We excluded this study from the primary analysis. The remaining study was at low risk of bias for this outcome (Franklin 2018).

Hospital length of stay (days)

HFNC versus CPAP (Risk of bias table for Analysis 1.6)

One study received a judgement of 'some concerns' for hospital length of stay (due to 'some concerns' with the randomisation process) (Gao 2017). The remaining two studies were at low risk of bias for this outcome (Cesar 2020; Manley 2019).

HFNC versus LFNC (Risk of bias table for Analysis 2.6)

Both studies investigating hospital length of stay were at low risk of bias for this outcome (Franklin 2018; Kepreotes 2017).

Adverse events

HFNC versus CPAP

Air leak syndrome (Risk of bias table for Analysis 1.7):
One study received a judgement of 'some concerns' for this outcome (due to 'some concerns' with the randomisation process) (Gao 2017). The remaining study was at low risk of bias for this outcome (Manley 2019).

Nasal trauma (Risk of bias table for Analysis 1.8):
One study investigated the incidence of nasal trauma and received a judgement of 'some concerns' for this outcome ('some concerns' with the randomisation process) (Gao 2017).

Abdominal overdistension (Risk of bias table for Analysis 1.9):
One study investigated the incidence of abdominal overdistension and received a judgement of 'some concerns' for this outcome ('some concerns' with the randomisation process) (Gao 2017).

HFNC versus LFNC

Both studies reported on adverse events and recorded zero events.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - High flow nasal cannula (HFNC) compared to continuous positive airway pressure (CPAP) for respiratory support in term infants (infants ≥ 37 weeks gestational age to the end of the neonatal period (up to 1 month postnatal age)); **Summary of findings 2** Summary of findings table - High flow nasal cannula (HFNC) compared to low flow nasal cannula (LFNC) for respiratory support in term infants (infants ≥ 37 weeks gestational age to the end of the neonatal period (up to 1 month postnatal age))

Below we detail two comparisons regarding the effects of high flow nasal cannula in term infants. Comparison one investigates HFNC versus CPAP. Comparison two investigates HFNC versus LFNC. See Summary of findings 1; Summary of findings 2.

Comparison one: HFNC versus CPAP in term infants requiring respiratory support

Four studies were included in this comparison with a total of 530 participants (Cesar 2020; Gao 2017; Manley 2019; Milesi 2017). One study was excluded due to a high risk of bias (Vahlkvist 2020). We assessed the studies for clinical or methodological differences and found them to be similar enough to perform meta-analysis for some outcomes. See Summary of findings 1.

Primary outcomes

1.1 Death

The outcome of death was reported in two studies (439 infants) but there were no events in either group (Manley 2019; Milesi 2017).

1.2 Treatment failure

Three studies (452 participants) were included in the primary analysis of treatment failure (Cesar 2020; Manley 2019; Milesi 2017). In assessing their clinical and methodological heterogeneity, we found slight variability in each study's definition of treatment failure (see Characteristics of included studies). However, we agreed that the study participants, interventions, and outcomes remained similar enough for their data to be combined in a meta-analysis.

Statistical heterogeneity was indicated for this outcome. This was due to a Chi^2 statistic that was greater than the degrees of freedom (df), and heterogeneity that reached our predetermined alpha value of 0.1 for statistical significance (Chi^2 = 5.57, df = 2, P = 0.06). We quantified the degree of heterogeneity using the I^2 statistic and deemed it to represent moderate heterogeneity (I^2 = 64%). As a result, we combined the data for these studies in meta-analysis using a random-effects model. HFNC may have little to no effect on treatment failure, but the evidence is very uncertain (risk ratio (RR) 0.98, 95% confidence interval (CI) 0.47 to 2.04; 3 trials, 452 infants; very low-certainty evidence; Analysis 1.2).

1.3 Chronic lung disease (need for supplemental oxygen at 28 days of life)

The outcome was reported in one study (375 participants) but there were no events in either group (Manley 2019).

Secondary outcomes

1.4 Duration (hours/days) of any form of respiratory support (any form of non-invasive respiratory support with or without supplemental oxygen)

Four studies (530 participants) reported on duration of respiratory support (Cesar 2020; Gao 2017; Manley 2019; Milesi 2017). Moderate statistical heterogeneity was indicated for this outcome (Chi^2 = 8.14, df = 3, P = 0.04, I^2 = 63%). As a result, we combined the data for these studies in meta-analysis using a random-effects model. HFNC may have little to no effect on the duration of respiratory support, but the evidence is very uncertain (MD 0.17 days, 95% CI -0.28 to 0.61; 4 trials, 530 infants; very low-certainty evidence; Analysis 1.4).

1.5 Length of stay at intensive care unit (ICU) (days)

Three studies (452 participants) contributed to the meta-analysis for length of ICU stay (Cesar 2020; Manley 2019; Milesi 2017). We used a fixed-effect model since statistical heterogeneity was not indicated (Chi^2 = 1.06, df = 2, P = 0.59, I^2 = 0%). HFNC likely results in little to no difference in the length of stay at the intensive care unit (MD 0.90 days, 95% CI -0.31 to 2.12; 3 trials, 452 infants; moderate-certainty evidence; Analysis 1.5).

1.6 Hospital length of stay (LOS) (days)

Three studies (466 participants) reported hospital LOS (Cesar 2020; Gao 2017; Manley 2019). Our meta-analysis used a fixed-effect model given there was no or low statistical heterogeneity (Chi^2 = 3.65, df = 2, P = 0.16, I^2 = 45%). HFNC may result in little to no difference in hospital LOS (MD 0.11 days, 95% CI -0.52 to 0.74; 3 trials, 466 infants; low-certainty evidence; Analysis 1.6).

1.7 Adverse events - air leak syndrome

Two studies (453 participants) assessed air leak syndromes (Gao 2017; Manley 2019). Our meta-analysis used a fixed-effect model given statistical heterogeneity was not indicated (Chi^2 = 0.88, df = 1, P = 0.35, I^2 = 0%). HFNC may result in little to no difference in the incidence of air leak syndromes (RR 0.75, 95% CI 0.41 to 1.36; 2 trials, 453 infants; low-certainty evidence; Analysis 1.7).

1.8 Adverse events - nasal trauma

One study (78 participants) assessed nasal trauma (Gao 2017). HFNC may reduce the incidence of nasal trauma, but the evidence is very uncertain (RR 0.16, 95% CI 0.04 to 0.66; 1 trial, 78 infants; very low-certainty evidence; Analysis 1.8). We used the methods described in Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* to calculate the number needed to treat for an additional beneficial outcome (NNTB) from the risk ratio, using the risk in comparator group as the 'assumed comparator risk' (ACR) (Higgins 2022). The NNTB was 4 (95% CI 4 to 10).

1.9 Adverse events - abdominal overdistension

One study (78 participants) investigated abdominal overdistension (Gao 2017). HFNC may reduce incidence of abdominal overdistension, but the evidence is very uncertain (RR 0.22, 95% CI 0.07 to 0.71; 1 trial, 78 infants; very low-certainty evidence; Analysis 1.9). The NNTB was 4 (95% CI 4 to 11).

Adverse events - nosocomial pneumonia

No numerical result was reported from any of the included studies for this outcome.

Comparison two: HFNC versus LFNC in term infants requiring respiratory support

Two studies were included in this comparison, with a total of 95 participants (Franklin 2018; Kepreotes 2017). One study was excluded due to a high risk of bias (Abboud 2015). We assessed the studies for clinical or methodological differences and found them to be similar enough to perform a meta-analysis for some outcomes. See Summary of findings 2.

Primary outcomes

2.1 Death

The outcome of death was reported in both studies (95 participants) but there were no events in either group (Franklin 2018; Kepreotes 2017).

2.2 Treatment failure

Both studies (95 participants) contributed to our meta-analysis (Franklin 2018; Kepreotes 2017). We used a fixed-effect model given that statistical heterogeneity was not indicated (Chi² = 0.1, df = 1, P = 0.75, I² = 0%). The evidence suggests that HFNC may reduce treatment failure slightly (RR 0.44, 95% CI 0.21 to 0.92; 2 trials, 95 infants; low-certainty evidence; Analysis 2.2). The NNTB was 5 (95% CI 4 to 34).

2.3 Chronic lung disease (need for supplemental oxygen at 28 days of life)

Neither of the studies (95 participants) included a comparison investigating chronic lung disease (need for supplemental oxygen at 28 days of life) (Franklin 2018; Kepreotes 2017).

Secondary outcomes

2.4 Duration (hours/days) of any form of respiratory support (any form of non-invasive respiratory support with or without supplemental oxygen)

One study (74 participants) compared the duration of any form of respiratory support (Franklin 2018). HFNC may have little to no effect on the duration of respiratory support, but the evidence is very uncertain (MD -0.07 days, 95% CI -0.83 to 0.69; 1 trial, 74 infants; very low-certainty evidence; Analysis 2.4).

2.5 Length of stay (LOS) at intensive care unit (ICU) (days)

One study (74 participants) investigated LOS at ICU (Franklin 2018). HFNC may have little to no effect on LOS at ICU, but the evidence is very uncertain (MD 0.49 days, 95% CI -0.83 to 1.81; 1 trial, 74 infants; very low-certainty evidence; Analysis 2.5).

2.6 Hospital length of stay (LOS) (days)

Two studies (95 participants) contributed to our meta-analysis (Franklin 2018; Kepreotes 2017). Moderate statistical heterogeneity was indicated for this outcome (Chi² = 2.80, df = 1, P = 0.09; I² = 64%). HFNC may have little to no effect on hospital LOS, but the evidence is very uncertain (MD -0.60 days, 95% CI -2.07 to 0.86; 2 trials, 95 infants; very low-certainty evidence; Analysis 2.6).

2.7 Adverse events

Adverse events was an outcome reported in both studies (95 participants) but there were no events in either group (Franklin 2018; Kepreotes 2017).

D I S C U S S I O N

Summary of main results

The aim of this review was to assess the safety and efficacy of high flow nasal cannula oxygen therapy for respiratory support in term infants during the neonatal period.

We included eight RCTs (18 references), with a total of 654 term infants in the review (see Characteristics of included studies table). There were five RCTs investigating high flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) (546 participants), and three RCTs investigating HFNC versus low flow nasal cannula (LFNC) (108 participants). We deemed two of the eight included studies to have high overall risk of bias (Abboud 2015; Vahlkvist 2020), so we excluded them from our primary

analysis. Therefore, our primary analyses included six studies (625 term infants).

Four studies (Cesar 2020; Gao 2017; Manley 2019; Milesi 2017), enrolling a total of 530 participants, contributed to our primary analysis comparison of HFNC versus CPAP (Summary of findings 1). The outcome of death was reported in two studies (Manley 2019; Milesi 2017) (439 infants), but there were no events in either group. HFNC may have little to no effect on treatment failure, but the evidence is very uncertain (RR 0.98, 95% CI 0.47 to 2.04; 3 trials, 452 infants; very low-certainty evidence). The outcome of chronic lung disease (need for supplemental oxygen at 28 days of life) was reported in one study (Manley 2019) (375 participants), but there were no events in either group. HFNC may have little to no effect on the duration of respiratory support (any form of non-invasive respiratory support with or without supplemental oxygen), but the evidence is very uncertain (MD 0.17 days, 95% CI -0.28 to 0.61; 4 trials, 530 infants; very low-certainty evidence). HFNC likely results in little to no difference in the length of stay at the intensive care unit (ICU) (MD 0.90 days, 95% CI -0.31 to 2.12; 3 trials, 452 infants; moderate-certainty evidence). HFNC may reduce the incidence of nasal trauma (RR 0.16, 95% CI 0.04 to 0.66; 1 trial, 78 infants; very low-certainty evidence) and abdominal overdistension (RR 0.22, 95% CI 0.07 to 0.71; 1 trial, 78 infants; very low-certainty evidence), but the evidence is very uncertain. We believe that larger, methodologically robust trials are required to precisely evaluate the possible health benefits or harms of HFNC use on clinically important outcomes in term infants requiring respiratory support.

Two studies, enrolling a total of 95 participants, contributed to our analysis of HFNC versus LFNC (Summary of findings 2) (Franklin 2018; Kepreotes 2017). The outcome of death was reported in both studies (95 participants) but there were no events in either group. The evidence suggests that HFNC may reduce treatment failure slightly (RR 0.44, 95% CI 0.21 to 0.92; 2 trials, 95 infants; low-certainty evidence). Neither study reported results for the outcome of chronic lung disease (need for supplemental oxygen at 28 days of life). HFNC may have little to no effect on the duration of respiratory support (MD -0.07 days, 95% CI -0.83 to 0.69; 1 trial, 74 infants; very low-certainty evidence), length of stay at the ICU (MD 0.49 days, 95% CI -0.83 to 1.81; 1 trial, 74 infants; very low-certainty evidence), or hospital length of stay (MD -0.60 days, 95% CI -2.07 to 0.86; 2 trials, 95 infants; very low-certainty evidence), but the evidence is very uncertain. Adverse events was an outcome reported in both studies (95 infants), but there were no events in either group. Similarly, we believe that larger, methodologically robust trials are required to precisely measure the effect of HFNC use in term infants requiring respiratory support.

Overall, there is insufficient evidence to enable the formulation of evidence-based guidelines on the use of HFNC for respiratory support in term infants. The evidence found in current studies is of moderate to very low certainty, making it difficult to establish reliable and evidenced-based recommendations regarding the effectiveness of HFNC therapy in term infants.

Overall completeness and applicability of evidence

Several of the included studies have small sample sizes, leading to imprecision in the findings. We also reported three ongoing studies and 10 are awaiting classification. The inclusion of these studies may have influenced the findings of this review, however we maintain that future research containing larger, methodologically

robust trials is key to evaluating the effects of HFNC in term infants requiring respiratory support.

Quality of the evidence

Using the GRADE approach, we graded the certainty of evidence for the primary and secondary outcomes listed in Summary of findings 1 and Summary of findings 2. We arrived at these conclusions by starting with a default of high certainty based on study design (RCT) and then downgraded based on risk of bias judgements and other GRADE considerations such as imprecision, indirectness, and inconsistency.

We downgraded the certainty of evidence by one level where the risk of bias judgement was 'some concerns'. Bias judgements of 'some concerns' do not always indicate serious limitations in design. However, given that our bias judgements were due to some concerns in the randomisation process, we felt this represented a potentially serious limitation and downgraded accordingly.

We downgraded the certainty of evidence one level for the presence of moderate heterogeneity, since this represented inconsistency across the results of the studies.

We downgraded the certainty of evidence by one level for imprecision where sample sizes were not sufficiently large. We downgraded two levels for imprecision where only one study contributed evidence to an outcome and we noted a wide CI in the effect.

Lastly, we downgraded the certainty of evidence by one level for indirectness if the findings were primarily related to a narrowly defined subgroup population. This was the case for several outcomes in the HFNC versus LFNC therapy comparison, where the studies were primarily limited to patients with clinical bronchiolitis. For these outcomes, the findings may be regarded as indirect in relation to the broader question of interest because the population primarily related to term infants with bronchiolitis rather than all term infants requiring respiratory support.

In the comparison of HFNC versus CPAP

We graded the certainty of evidence for the outcome of ICU length of stay as moderate, downgraded by one level for imprecision. This reflects moderate confidence in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different).

We graded the certainty of evidence for the following three outcomes as low: treatment failure (downgraded by one level for inconsistency and one level for imprecision), hospital length of stay, and incidence of air leak syndromes (both downgraded by one level for risk of bias and one level for imprecision). This reflects limited confidence in the effect estimate (the true effect may be substantially different from the estimate of the effect).

We graded the certainty of evidence for the following three outcomes as very low: duration of any form of respiratory support (downgraded by one level for risk of bias, one level for imprecision, and one level inconsistency), incidence of nasal trauma, and incidence abdominal overdistension (both downgraded by one level for risk of bias and two levels for imprecision). This reflects very limited confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of the effect).

In the comparison of HFNC versus LFNC

We graded the certainty of evidence for the outcome of treatment failure as low, downgraded by one level for imprecision and one level for indirectness. This reflects limited confidence in the effect estimate (the true effect may be substantially different from the estimate of the effect).

We graded the certainty of evidence for the following three outcomes as very low: hospital length of stay (downgraded by one level for indirectness, one level for inconsistency, and one level for imprecision), duration of any form of respiratory support, and length of stay at ICU (both downgraded by one level for indirectness and two levels for imprecision). This reflects very limited confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of the effect).

Potential biases in the review process

We used the standard methods recommended by Cochrane Neonatal to minimise the risk of bias in our review. We used prespecified eligibility criteria and performed an extensive search of the literature; we are confident that our search strategy was sensitive enough to capture all presently available RCTs investigating HFNC therapy for respiratory support in term infants. Two authors independently assessed the eligibility of studies, extracted data, evaluated risk of bias, and graded the certainty of the evidence (with differences resolved by discussion or by a third author).

We could not assess possible publication bias or reporting bias, since each meta-analysis contained insufficient studies for funnel plot inspection and regression analysis to be valid and reliable (Higgins 2022). However, we attempted to minimise the threat of publication bias by screening the reference lists of included trials and related reviews and searching the proceedings of international conferences to identify trial reports that were not published in academic journals.

Agreements and disagreements with other studies or reviews

We are unaware of any other systematic reviews addressing the objectives of this review.

AUTHORS' CONCLUSIONS

Implications for practice

When compared with continuous positive airway pressure (CPAP), high flow nasal cannula (HFNC) may have little to no effect on treatment failure or the duration of respiratory support (any form of non-invasive respiratory support with or without supplemental oxygen), but the evidence is very uncertain. HFNC likely results in little to no difference in the length of stay at the intensive care unit. HFNC may reduce the incidence of nasal trauma and abdominal overdistension, but the evidence is very uncertain.

When compared with LFNC, HFNC may reduce treatment failure slightly. HFNC may have little to no effect on the duration of respiratory support, length of stay at the intensive care unit (ICU), or hospital length of stay, but the evidence is very uncertain.

There is insufficient evidence to enable the formulation of evidence-based guidelines on the use of HFNC for respiratory

support in term infants. Larger, methodologically robust trials are required to further evaluate the possible health benefits or harms of HFNC in this patient population.

Implications for research

The findings of this review highlight the lack of quality evidence guiding the use of HFNC in term infants. Future research should include larger, methodologically robust trials to further evaluate the effects of HFNC on clinically important outcomes. No studies were set up to specifically investigate term infants during the neonatal period, suggesting that this population could be underrepresented in the literature. More focused research is therefore needed to investigate clinically important outcomes in this patient population.

REFERENCES

References to studies included in this review

Abboud 2015 *{published data only}*

Abboud P, Roth P, Yacoub N, Stolfi A. Efficacy of high flow/high humidity nasal cannula therapy in viral bronchiolitis. *Critical Care Medicine* 2015;**43**(12):177. [DOI: 10.1097/01.ccm.0000474530.04830.28]

Cesar 2020 *{published data only}*

Cesar RG, Bispo BR, Felix PH, Modolo MC, Souza AF, Horigoshi NK, et al. A randomized controlled trial of high-flow nasal cannula versus CPAP in critical bronchiolitis. *Critical Care Medicine* 2018;**46**(1):553.

* Cesar RG, Bispo BR, Felix PH, Modolo MC, Souza AF, Horigoshi NK, et al. High-flow nasal cannula versus continuous positive airway pressure in critical bronchiolitis: a randomized controlled pilot. *Journal of Pediatric Intensive Care* 2020;**9**(4):248-55. [PMID: 33133739]

Franklin 2018 *{published data only}*

Franklin D, Babl F, Schibler A. Nasal high flow in children with acute hypoxemic respiratory failure. A paediatric acute respiratory intervention study (PARIS). *Pediatric Critical Care Medicine* 2021;**22**(Suppl 1):1-2.

* Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *New England Journal of Medicine* 2018;**378**(12):1121-31. [PMID: 29562151]

Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, et al. Nasal high flow in room air for hypoxemic bronchiolitis infants. *Frontiers in Pediatrics* 2019;**7**:426.

Franklin D, Dalziel S, Schlapbach LJ, Babl FE, Oakley E, Craig SS, et al. Early high flow nasal cannula therapy in bronchiolitis, a prospective randomised control trial (protocol): A Paediatric Acute Respiratory Intervention Study (PARIS). *BMC Pediatrics* 2015;**15**(1):183.

Gao 2017 *{published data only}*

Gao XY, Feng L, Qiu YF, Pan XN. Application of humidified high-flow nasal cannula in neonates with meconium aspiration syndrome and pulmonary hypertension after extubation. *Chinese Journal of Contemporary Pediatrics* 2017;**19**:393-7. [PMID: 28407823]

Kepreotes 2017 *{published data only}*

Kepreotes E, Whitehead B, Attia J, Oldmeadow C, Collison A, Searles A, et al. A randomized controlled trial examining high-flow oxygen in the management of infants with moderate bronchiolitis. *European Respiratory Journal* 2016;**48**(Suppl 60):498.

Kepreotes E, Whitehead B, Attia J, Oldmeadow C, Collison A, Searles A, et al. High-flow oxygen compared to standard nasal cannula oxygen does not reduce the median time on oxygen for infants with moderate bronchiolitis. *Respirology* 2016;**21**:52.

* Kepreotes E, Whitehead B, Attia J, Oldmeadow C, Collison A, Searles A, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. *Lancet* 2017;**389**(10072):930-9. [PMID: 28161016]

Manley 2019 *{published data only}*

Manley BJ, Arnolda GR, Wright IM, Owen LS, Foster JP, Huang L, et al. A multicentre, randomised controlled, non-inferiority trial, comparing nasal high flow with nasal continuous positive airway pressure as primary support for newborn infants with early respiratory distress born in Australian non-tertiary special care nurseries (the HUNTER trial): Study protocol. *BMJ* 2017;**7**(6):e016746.

* Manley BJ, Arnolda GR, Wright IM, Owen LS, Foster JP, Huang L, et al. Nasal high-flow therapy for newborn infants in special care nurseries. *New England Journal of Medicine* 2019;**380**(21):2031-40. [PMID: 31116919]

Manley BJ, Arnolda GR, Wright IM, Owen LS, Foster JP, Huang L, et al. Nasal high-flow for early respiratory support of newborn infants in Australian non-tertiary special care nurseries (the Hunter trial): a multicentre, randomised, non-inferiority trial. *Journal of Paediatrics & Child Health* 2018;**54**:4.

Milesi 2017 *{published data only}*

Milesi C, Essouri S, Pouyau R, Liet JM, Afanetti M, Portefaix A, et al. Interest of high flow nasal cannula versus nasal continuous positive airway pressure during the management of severe bronchiolitis in infants: a multicenter randomized controlled trial. *European Journal of Pediatrics* 2016;**175**(11):1436.

Milesi C, Essouri S, Pouyau R, Liet JM, Afanetti M, Portefaix A, et al. Interest of high-flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) during the initial management of severe bronchiolitis in infants: a multicenter randomized controlled trial. *Annals of Intensive Care* 2016;**6**(Suppl 1):S50.

* Milesi C, Essouri S, Pouyau R, Liet JM, Afanetti M, Portefaix A, et al, Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP). High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). *Intensive Care Medicine* 2017;**43**(2):209-16. [PMID: 28124736]

Vahlkvist 2020 *{published data only}*

Vahlkvist S, Jürgensen L, Cour Amalie L, Markoew S, Petersen T, Kofoed P. High flow nasal cannula and continuous positive airway pressure therapy in treatment of viral bronchiolitis: a randomized clinical trial. *European Journal of Pediatrics* 2020;**179**(3):513-8. [PMID: 31828528]

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References to studies excluded from this review

ACTRN12611000233921 {published data only}

ACTRN12611000233921. The use of headbox oxygen versus high flow nasal cannula (HFNC) for neonatal respiratory distress in non-tertiary hospitals. anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12611000233921 (first received 3 March 2011).

Akyildiz 2018 {published data only}

Akyildiz B, Ozturk S, Ulgen-Tekerek N, Doganay S, Gorkem SB. Comparison between high-flow nasal oxygen cannula and conventional oxygen therapy after extubation in pediatric intensive care unit. *Turkish Journal of Pediatrics* 2018;**60**(2):126-33. [PMID: 30325117]

Campaña 2014 {published data only}

Campaña MB, Ortiz JO, Muñoz CN, Lucas MR, Rincón AF, Hernández OP, et al. High flow therapy versus hypertonic saline in bronchiolitis: randomised controlled trial. *Archives of Disease in Childhood* 2014;**99**(3):511-5.

Chen 2019 {published data only}

Chen DY, Zee ED, Gildengorin G, Fong EW. A pilot study of heated and humidified low flow oxygen therapy: an assessment in infants with mild and moderate bronchiolitis (HHOT AIR study). *Pediatric Pulmonology* 2019;**54**(5):620-7.

Chisti 2015 {published data only}

Chisti MJ, Salam A, Smith JH, Ahmed T, Pietroni MA, Shahunja KM, et al. Bubble continuous positive airway pressure for children with severe pneumonia and hypoxaemia in Bangladesh: an open, randomised controlled trial. *Lancet* 2015;**386**(9998):1057-65.

Christophe 2018 {published data only}

Milési C, Pierre AF, Deho A, Pouyau R, Liet JM, Guillot C, et al. Proceedings of reanimation 2018, the French Intensive Care Society International Congress. *Annals of Intensive Care* 2018;**8**:13.

Ergul 2018 {published data only}

Ergul A B, Caliskan E, Samsa H, Gokcek I, Kaya A, Zararsiz GE, et al. Using a high-flow nasal cannula provides superior results to OxyMask delivery in moderate to severe bronchiolitis: a randomized controlled study. *European Journal of Pediatrics* 2018;**177**(8):1299-307.

Hough 2011 {published data only}

Hough JL, Pham TM, Schibler A. Delivery of high flow nasal prong oxygen: the effect CPAP exposed. *Pediatric Critical Care Medicine* 2011;**12**:7.

Iranpour 2012 {published data only}

Iranpour R, Sadeghnia A, Hesaraki M. High-flow nasal cannula versus nasal continuous positive airway pressure in the management of respiratory distress syndrome. *Archives of Disease in Childhood* 2012;**97**(Suppl 2):A115-6.

JPRN-UMIN000013907 {published data only}

JPRN-UMIN000013907. A randomized controlled trial to compare high-flow nasal cannula with nasal CPAP in infants more than 34 weeks of gestational age with respiratory disorders. center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000016212 (first received 8 May 2014).

JPRN-UMIN000018983 {published data only}

JPRN-UMIN000018983. Effective and safe use of heated humified high flow nasal cannula in neonates. center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000021932 (first received 11 September 2015).

Juretschke 2004 {published data only}

Juretschke R, Spoula R. High flow nasal cannula in the neonatal population. *Neonatal Intensive Care* 2004;**17**(6):20-1.

Kamerkar 2014 {published data only}

Kamerkar A, Hotz J, Morzov R, Ross PA, Newth C, Khemani RG. Comparison of effort of breathing on humidified high-flow nasal cannula versus synchronized nasal intermittent mechanical ventilation in infants. American Journal of Respiratory and Critical Care Medicine 2014;**189**(Meeting Abstracts):A2602.

Kefala 2015 {published data only}

Kefala K, Nyamugabo K, Farhat N, Janssen A, Seghaye MC. High-flow nasal cannula heated-humidified (HFNC) oxygen at 2 litres (lt)/kg/min versus low-flow O2 (up to 2lt/min) in pediatric emergency department (PED) and pediatric ward (PW) in infants with bronchiolitis who need O2 administration: a combined prospective randomized controlled and retrospective study: preliminary results. European Respiratory Journal 2015;**46**(Suppl 59):Pa2173.

Kugelman 2012 {published data only}

Kugelman A, Riskin A, Said W, Shoris I, Mor F, Bader D. High flow nasal cannula versus nasal intermittent positive pressure ventilation for the primary treatment of respiratory distress syndrome: a randomized, controlled, prospective Study. *Journal of Pediatrics* 2012;**150**(5):521-6.

Liu 2020 {published data only}

Liu C, Cheng WY, Li JS, Tang T, Tan PL, Yang L. High-flow nasal cannula vs. continuous positive airway pressure therapy for the treatment of children <2 years with mild to moderate respiratory failure due to pneumonia. *Frontiers in Pediatrics* 2020;**8**:590906.

Ma 2014 {published data only}

Ma L, Liu CQ, Gu XH, Liu, XJ. The efficacy and safety of heated humidified high-flow nasal cannula for prevention of extubation failure in neonates. *Journal of Maternal-Fetal & Neonatal Medicine* 2014;**27**:208-9.

Maitland 2017 {published data only}

Maitland K, Kiguli S, Opoka RO, Olupot-Olupot P, Engoru C, Njiguna P. Children's oxygen administration strategies trial (COAST): a randomised controlled trial of high flow versus oxygen versus control in African children with severe pneumonia. *Wellcome Open Research* 2017;**2**:100.

Maitland 2021 *{published data only}*

Maitland K, Kiguli S, Olupot-Olupot P, Hamaluba M, Thomas K, Alaroker F, et al. Randomised controlled trial of oxygen therapy and high-flow nasal therapy in African children with pneumonia. *Intensive Care Medicine* 2021;**47**(5):566-76.

Mayfield 2014 *{published data only}*

Mayfield S, Bogossian F, O'Malley L, Schibler A. High-flow nasal cannula oxygen therapy for infants with bronchiolitis: pilot study. *Journal of Paediatrics and Child Health* 2014;**50**(5):373-8.

Mazmanyan 2013 *{published data only}*

Mazmanyan P, Darakchyan M. Humidified high flow nasal cannula for the treatment of respiratory distress in premature newborns > 34 weeks gestation. *Journal of Perinatal Medicine* 2013;**41**(1):49-52.

Mazmanyan 2016 *{published data only}*

Mazmanyan P, Darakchyan M, Moylan M, Tatkov S. Nasal high flow reduces minute ventilation in neonates. *European Respiratory Journal* 2016;**48**:18-61.

Milani 2016 *{published data only}*

Milani GP, Plebani AM, Arturi E, Brusa D, Esposito S, Dell'Era L, et al. Using a high-flow nasal cannula provided superior results to low-flow oxygen delivery in moderate to severe bronchiolitis. *Acta Paediatrica* 2016;**105**(8):e368-72.

Mostafa-Gharehbaghi 2015 *{published data only}*

Mostafa-Gharehbaghi M, Mojabi H. Comparing the effectiveness of nasal continuous positive airway pressure (NCPAP) and high flow nasal cannula (HFNC) in prevention of post extubation assisted ventilation. *Zahedan Journal of Research in Medical Sciences* 2015;**17**(6):e984.

NCT00356668 *{published data only}*

NCT00356668. Humidified high flow nasal cannula as compared to nasal continuous positive airway pressure. clinicaltrials.gov/show/NCT00356668 (first received 26 July 2006).

NCT01189162 *{published data only}*

NCT01189162. High flow nasal cannula (HFNC) versus nasal inntermittent mandatory ventilation (NIMV) for respiratory distress syndrome (RDS): a randomized, controlled, prospective study. clinicaltrials.gov/show/NCT01189162 (first received 26 August 2010).

NCT01270581 *{published data only}*

NCT01270581. High flow nasal cannula versus bubble nasal CPAP for the treatment of transient tachypnea of the newborn in Infants ≥ 35 weeks gestation. https://clinicaltrials.gov/ct2/show/NCT01270581 (first received 5 January 2011).

NCT01662544 *{published data only}*

NCT01662544. Heated high flow oxygen use in infants with bronchiolitis and hypoxia. clinicaltrials.gov/show/NCT01662544 (first received 10 August 2012).

NCT01944995 *{published data only}*

NCT01944995. Work of breathing in nasal CPAP versus high flow nasal prong in infants with severe acute bronchiolitis. clinicaltrials.gov/show/NCT01944995 (first received 18 September 2013).

NCT02457013 *{published data only}*

NCT02457013. Interest of high flow nasal cannula (HFNC) versus non invasive ventilation during the initial management of severe bronchiolitis in infants. clinicaltrials.gov/show/NCT02457013 (first received 29 May 2015).

NCT02499744 *{published data only}*

NCT02499744. Humidified high flow nasal cannula versus nasal intermittent positive ventilation in neonates. clinicaltrials.gov/show/NCT02499744 (first received 16 July 2015).

NCT02587832 *{published data only}*

NCT02587832. High flow nasal cannula in comparison with nasal continuous positive airway pressure in the management of respiratory distress syndrome. clinicaltrials.gov/show/NCT02587832 (first received 27 October 2015).

NCT02632799 *{published data only}*

NCT02632799. Airway pressure during nasal high flow and CPAP in neonates. clinicaltrials.gov/show/NCT02632799 (first received 17 December 2015).

NCT02632825 *{published data only}*

NCT02632825. Effects of nasal high flow therapy on ventilation and gas exchange in healthy newborns. clinicaltrials.gov/show/NCT02632825 (first received 17 December 2015).

NCT02737280 *{published data only}*

NCT02737280. High flow nasal cannula use in infants with bronchiolitis. clinicaltrials.gov/show/NCT02737280 (first received 13 April 2016).

NCT02824744 *{published data only}*

NCT02824744. Comparison between 2l vs 3l in HFNC during the initial management of severe bronchiolitis in infants. clinicaltrials.gov/show/NCT02824744 (first received 7 July 2016).

NCT03015051 *{published data only}*

NCT03015051. High flow nasal cannula vs low flow oxygen therapy in bronchiolitis. clinicaltrials.gov/show/NCT03015051 (first received 9 January 2016).

NCT03252119 *{published data only}*

NCT03252119. High flow oxygen therapy vs standard care in infants with viral bronchiolitis. clinicaltrials.gov/show/NCT03252119 (first received 17 August 2017).

NCT03689686 *{published data only}*

NCT03689686. High flow nasal cannulas in children. clinicaltrials.gov/show/NCT03689686 (first received 28 September 2018).

NCT03967769 *{published data only}*

NCT03967769. Apneic oxygenation by nasal canula during infants airway management: a randomized double-blinded study. clinicaltrials.gov/show/NCT03967769 (first received 30 May 2019).

NCT04245202 *{published data only}*

NCT04245202. Comparison of high flow nasal cannula and standard face mask oxygen treatment in children with acute bronchiolitis. clinicaltrials.gov/show/NCT04245202 (first received 28 January 2020).

Parmekar 2018 *{published data only}*

Parmekar S, Hagan J. How does high-flow nasal cannulae compare to nasal CPAP for treatment of early respiratory distress? *Journal of Perinatology* 2018;**38**(1):23-5.

Pediatric Academic Societies 2011 *{published data only}*

Pediatric Academic Societies. Pediatric Academic Societies 2011 Annual Meeting, 2011 April 30 - May 03; Colorado (CO). Pediatric Academic Societies 2011;(Meeting Abstracts).

Pediatric Academic Societies 2013 *{published data only}*

Pediatric Academic Societies. Pediatric Academic Societies 2013 Annual Meeting, 2013 May 03-7; Washington (WA). Pediatric Academic Societies Annual Meeting 2013;(Meeting Abstracts).

Sahhar 2015 *{published data only}*

Sahhar H, Cantrell K, Myles D, Rishmawi S. Effectiveness of heliox as adjunct therapy with HFNC in children with respiratory distress. Critical Care Medicine 2015;**43**(12 Suppl 1):182-3.

Sarkar 2018 *{published data only}*

Sarkar M, Sinha R, Roychowdhoury S, Mukhopadhyay S, Ghosh P, Dutta K, et al. Comparative study between noninvasive continuous positive airway pressure and hot humidified high-flow nasal cannulae as a mode of respiratory support in infants with acute bronchiolitis in pediatric intensive care unit of a tertiary care hospital. *Indian Journal of Critical Care Medicine* 2018;**22**(2):85-90.

Schibler 2010 *{published data only}*

Schibler A, Hough J, Pham T. Delivery of high flow nasal prong oxygen: the continuous positive airway pressure effect exposed. *Anaesthesia and Intensive Care* 2010;**38**(6):1127-8.

Shetty 2015 *{published data only}*

Shetty S, Rafferty G, Greenough A. Humidified high flow nasal cannula (HFFNC) and continuous positive airways pressure (CPAP) in infants with evolving bronchopulmonary dysplasia (BPD). European Respiratory Journal 2015;**46**(Suppl 59):Pa1869.

Sitthikarnkha 2018 *{published data only}*

Sitthikarnkha P, Samransamruajkit R, Prapphal N, Deerojanawong J, Sritippayawan S. High-flow nasal cannula versus conventional oxygen therapy in children with respiratory distress. *Indian Journal of Critical Care Medicine* 2018;**22**(5):321-5.

SLCTR/2017/017 *{published data only}*

SLCTR/2017/017. Comparing the effectiveness, safety and cost of high flow oxygen and standard (low flow) oxygen in infants with bronchiolitis. slctr.lk/trials/slctr-2017-017 (first received 22 June 2017).

Song 2017 *{published data only}*

Song HZ, Gu JX, Xiu HQ, Cui W, Zhang GS. The value of high-flow nasal cannula oxygen therapy after extubation in patients with acute respiratory failure. *Clinics (Sao Paulo, Brazil)* 2017;**72**(9):562-7.

Sood 2012 *{published data only}*

Sood R, Stolfi A, Rowin M. Use of high flow high humidity nasal cannula therapy for infants with bronchiolitis. *Journal of Investigative Medicine* 2012;**60**(1):453.

Soonsawad 2015 *{published data only}*

Soonsawad S, Nuntnarumit P, Tongsawang N. Heated humidified high-flow nasal cannula for weaning from continuous positive airway pressure in preterm infants: a randomized controlled trial. *Neonatology* 2016;**110**:204-9.

Swayampakula 2016 *{published data only}*

Swayampakula A, Eguchi J, Juma D, Wilson M, Ejike J. Use of external nasal dilator as an adjuvant to high-flow nasal cannula oxygen therapy in children. Conference: 46th Critical Care Congress of the Society of Critical Care Medicine 2016;**44**(12 Suppl 1):310.

TCTR20170222007 *{published data only}*

TCTR20170222007. High flow nasal cannula versus conventional oxygen therapy in children with respiratory distress. thaiclinicaltrials.org/show/TCTR20170222007 (first received 22 February 2017).

Vitaliti 2017 *{published data only}*

Vitaliti G, Vitaliti MC, Finocchiaro MC, Di Stefano VA, Pavone P, Matin N, et al. Randomized comparison of helmet CPAP versus high-flow nasal cannula oxygen in pediatric respiratory distress. *Respiratory Care* 2017;**62**(8):1036-42.

Vitaliti 2018 *{published data only}*

Vitaliti G, Vitaliti MC, Finocchiaro MC, Di Stefano VA, Pavone P, Matin N, et al. Randomized comparison of helmet CPAP versus high-flow nasal cannula oxygen in pediatric respiratory distress. *Respiratory Care* 2018;**62**(8):1036-42.

Woodhead 2006 *{published data only}*

Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomized, masked, crossover trial. *Journal of Perinatology* 2006;**26**(8):481-5.

Yengkhom 2021 *{published data only}*

Yengkhom R, Suryawanshi P, Gupta B, Deshpande S. Heated humidified high-flow nasal cannula vs. nasal continuous positive airway pressure for post-extubation respiratory support in preterm infants: a randomized controlled trial. *Journal of Tropical Pediatrics* 2021;**67**(1):1-8.

References to studies awaiting assessment

Borgi 2021 *{published data only}*

Borgi A, Louati A, Ghali N, Hajji A, Ayari A, Bouziri A, et al. High flow nasal cannula therapy versus continuous positive airway pressure and nasal positive pressure ventilation in infants with severe bronchiolitis: a randomized controlled trial. *Pan African Medical Journal* 2021;**40**(133):2-10.

Durand 2020 *{published data only}*

* Durand P, Guiddir T, Kyheng C, Blanc F, Vignaud O, Epaud R, et al. A randomised trial of high-flow nasal cannula in infants with moderate bronchiolitis. *European Respiratory Journal* 2020;**56**(1):1901926.

Durand P, Guiddir T, Kyheng C, Blanc F, Vignaud O, Epaud R, et al. High-flow nasal canula (HFNC) in infant hospitalized with moderate bronchiolitis-results of a multicenter open-label RCT in pediatric health care. *Annals of Intensive Care* 2019;**9**(1):40.

Franklin 2021 *{published data only}*

Franklin D, Shellshear D, Babl FE, Hendrickson R, Williams A, Gibbons K, et al. High flow in children with respiratory failure: a randomised controlled pilot trial – a paediatric acute respiratory intervention study. *Journal of Paediatrics and Child Health* 2021;**57**(2):273-81.

Hathorn 2014 *{published data only}*

Hathorn C, Ernst G, Hasan S, Wong D, Seear M. The hi-flo study: a prospective open randomised controlled trial of high flow nasal cannula oxygen therapy against standard care in bronchiolitis. *Thorax* 2014;**69**(Suppl 2):A38.

Ji 2021 *{published data only}*

Ji J, Li P, Zhu L, Xue M, Zhu S. Effect of sequential high-flow nasal cannula oxygen therapy on blood gas parameters and prognosis after weaning from mechanical ventilation in neonates. *International Journal of Clinical and Experimental Medicine* 2021;**14**(1):711-7.

Liu 2014 *{published data only}*

Collaborative group for the multicenter study on heated humidified high-flow nasal cannula ventilation. Efficacy and safety of heated humidified high·flow nasal cannula for prevention of extubation failure in neonates [应用加温湿化高流量鼻导管通气预防 新生儿拔管失败的临床研究] . *Chinese Journal of Pediatrics* 2014;**52**(4):271-6.

Ramnarayan 2018 *{published data only}*

Ramnarayan P, Lister P, Dominguez T, Habibi P, Edmonds N, Canter R, et al. FIRST-line support for assistance in breathing in children (FIRST-ABC): protocol for a multicentre randomised feasibility trial of non-invasive respiratory support in critically ill children. *BMJ Open* 2017;**7**(6):e016181.

* Ramnarayan P, Lister P, Dominguez T, Habibi P, Edmonds N, Canter RR, et al. FIRST-line support for assistance in breathing in children (FIRST-ABC): a multicentre pilot randomised controlled trial of high-flow nasal cannula therapy versus continuous positive airway pressure in paediatric critical care. *Critical Care* 2018;**22**(1):144.

Ramnarayan P, Richards-Belle A, Drikite L, Saull M, Orzechowska I, Darnell R, et al. Effect of high-flow nasal cannula therapy vs continuous positive airway pressure following extubation on liberation from respiratory support in critically ill children: a randomized clinical trial. *JAMA* 2022;**327**(16):1555-65.

Ramnarayan P, Richards-Belle A, Drikite L, Saull M, Orzechowska I, Darnell R, et al. Effect of high-flow nasal cannula therapy vs continuous positive airway pressure therapy on liberation from respiratory support in acutely ill children admitted to pediatric critical care units: a randomized clinical trial. *JAMA* 2022;**328**(2):162-72.

Selvaraj 2022 *{published data only}*

Selvaraj S, Muthu S, Chandramouli H, Periyasamy B. Efficacy of oxygen delivered through high flow nasal cannula versus non rebreathing mask in infants with mild and moderate bronchiolitis: an open-labelled randomised controlled trial. *Journal of Clinical and Diagnostic Research* 2022;**16**(7):SC1-4.

Testa 2014 *{published data only}*

Testa G, Iodice F, Ricci Z, Vitale V, De Razza F, Haiberger R, et al. Comparative evaluation of high-flow nasal cannula and conventional oxygen therapy in paediatric cardiac surgical patients: a randomized controlled trial. *Interactive CardioVascular and Thoracic Surgery* 2014;**19**(3):456-61.

Yoder 2013 *{published data only}*

Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. *Pediatrics* 2013;**131**(5):e1482-90.

References to ongoing studies

NCT02913040 *{published data only}*

NCT02913040. High flow in infants with bronchiolitis. clinicaltrials.gov/show/NCT02913040 (first received 23 September 2016).

NCT03095495 *{published data only}*

NCT03095495. High flow nasal cannula therapy in bronchiolitis: early vs rescue. clinicaltrials.gov/show/NCT03095495 (first received 29 March 2017).

NCT03505814 *{published data only}*

NCT03505814. Interest of high flow nasal cannula oxygen therapy in pediatric intensive care unit. clinicaltrials.gov/show/NCT03505814 (first received 23 April 2018).

Additional references

ARDS Network 2000

The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New England Journal of Medicine* 2000;**342**(18):1301-8.

Beggs 2014

Beggs S, Wong ZH, Kaul S, Ogden KJ, Walters JAE. High-flow nasal cannula therapy for infants with bronchiolitis. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No: CD009609. [DOI: 10.1002/14651858.CD009609.pub2]

Cingi 2015

Cingi C, Muluk NB, Cobanoglu B, Çatli T, Dikici C. Nasobronchial interaction. *World Journal of Clinical Cases* 2016;**3**(6):499-503.

Covidence 2021 [Computer program]

Covidence. Version accessed 20 June 2021. Melbourne, Australia: Veritas Health Innovation. Available at www.covidence.org.

Dahlem 2003

Dahlem P, van Aslderen WM, Hamaker ME, Dijkfraaf MG, Bos AP. Incidence and short-term outcome of acute lung injury in mechanically ventilated children. *European Respiratory Journal* 2003;**22**(6):980-5.

de Klerk 2008

de Klerk A. Humidified high-flow nasal cannula: is it the new and improved CPAP? *Advances in Neonatal Care* 2008;**8**(2):98-106.

Dysart 2009

Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. *Respiratory Medicine* 2009;**103**(10):1400-5.

Frey 2001

Frey B, McQuillan PJ, Shann F, Freezer N. Nasopharyngeal oxygen therapy produces positive end-expiratory pressure in infants. *Europoean Journal of Pediatrics* 2001;**160**(9):556-60.

GRADEpro GDT [Computer program]

GRADEpro GDT. Version accessed 1 April 2022. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

Griffith University 2017

Pickering C, Griffith University. Advanced workshop on Systematic Quantitative Literature Reviews. Available at www.griffith.edu.au/__data/assets/pdf_file/0016/160504/WEB_Advanced-SQLR,-July-2017.pdf (accessed 10 December 2022).

Higgins 2022

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Available from www.training.cochrane.org/handbook 2022.

Hough 2012

Hough JL, Shearman AD, Jardine LA, Davies MW. Humidified high flow nasal cannulae: current practice in Australasian nurseries, a survey. *Journal of Paediatrics and Child Health* 2012;**48**(2):106-13. [PMID: 21470336]

Lampland 2009

Lampland A, Plumm B, Meyers P, Worwa C, Mammel M. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. *Journal of Pediatrics* 2009;**154**(2):177-82.

Lewis 2021

Lewis SR, Baker PE, Parker R, Smith AF. High-flow nasal cannulae for respiratory support in adult intensive care patients. *Cochrane Database of Systematic Reviews* 2021, Issue 3. Art. No: CD010172. [DOI: 10.1002/14651858.CD010172.pub3]

Mayfield 2014a

Mayfield S, Jauncey-Cooke J, Hough JL, Schibler A, Gibbons K, Bogossian F. High-flow nasal cannula therapy for respiratory support in children. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No: CD009850. [DOI: 10.1002/14651858.CD009850.pub2]

McKiernan 2010

McKiernan C, Chua LC, Visintainer AF, Allen H. High flow nasal cannulae therapy in infants with bronchiolitis. *Journal of Pediatrics* 2010;**156**(4):634-8.

RevMan Web 2020 [Computer program]

Review Manager Web (RevMan Web). Version accessed 1 September 2021. The Cochrane Collaboration, 2020. Available at revman.cochrane.org.

Roca 2010

Roca O, Riera J, Torres F, Masclans J. High-flow oxygen therapy in acute respiratory failure. *Respiratory Care* 2010;**55**(4):408-13.

Saslow 2006

Saslow JG, Aghai ZH, Nakhla TA, Hart JJ, Lawrysh R, Stahl GE, et al. Work of breathing using high-flow nasal cannula in preterm infants. *Journal of Perinatology* 2006;**26**(8):476-80.

Schibler 2011

Schibler A, Pham T, Dunster K, Forster K, Barlow A, Gibbons K, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. *Intensive Care Medicine* 2011;**37**(5):847-52.

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/handbook.

Screenan 2001

Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. *Pediatrics* 2001;**107**(5):1081-3.

Spence 2007

Spence KL, Murphy D, Kilian C, McGonigle R, Kilani RA. High-flow nasal cannula as a device to provide continuous

positive airway pressure in infants. *Journal of Perinatology* 2007;**27**(12):772-5.

Spentzas 2009

Spentzas T, Minarik M, Patters AB, Vinson B, Stidham G. Children with respiratory distress treated with high-flow nasal cannula. *Journal of Intensive Care Medicine* 2009;**24**(5):323-38.

Sterne 2019

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials.. *BMJ* 2019;**366**:l4898.

Wilkinson 2011

Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG. High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database of Systematic Reviews* 2011, Issue 5. Art. No: CD006405. [DOI: 10.1002/14651858.CD006405.pub2]

Wilkinson 2016

Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No: CD006405. [DOI: 10.1002/14651858.CD006405.pub3]

Wing 2012

Wing R, James C, Maranda L, Armsby C. Use of high-flow nasal cannula support in the emergency department reduces the need for intubation in paediatric acute respiratory insufficiency. *Pediatric Emergency Care* 2012;**28**(11):1117-23.

Yong 2005

Yong SC, Chen SJ, Boo NY. Incidence of nasal trauma associated with nasal prong versus nasal mask during continuous positive airway pressure in very low birthweight infants: a randomised control study. *Archives of Diseases in Childhood* 2005;**90**(6):F480-3.

References to other published versions of this review

Mayfield 2014b

Mayfield S, Jauncey-Cooke J, Schibler A, Hough JL, Bogossian F. High flow nasal cannula for respiratory support in term infants. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No: CD011010. [DOI: 10.1002/14651858.CD011010]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abboud 2015

Study characteristics	
Methods	• Conference poster of RCT • Study period: 4 winter seasons 2011 to July 2014 • Study setting: United States
Participants	• Sample size: 51 total participants in study, 13 term infants (12 HFNC, 1 standard nasal cannula oxygen) • Inclusion criteria: up to 13 months age, clinical signs and symptoms of viral bronchiolitis or confirmed laboratory evidence of viral infection • Exclusion criteria: 1 of the following conditions: cyanotic heart disease, neuromuscular disease, multiple congenital abnormalities, immunocompromised, or the presence of a tracheostomy or intubation
Interventions	• Participants were randomised to either the traditional NC oxygen group or the high flow high humidity NC group • The details and settings of the interventions were omitted from the conference poster
Outcomes	• Primary outcome: treatment failure, defined as progression to HFHHNC (NC group only), CPAP or intubation • Secondary outcomes: PICU LOS, RR, WOB, capillary pH and pCO_2, desaturations, and grunting pre and 1 hour post therapy initiation
Notes	Details of funding sources and declarations of interest were not stated

Cesar 2020

Study characteristics

Methods	• Single-centre RCT in the PICU of the "Hospital Infantil Sabará", in São Paulo, Brazil • Study period: September 2016 to July 2017
Participants	• Sample size: 63 total participants in study, 13 term infants (7 CPAP group; 6 HFNC group) • Inclusion criteria: up to 9 months age, primary diagnosis of critical bronchiolitis of moderate severity or greater (a modified Wood–Downes score of at least 4), preserved respiratory drive • Exclusion criteria: 1 of the following conditions: congenital or acquired heart disease, neuromuscular disease, chronic lung disease, pulmonary malformations, or the presence of a tracheostomy
Interventions	• Participants were randomised to either the HFNC group or the CPAP group • Children allocated to the CPAP group were fitted with nasal prongs with CPAP set at 6 cmH$_2$O for all patients • Children allocated to the HFNC group were fitted with a nasal cannula, with flow rates titrated up to a maximum of 1.5 L/kg/min • For both experimental groups, FiO$_2$ was adjusted to achieve a SpO$_2$ > 93%
Outcomes	• Primary outcome: rate of treatment failure, defined as the need to escalate support to non-invasive bilevel pressure ventilation, or endotracheal intubation • Secondary outcomes: duration of the primary treatment, PICU and hospital length of stay, development of apnoea
Notes	Details of funding sources: This study was supported by Hospital Infantil Sabará and Instituto PENSI. High flow devices and circuits were provided by Vapotherm, Inc. at no cost to the investigators. Vapotherm was not involved in the planning, execution, data analysis, data interpretation, or writing of the manuscript, and was not privy to its results. Declarations of interest: A.T.R. is a scientific advisory board member for Breas Medical U.S., received honoraria for lecturing and developing educational materials for Vapotherm, Inc., and continues to receive royalties from Elsevier for editorial work on a paediatric critical care textbook. The other authors have no potential conflicts of interest to disclose.

Franklin 2018

Study characteristics

Methods	• Multi-centre RCT across emergency departments and general paediatric inpatient units in 17 tertiary and regional hospitals in Australia and New Zealand • Study period: October 2013 to December 2016
Participants	• Sample size: 1472 total participants in study, 74 term infants (28 standard therapy group; 46 high flow group) • Inclusion criteria: up to 12 months of age, clinical signs of bronchiolitis, a need for supplemental oxygen therapy to keep the oxygen saturation level in the range of 92% to 98% • Exclusion criteria: critically ill infants who had an immediate need for respiratory support and ICU admission; infants with cyanotic heart disease, basal skull fracture, upper airway obstruction, or craniofacial malformation; infants who were receiving oxygen therapy at home
Interventions	• Participants were randomised to either the standard therapy group or the high flow group • Infants in the standard-therapy group received standard therapy, defined in their study as supplemental oxygen through a nasal cannula up to a maximum of 2 L/min, to maintain an oxygen saturation level in the range of 92% to 98%

Franklin 2018 *(Continued)*

- Infants in the high flow group received heated and humidified high flow oxygen at a rate of 2 L/kg/min. FiO_2 was adjusted to obtain oxygen saturation levels in the range of 92% to 98%

Outcomes	• Primary outcome: escalation of care due to treatment failure (defined as meeting ≥ 3 of 4 clinical criteria: persistent tachycardia, tachypnoea, hypoxaemia, and medical review triggered by a hospital early-warning tool) • Secondary outcomes included duration of hospital stay, duration of oxygen therapy, and rates of transfer to a tertiary hospital, ICU admission, intubation, and adverse events
Notes	Details of funding sources: Supported by a project grant (GNT1081736) from the National Health and Medical Research Council (NHMRC) and by the Queensland Emergency Medical Research Fund. Regional site funding was obtained for Ipswich Hospital from the Ipswich Hospital Foundation and for the Gold Coast University Hospital (GCUH) from the GCUH Foundation. Dr. Babl was supported in part by a Royal Children's Hospital Foundation grant, a Melbourne Campus Clinician Scientist Fellowship, and an NHMRC Practitioner Fellowship. Drs Fraser and Schibler received a research fellowship from the Queensland Health Department. The Paediatric Research in Emergency Departments International Collaborative (PREDICT) sites were supported by a Centre of Research Excellence grant (GNT1058560) for paediatric emergency medicine from the NHMRC. Sites in Victoria, Australia, received infrastructure support from the Victorian Government Infrastructure Support Program, Melbourne. Dr. Dalziel was supported in part by a grant from the Health Research Council of New Zealand, Auckland. The Townsville Hospital was supported in part by a SERTA (Study, Education, and Research Trust Account) grant. Declarations of interest: Dr. Babl reports grants from NHMRC project grant, grants from NHMRC centre of research excellence grant, grants from NHMRC practitioner fellowship, during the conduct of the study; grants from Melbourne Children's Clinician Scientist, grants from NHMRC project grants, outside the submitted work. Dr. Craig reports non-financial support from Fisher & Paykel Health Care, Auckland and grants from National Health Medical Research Council, Australia (GNT1081736) during the conduct of the study.Dr. Dalziel reports grants from National Health Medical Research Council, Australia (GNT1081736), non-financial support from Fisher & Paykel Health Care, Auckland, during the conduct of the study; other from Fisher & Paykel Health Care, Auckland, outside the submitted work. Dr. Franklin reports grants from National Health Medical Research Council, Australia, grants from Queensland Emergency Medical Research Fund, grants from Foundation Ipswich Hospital, grants from Gold Coast Hospital University Hospital Foundation, and non-financial support from Fisher & Paykel Health Care, Auckland during the conduct of the study and non-financial support from Fisher & Paykel outside the submitted work. Dr. Fraser reports grants from National Health Medical Research Council, Australia, grants from Queensland Health Medical Research Fellowship, and non-financial support from Fisher & Paykel Healthcare, Auckland during the conduct of the study and non-financial support from Fisher & Paykel Healthcare, Auckland outside the submitted work. Dr. Furyk reports grants from National Health and Medical Research Council during the conduct of the study. Dr. Jones reports grants from National Health and Medical Research Council outside the submitted work. Dr. Neutze reports grants from National Health Medical Research Council, Australia (GNT1081736) and non-financial support from Fisher & Paykel Health Care, Auckland during the conduct of the study. Dr. Oakley reports grants from National Health Medical Research Council, Australia and non-financial support from Fisher & Paykel Health Care, Auckland during the conduct of the study. Dr. Schibler reports grants from National Health Medical Research Council, Australia, grants from Queensland Emergency Medical Research Fund, grants from Foundation Ipswich Hospital, grants

Franklin 2018 *(Continued)*

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Gao 2017

Study characteristics	
Methods	• Single-centre RCT in the Department of Neonatology of the Maternal and Child Health Hospital of Guangxi Zhuang Region • Study period: January 2013 to December 2015
Participants	• Sample size: 78 term infants (38 nCPAP group; 40 HFNC group) • Inclusion criteria: gestational age 37 to 42 weeks; birth weight 2500 g to 4000 g; high-frequency oscillatory ventilation combined with nitric oxide inhalation therapy • Exclusion criteria: severe asphyxia; hypoxic ischaemic encephalopathy; congenital malformations; inherited metabolic diseases
Interventions	• Participants were randomised to either the nCPAP group or the HFNC group • Infants in the HFNC group received heated and humidified inhaled gas at 37 °C, with flow rates set at 2 to 8 L/min and an FiO_2 of 0.3 to 0.4. The infants were connected to the Fisher & Paykel OptiflowTM nasal cannula oxygen inhalation System. • Infants in the nCPAP group received an initial gas flow of 8 to 10 L/min, PEEP 4 to 6 cm H_2O, and an FiO_2 of 0.3 to 0.45. The nCPAP device used was the Paediatric CPAP Series (Stephan CPAP B Plus).
Outcomes	• Primary outcome: weaning failure • Secondary outcomes: time of non-invasive respiratory support; establishment of total enteral feeding; hospital length of stay; incidence of nasal injury, abdominal overdistension, air leak, and intraventricular haemorrhage
Notes	Details of funding sources and declarations of interest were not stated

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Kepreotes 2017

Study characteristics	
Methods	• Single-centre RCT in the emergency department of the John Hunter Hospital and the medical unit of the John Hunter Children's Hospital, Australia • Study period: July 2012 to May 2015
Participants	• Sample size: 202 total participants in study, 21 term infants (10 standard therapy group; 11 HFWHO group) • Inclusion criteria: up to 24 months of age; clinical diagnosis of bronchiolitis that was assessed as being of moderate severity using the NSW Health clinical practice guideline; required supplemen-

Kepreotes 2017 *(Continued)*

tal oxygen. Infants with chronic neonatal lung disease on home oxygen could be included, but they were weaned to their home oxygen rate rather than to room air.

- Exclusion criteria: children with mild bronchiolitis not requiring oxygen; children admitted to the ward after ICU management; children transferred from other facilities if they had received supplemental oxygen prior to arrival; a known diagnosis of asthma; the presence of pneumothorax or nasal trauma; children with severe or life-threatening bronchiolitis as defined by NSW Health including any of the following: a witnessed apnoea, severe tachypnoea (> 70 breaths per min) or bradypnoea (< 30 breaths per min), moderate–severe grunting, cyanosis or pallor, SpO_2 less than 90% on room air or less than 92% on 2 L/min oxygen via nasal cannulae (standard therapy), marked tachycardia (> 180 beats per min) or bradycardia (< 100 beats per min)

Interventions	- Participants were randomised to either the standard therapy group or the HFWHO group - Participants allocated to the standard therapy group received standard therapy, defined in their study as being fitted with nasal cannulae and receiving cold wall oxygen 100% at low flow to a maximum of 2 L/min - HFWHO was delivered via age-appropriate Optiflow Junior nasal cannulae and the MR850 humidifier (Fisher and Paykel Healthcare; Auckland, New Zealand) up to a limit of 20 L/min using 1:1 air–oxygen ratio, resulting in a maximum FiO_2 of 0.6
Outcomes	- Primary outcome: time to weaning off oxygen - Secondary outcomes: time to treatment failure, proportion of treatment failure, proportion of serious adverse events, transfer to ICU, length of hospital stay, and baseline-adjusted heart rate and respiratory rate at 4 hours and 24 hours. Parent-reported outcomes via phone follow-up included delayed serious adverse events, subsequent medical care, parental concern with the oxygen therapy, and parental rating of their child's comfort, ability to feed, and sleep quality on the allocated treatment using a 5-point Likert scale.
Notes	Details of funding sources: Hunter Children's Research Foundation, John Hunter Hospital Charitable Trust, and the University of Newcastle Priority Research Centre GrowUpWell Declarations of interest: The other authors have no competing interests to declare

Manley 2019

Study characteristics

Methods	- Multi-centre RCT across 9 Australian non-tertiary centres - Study period: April 2015 to November 2017
Participants	- Sample size: 768 total participants in study, 475 term infants (179 CPAP group; 196 HFNC group) - Inclusion criteria: less than 24 hours of age; born at a gestational age of 31 weeks 0 days or later; birth weight of at least 1200 grams; non-invasive respiratory support was indicated; the infant had received supplemental oxygen for more than 1 hour
Interventions	- Participants were randomised to either the standard therapy group or the HFWHO group - For infants who were assigned to CPAP, the starting pressure was 6 cmH_2O delivered through short binasal prongs or a nasal mask. The maximum permissible CPAP pressure was 8 cmH_2O. Infants who met the criteria for treatment failure while receiving CPAP receive endotracheal intubation as appropriate. - Infants assigned to the high flow group received an initial gas flow of 6 L/min from the Optiflow Junior device (Fisher and Paykel Healthcare). The maximum permissible gas flow was 8 L/min. If the criteria for treatment failure was met, the infants could receive CPAP as rescue therapy initiated at a pressure of 8 cmH_2O.

Manley 2019 *(Continued)*

Outcomes	• Primary outcome: treatment failure within 72 hours after randomisation defined as meeting one or more of the following criteria: FiO_2 of 0.4 or higher for more than 1 hour to maintain target SpO_2 levels of 91% to 95%; a pH of less than 7.2 plus a pCO_2 greater than 60 mmHg in 2 samples of arterial or capillary blood obtained at least 1 hour after commencement and obtained 1 hour apart; 2 or more episodes of apnoea for which positive-pressure ventilation was indicated within a 24-hour period or 6 or more episodes for which any intervention was indicated within a 6-hour period; need for endotracheal intubation and mechanical ventilation or required transfer to a NICU; respiratory management was escalated at the discretion of the clinician • Secondary outcomes: reason or reasons for treatment failure; endotracheal intubation; transfer to NICU; the duration of respiratory support, supplemental oxygen, and hospitalisation; and the cost of care
Notes	Details of funding sources: Funded by the Australian National Health and Medical Research Council and Monash University Declarations of interest: No potential conflict of interest relevant to this article was reported

Milesi 2017

Study characteristics	
Methods	• Multicentre RCT across 5 PICUs from French university hospital centres • Study period: September 2016 to July 2017
Participants	• Sample size: 142 total participants in study, 64 term infants (35 nCPAP group; 29 HFNC group) • Inclusion criteria: 1 day to 6 months of age; moderate to severe respiratory distress (defined by a modified Wood's Clinical Asthma Score (mWCAS) > 3); no underlying cardiac or neuromuscular disease and no pneumothorax on chest radiograph; absence of indication for imminent intubation; authorisation to perform the study signed by both parents
Interventions	• Participants were randomised to either the nCPAP group or HFNC group • Infants allocated to the nCPAP group received positive continuous pressure set at +7 cmH_2O • Infants allocated to the HFNC group received flow delivered at 2 L/kg/min, with the device equipped with a pressure release valve set at 45 cmH_2O • For both experimental groups, FiO_2 was titrated in order to achieve a normoxic SpO_2 of 94% to 97% • The protocol lasted a minimum of 24 hours after the allocated treatment had begun • Occurrence of at least one failure criterion justified a switch to the alternative respiratory support. Patients switched from one group to the other were maintained on the second support for 24 hours
Outcomes	• The primary outcome was treatment failure within 24 hours after randomisation • Secondary outcomes included delay, causes, and predictors of failure; success rate after crossover; intubation rate; occurrence of skin lesions; length of stay; serious adverse events (air leak syndrome and death)
Notes	Details of funding sources: All phases of this study were supported by Montpellier University Hospital (Grant: research contract 2012–2015). This study has also been supported by Fisher and Paykel Healthcare with the provision of 30 HFNC circuits. Fisher and Paykel was not involved in the study design and had no role in data management, data analysis and data interpretation, nor in the writing of the report and the decision to submit it for publication. Declarations of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Vahlkvist 2020

Study characteristics

Methods	• Multi-centre RCT in the paediatric department at the Hospital of South West Jutland, Denmark, and the Department of Paediatrics at Kolding Hospital, Denmark • Study period: December 2015 to May 2018
Participants	• Sample size: 50 total participants in study, 16 term infants (10 CPAP group; 6 HFNC group) • Inclusion criteria: children (up to 2 years of age) with bronchiolitis and need for respiratory support • Exclusion criteria: previous chronic disease or severe respiratory insufficiency with decreased consciousness; need for urgent treatment; a capillary pCO_2 > 9.0
Interventions	• Participants were randomised to either the CPAP group or the HFNC group • Children allocated to the CPAP group were fitted with nasal prongs and an initial flow rate of 12 to 14 L/min • Children allocated to the HFNC group were fitted with a nasal cannula, with an initial flow rates of 2 L/kg/min • For both experimental groups, flow could be increased to a maximum of 15L/min and oxygen supply was delivered as needed to maintain a SpO_2 above 92%
Outcomes	• Primary outcomes: change in pCO_2, RR, and M-WCAS scores from time 0 to 48 hours after initiation of the treatment • Secondary outcomes included differences in pain scores; treatment duration; frequency of system failure
Notes	Details of funding sources: not stated Declarations of interest: The authors declare that they have no conflicts of interest.

CPAP/nCPAP: continuous positive airway pressure/nasal continuous positive airway pressure
cmH_2O: centimetre of water
FiO_2: fraction of inspired oxygen
HFNC: high flow nasal cannula
HFWHO: high flow warm humidified oxygen
HHHFNC: heated, humidified, high flow nasal cannula
ICU: intensive care unit
LOS: length of stay
L/min: litres per minute
L/kg/min: litres per kilogram of body weight per minute
M-WCAS: modified Wood's Clinical Asthma Score
NC: nasal cannula
nCPAP: nasal CPAP
pCO_2: peripheral carbon dioxide saturation
PEEP: positive end-expiratory pressure
PICU: paediatric intensive care unit
RCT: randomised controlled trial
RR: respiratory rate
SpO_2: peripheral oxygen saturation
WOB: work of breathing

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

Study	Reason for exclusion
ACTRN12611000233921	Study terminated
Akyildiz 2018	Wrong patient population - participants aged greater than 1 month postnatal age
Campaña 2014	Wrong comparator - hypertonic saline
Chen 2019	Wrong comparator - low flow rates contained greater than 2 L/min
Chisti 2015	Wrong patient population - participants aged greater than 1 month postnatal age
Christophe 2018	Wrong comparator - high flow nasal cannula versus high flow nasal cannula
Ergul 2018	Wrong patient population - participants aged greater than 1 month postnatal age
Hough 2011	Wrong comparator - study compares different flow rates of HFNC
Iranpour 2012	Wrong patient population - preterm
JPRN-UMIN000013907	Study terminated
JPRN-UMIN000018983	Wrong patient population - participants were aged less than 37 weeks gestational age (preterm)
Juretschke 2004	Wrong patient population - participants were aged less than 37 weeks gestational age (preterm)
Kamerkar 2014	Wrong outcomes - WOB, RR, oesophageal pressure
Kefala 2015	Wrong comparator - high flow nasal cannula versus low flow nasal cannula
Kugelman 2012	Wrong patient population - preterm
Liu 2020	Wrong patient population - participants aged greater than 1 month postnatal age
Ma 2014	Wrong patient population - preterm
Maitland 2017	Wrong patient population - participants were aged greater than 1 month postnatal age
Maitland 2021	Wrong patient population - participants were aged greater than 1 month postnatal age
Mayfield 2014	Wrong patient population - participants aged greater than 1 month postnatal age
Mazmanyan 2013	Wrong patient population - preterm
Mazmanyan 2016	Wrong outcomes - transcutaneous CO_2, SpO_2, RR, minute ventilation
Milani 2016	Wrong patient population - participants were aged greater than 1 month postnatal age
Mostafa-Gharehbaghi 2015	Wrong patient population - preterm
NCT00356668	Wrong study design - observational study
NCT01189162	Wrong patient population - preterm
NCT01270581	Study terminated
NCT01662544	Wrong patient population - participants aged greater than 1 month postnatal age

Study	Reason for exclusion
NCT01944995	Wrong outcomes - WOB, respiratory rate, heart rate, FiO_2, SpO_2
NCT02457013	Wrong outcomes - WOB, RR, HR, FiO_2, SpO_2
NCT02499744	Study terminated
NCT02587832	Wrong patient population - preterm
NCT02632799	Wrong outcomes - airway pressure
NCT02632825	Wrong outcomes - blood CO_2, ventilation, sleep/awake status
NCT02737280	Study terminated
NCT02824744	Wrong comparator - high flow nasal cannula versus high flow nasal cannula
NCT03015051	Wrong patient population - participants aged greater than 1 month postnatal age
NCT03252119	Study terminated
NCT03689686	Wrong outcomes - oesophageal pressure
NCT03967769	Wrong outcomes - time between onset of apnoea and desaturation ($SPO_2 < 95\%$)
NCT04245202	Wrong patient population - participants aged greater than 1 month postnatal age
Parmekar 2018	Wrong patient population - preterm
Pediatric Academic Societies 2011	Wrong patient population - patients with congenital hernias
Pediatric Academic Societies 2013	Wrong patient population - preterm
Sahhar 2015	Wrong comparator - heliox
Sarkar 2018	Wrong patient population - participants were aged greater than 1 month postnatal age
Schibler 2010	Wrong comparator - comparing different flow rates of HFNC
Shetty 2015	Wrong patient population - preterm
Sitthikarnkha 2018	Wrong patient population - participants were aged greater than 1 month postnatal age
SLCTR/2017/017	Wrong intervention - flow rates < 2 L/min
Song 2017	Wrong patient population - participants were aged greater than 1 month postnatal age
Sood 2012	Wrong comparator - high flow nasal cannula versus high flow nasal cannula
Soonsawad 2015	Wrong patient population - preterm
Swayampakula 2016	Wrong comparator - external nasal dilator

Study	Reason for exclusion
TCTR20170222007	Wrong patient population - participants aged greater than 1 month postnatal age
Vitaliti 2017	Wrong patient population - participants were aged greater than 1 month postnatal age
Vitaliti 2018	Wrong patient population - participants were aged greater than 1 month postnatal age
Woodhead 2006	Wrong patient population - preterm
Yengkhom 2021	Wrong patient population - preterm

CO_2: carbon dioxide
FiO_2: fraction of inspired oxygen
HFNC: high flow nasal cannula
HR: heart rate
RR: respiratory rate
SpO_2: peripheral oxygen saturation
WOB: work of breathing

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

Borgi 2021

Methods	• Single-centre RCT in the PICU of the Children's Bechir Hamza Hospital of Tunis, Tunisia • Study period: December 2013 to March 2017
Participants	• Sample size: 268 (125 CPAP/NPPV group; 130 HFNC group) • Inclusion criteria: patients aged from 7 days to 6 months and hospitalised in the PICU, were eligible once all inclusion criteria were verified; (i) clinical diagnosis of bronchiolitis defined as the first viral episode of respiratory distress, presenting with rhinitis, tachypnoea, cough, wheezing, prolonged expiratory time, crackles and use of accessory muscles, with or without fever, with or without infiltrate on the chest X-ray, (ii) bronchiolitis severity Wang modified score ≥ 10 • Exclusion criteria: patients with recurrent wheezing, heart disease, chronic lung disease, neuromuscular disease, or with an immediate need for intubation. Immediate intubation is indicated in critically ill infants to avoid respiratory arrest, and in patients with a history of cardiorespiratory arrest, a poor neurologic status, an increased WOB (retractions, flaring, grunting), or poor perfusion requiring vasoactive treatment. If the primary or final diagnosis was other than bronchiolitis such as bacterial pneumonia and pertussis, patients were also excluded from the study.
Interventions	• Infants were allocated to either the CPAP/NPPV group or HFNC group • The CPAP/NPPV group received at first CPAP using a neonatal ventilator (Babylog 8000). The recommended starting pressure for CPAP was +6 cmH_2O. Positive continuous pressure could be increased to a maximum of +8 cmH_2O. Optimal PEEP was what could maintain SpO_2 of 94% using the lowest fraction of inspired oxygen. Positive end-expiratory pressure was progressively decreased by 1 cmH_2O every 6 hours from the optimal PEEP when FiO_2 < 30% and if there was no increase of WOB. Either a nasal mask or nasal prongs were determined by the patient's comfort, the size of the patient's nostrils, and at the discretion of the physician. Weaning from CPAP was started if PEEP < 6 cmH_2O and FiO_2 < 30% after at least 6 hours. If CPAP failed to improve clinical respiratory distress, the infant was allocated to the NPPV strategy. Ventilator parameters were adjusted according to clinical outcome and arterial blood gas monitoring. The starting inspiratory pressure was 20 cmH_2O with a maximum pressure at 30, maximum PEEP was +8 cmH_2O and maximum frequency was 35 cycles/min, inspiratory time was 0.7 seconds, and flow gas was 15 L/min. Patients were progressively weaned if FiO_2 < 30% and if there was no increase of WOB after 6 hours at least. If the patient was weaned from NPPV, the same criteria for weaning from CPAP were used.

Borgi 2021 *(Continued)*

- Infants in the HFNC group received heated and humidified gas flow with the Fisher and Paykel Healthcare® HFNC system. The size of the cannula fitted the child's nares without occlusion. The flow rate was usually started at the maximum flow rate for the size of the cannula and a constant flow temperature of 37 °C. The starting FiO_2 was what could maintain SpO_2 of 94%. The flow rate was decreased when $FiO_2 < 30\%$ in stages: 1 litre every 2 hours to reach 2 L/min and if there is no increase of WOB. Weaning from HFNC was started if $FiO_2 < 30\%$ and flow rate ≤ 2 L/min after 6 hours at least. If the HFNC failed, the switch to CPAP then NPPV if necessary was allowed before intubation for ethical considerations.

Outcomes	- Primary outcome: treatment failure as defined by the following criteria; $FiO_2 > 60\%$ to maintain $SpO_2 \leq 90\%$ or increasing of WOB. All patients received adequate oral sedation, hydration, and enteral feeding. - Secondary outcomes: predictors of failure, intubation rate, stay length, bacterial coinfection, serious adverse events (air leak), and mortality in each group
Notes	This study was a newly identified potentially relevant study following the search conducted prior to publication in December 2022. It is awaiting assessment pending a response from the corresponding author to our request for further information to confirm study inclusion and obtain the results for any participants matching our inclusion criteria.

Durand 2020

Methods	- Multi-centre RCT across the emergency departments and general paediatric wards of 17 hospitals in Paris, France - Study period: November 2016 to March 2017
Participants	- Sample size: 268 (133 control group; 135 treatment group) - Inclusion criteria: aged 7 days to 6 months; 1 episode of $SpO_2 < 95\%$ while on room air at any time before randomisation and m-WCAS score between 2 and 5 - Exclusion criteria: urgent need for mechanical ventilation support either by nCPAP or the endotracheal route; a severe form of bronchiolitis defined by m-WCAS > 5 and the requirement for non-invasive ventilation; uncorrected cyanotic heart disease; innate immune deficiency; craniofacial malformation; congenital stridor and tracheotomy
Interventions	- Infants were allocated to either the HFNC group or standard oxygen therapy group - The HFNC group received gas flow rates of 3 L/kg/min up to a maximum of 20 L/min, delivered via an Airvo 2 turbine through an Optiflow junior infant size cannula (OPT316) (Fisher & Paykel Healthcare, Auckland, New Zealand). FiO_2 was adjusted to obtain an SpO_2 of ≥ 94%. - The standard oxygen therapy group received standard therapy, defined in their study as supplemental oxygen at flow rates up to 2 L/min to maintain SpO_2 at ≥ 94%
Outcomes	- Primary outcome: treatment failure, defined as the application of noninvasive or invasive ventilation in the overall population or the use of HFNC in the control group - Secondary outcomes: rates of transfer to the PICU; an assessment of short-term respiratory status; paediatric general ward unit length of stay; oxygen support-free days; and artificial nutritional support-free days
Notes	We attempted to contact the corresponding author requesting further information to confirm study inclusion and obtain the results and data for any participants matching our inclusion criteria. However, we did not receive a reply.

Franklin 2021

Methods	• Multi-centre RCT across 2 tertiary children's hospitals in Australia
Participants	• 563 participants • Inclusion criteria: aged 0 to 16 years; respiratory failure with oxygen requirement to maintain SpO_2 ≥ 92%; admission to hospital • Excluded were infants with bronchiolitis and aged < 12 months as they were studied in the previous study; children with previous high flow therapy during the current illness; upper airway obstruction; craniofacial malformation; critically ill requiring immediate higher level of care with invasive or non-invasive ventilation; basal skull fracture; trauma; cyanotic heart disease; home oxygen therapy; cystic fibrosis; palliative care and oncology
Interventions	• Participants were randomised to either the standard oxygen group or HFNC group • The standard oxygen group received standard therapy, defined in their study as subnasal oxygen to a maximum of 4 L/min or via Hudson mask 4 to 8 L/min to maintain SpO_2 between 92% and 98% • The HFNC group received weight-specific flows starting at 2 L/kg/min delivered via age-appropriate nasal interfaces
Outcomes	• Primary outcomes: treatment failure • Secondary outcomes: proportion of children requiring intensive care admission, escalation of care and adverse events, length of oxygen therapy, length of hospital stay, and intubation
Notes	Status: awaiting publication of dataset

Hathorn 2014

Methods	• Single-centre RCT in a tertiary referral children's hospital in Canada over a 2-year study period
Participants	• Study enrolled 72 participants (up to 18 months of age) with a clinical diagnosis of bronchiolitis
Interventions	• Subjects were randomised to standard supportive care with low flow oxygen up to 2 L/min or HFNC oxygen at 8 L/min • Fractional inspired concentration of oxygen was titrated to maintain saturations > 92%
Outcomes	• Primary outcome: time to resolution of respiratory distress; oxygen requirements • Secondary outcome: adverse effects
Notes	We attempted to contact the corresponding author requesting further information to confirm study inclusion and obtain the results and data for any participants matching our inclusion criteria. However, we did not receive a reply.

Ji 2021

Methods	• Single-centre RCT performed in the Taizhou People's Hospital, China • Study period: February 2018 to January 2020
Participants	• Study enrolled 88 neonates (up to 42 weeks gestational age) who had idiopathic diseases such as respiratory distress syndrome, severe pneumonia, or respiratory failure • Other inclusion criteria: neonates who met weaning criteria from mechanical ventilation, and were ready for weaning; neonates who underwent mechanical ventilation not less than 24 hours

Ji 2021 *(Continued)*

	• Exclusion criteria: neonates born either at < 34 weeks or > 42 weeks of gestation; neonates with birth weight < 1500 grams; neonates with pulmonary malformations, or those who were combined with other congenital diseases such as lung diseases
Interventions	• The control group was given oxygen inhalation using a head box • The research group was given HFNC therapy at flow rates of 2 to 6 L/min, airway humidification temperature 37 °C, initial FiO_2 of 0.4, and gradual adjustment to maintain SpO_2 between 90% to 95%
Outcomes	• Primary outcome: clinical efficacy, defined as: the clinical symptoms and pulmonary crackles of the neonates disappeared after treatment; oxygen saturation was ≥ 95%, and arterial blood gas results returned to normal • Secondary outcomes: weaning failure; complications such as nosocomial infection, nasal mucosal injury, nasal and facial pressure ulcers
Notes	We attempted to contact the corresponding author requesting further information to confirm study inclusion and obtain the results and data for any participants matching our inclusion criteria. However, we did not receive a reply.

Liu 2014

Methods	• Multi-centre study RCT across 12 tertiary hospital NICUs in Hebei Province, China • Study period: December 2012 to May 2013
Participants	• 255 infants (< 7 days old), 150 were preterm • Exclusion criteria: life-threatening congenital malformations; congenital distortions that require surgical treatment; congenital respiratory malformations; uncontrolled moveable air leakage syndrome
Interventions	• Infants were randomised to either HFNC or nCPAP • Infants in the HFNC group received gas flow rates of 3 to 8 L/min • The nCPAP group flow rate was to 6 to 10 L/min and continued with the positive pressure set at pre-extubation
Outcomes	• Primary outcomes: treatment failure (defined as reintubation within 7 days), death • Secondary outcomes: total on-board time, non-invasive auxiliary ventilation time and total oxygen use time before discharge; incidence of adverse events including significant apnoea, nasal mucosa (septum) injury, lung air leakage, abdominal overdistension, necrotising enterocolitis, intestinal perforation; time of oral feeding
Notes	We attempted to contact the corresponding author requesting further information to confirm study inclusion and obtain the results and data for any participants matching our inclusion criteria. However, we did not receive a reply.

Ramnarayan 2018

Methods	• Multi-centre RCT across 3 hospitals in London, United Kingdom • Study period: phase III trials estimated completion 2022
Participants	• Group A inclusion criteria: aged > 36 weeks corrected gestational age and < 16 years, and deemed to require non-invasive respiratory support by the treating clinician for an acute illness, and satisfies one or more of the following criteria: hypoxia; acute respiratory acidosis; moderate respiratory distress

Ramnarayan 2018 *(Continued)*

	• Group B inclusion criteria: aged > 36 weeks corrected gestational age and < 16 years, and deemed to require non-invasive respiratory support by the treating clinician after extubation • Exclusion criteria: deemed by the treating clinician to require immediate intubation; tracheostomy in place; pre-existing air-leak syndrome; midfacial/craniofacial anomalies; agreed limitation of intensive care treatment plan in place; on domiciliary non-invasive ventilation prior to PICU admission; managed on either HFNC and/or CPAP (or other form of non-invasive ventilation) in the preceding 24 hours
Interventions	• Experimental: heated humidified high flow nasal cannula therapy delivered at 2 L/kg/min gas flow rate • Active comparator: CPAP will be provided using a set expiratory pressure of 6 to 8 cmH$_2$O
Outcomes	• Primary outcomes: proportion of patients adherent to the study treatment; mean COMFORT score; number of parents completing the Parental Stressor Scale • Secondary outcomes: adverse events (pneumothorax, pneumomediastinum, nasal or facial trauma, abdominal overdistension, nosocomial infection); improvement in oxygenation, PaCO$_2$ levels, HR, RR, WOB; length of PICU and hospital stay ventilator-free days at day 28; mortality discharge
Notes	Status: phase III trials estimated completion 2022

Selvaraj 2022

Methods	• Single-centre RCT in the paediatric ward of the Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India • Study period: January 2017 to August 2018
Participants	• Study enrolled 80 infants (aged less than 12 months) • Inclusion criteria: aged less than 12 months with clinical diagnosis of mild and moderate bronchiolitis (graded based on Wood Downes Ferres scoring) requiring oxygen support • Exclusion criteria: parents who do not consent for the study, severe bronchiolitis, upper airway obstruction, craniofacial malformation
Interventions	• Infants were randomised to either HFNC or non rebreathing mask (NRM) group • Infants in the HFNC group received gas flow rates of 2 L/kg/minute, up to 10 kg, with an addition of 0.5 L/kg for each kilogram more than 10 kg • The NRM group received conventional oxygen through non rebreathing mask at a flow rate of 2 to 10 L/minute (adjusted individually, up to 10 L/minute)
Outcomes	• Primary outcomes: duration for which oxygen was required and length of hospital stay • Secondary outcomes: haemodynamic parameters including mean heart rate, percentage reduction in heart rate, mean respiratory rate, percentage reduction in respiratory rate, mean difference in saturation levels, adverse events including PICU admission/invasive ventilation
Notes	This study was a newly identified potentially relevant study following the search conducted prior to publication in December 2022. It is awaiting assessment pending a response from the corresponding author to our request for further information to confirm study inclusion and obtain the results for any participants matching our inclusion criteria.

Testa 2014

Methods	• Single centre RCT in the PICU of the Children's Hospital Bambino Gesu', Rome, Italy

Testa 2014 *(Continued)*

	• Study period: May 2012 to January 2013
Participants	• Study enrolled 94 participants (aged less than 18 months) • Inclusion criteria: elective cardiac surgery with cardio-pulmonary bypass and a Risk Adjustment for Congenital Heart Surgery (RACHS) score of 2 and above • Exclusion criteria: the presence of major congenital malformations or neuromuscular disease, the postoperative presence, before weaning, of a non-drained pneumothorax or pleural effusions and the absence of informed consent
Interventions	• Participants were allocated to either the HFNC group or the oxygen therapy group • The HFNC group received flow rates at 2 L/kg/min. A pressure-limited valve was interposed in the HFNC circuit. • The oxygen therapy group received flow rates up to a maximum of 2 L/min • In all patients, the gas mixture was heated (temperature 36.7 °C) and humidified and delivered via a Fisher and Paykel blender
Outcomes	• Primary outcomes: treatment failure defined as meeting 2 or more of the criteria for cardiac and respiratory failure: hypoxaemia (decrease > 20% from baseline); hypercarbia (> 20% pre-extubation); upper respiratory tract disease/airway oedema; respiratory rate (> 20% pre-extubation); dyspnoea; complete lung atelectasia. Criteria for cardiac treatment failure: cardiac rhythm disturbance; hypotension (< 20% pre-extubation); cardiac dysfunction Increase in lactates (> 20% pre-extubation). • Secondary outcomes: HR, BP, RR, ABG at 1, 6, 12, 24, and 48 hours after extubation; presence of nasal ulcers; need of supplemental sedation; gastric distension; length of mechanical ventilation and PICU stay
Notes	We attempted to contact the corresponding author requesting further information to confirm study inclusion and obtain the results and data for any participants matching our inclusion criteria. However, we did not receive a reply.

Yoder 2013

Methods	• Multi-centre RCT across 4 hospitals in the USA and 1 in China • Study period: December 2007 to April 2012
Participants	• The study enrolled 432 infants (28 to 32 weeks gestational age) where non-invasive respiratory support was indicated • Exclusion criteria: birth weight < 1000 grams; presence of an active air leak syndrome; abnormalities of upper and lower airways; serious abdominal, cardiac, or respiratory malformations
Interventions	• Infants were allocated to either receive HHHFNC or nCPAP • Initial flow rate for HHHFNC was determined by infant weight. Flow rate could be increased by a maximum of 3 L/min above the starting flow rate.The devices used for HHHFNC included Comfort Flo, Fisher and Paykel Healthcare, and Vapotherm • The starting pressure for nCPAP was 5 to 6 cmH$_2$O, which could be increased to a maximum of 8 cmH$_2$O. nCPAP was provided by various interfaces including bubble, Infant Flow nCPAP System.
Outcomes	• Primary outcome: need for intubation within 72 hours of applied non-invasive therapy • Secondary outcomes: total ventilator days; days of non-invasive support and oxygen use up to the time of discharge; frequency of adverse events; assessment of nasal mucosal injury; overall comfort; incidence of bronchopulmonary dysplasia; discharge from hospital on oxygen

Yoder 2013 *(Continued)*

Notes	We attempted to contact the corresponding author requesting further information to confirm study inclusion and obtain the results and data for any participants matching our inclusion criteria. However, we did not receive a reply.

ABG: arterial blood gas
BP: blood pressure
cmH_2O: centimetre of water
CPAP: continuous positive airway pressure
FiO_2: fraction of inspired oxygen
HFNC: high flow nasal cannula
HHHFNC: heated, humidified high flow nasal cannula
HR: heart rate
L/min: litres per min
LOS: length of stay
m-WCAS: modified Wood's Clinical Asthma Score
nCPAP: nasal continuous positive airway pressure
NICU: neonatal intensive care unit
NPPV: nasal positive pressure ventilation
PEEP: positive end-expiratory pressure
PEWS: Paediatric Early Warning Score
PICU: paediatric intensive care unit
RCT: randomised controlled trial
RDAI: respiratory distress assessment instrument
RR: respiratory rate
SpO_2: peripheral oxygen saturation

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

NCT02913040

Study name	High flow in infants with bronchiolitis
Methods	• Multi-centre RCT in the paediatric (non-intensive care) units of 5 different hospitals in the Netherlands • Study period: December 2016 to March 2020
Participants	• Children < 2 years of age hospitalised for bronchiolitis with moderate-severe dyspnoea • Inclusion criteria: bronchiolitis (PEWS 0 to 28), SpO_2 < 92% • Exclusion criteria: chronic lung disease, haemodynamic significant heart disease, syndromal disease, facial abnormalities
Interventions	• High flow nasal cannula (oxygen delivery through heated humidified high flow nasal cannula) • Active comparator: low flow nasal prongs (oxygen delivery through low flow nasal prongs)
Outcomes	• Primary outcome: PEWS • Secondary outcomes: comfort, ability to feed, duration of hospitalisation in days, admission to PICU
Starting date	1 December 2016
Contact information	Principal Investigator: Jolita Bekhof, MD, PhD
Notes	Principal Investigator: Jolita Bekhof, MD, PhD Status: trial listed as completed. No results posted

NCT02913040 *(Continued)*

We attempted to contact the responsible party for further information on when results will be published. However, we did not receive a reply.

NCT03095495

Study name	High flow nasal cannula therapy in bronchiolitis: early vs rescue
Methods	• Single-centre RCT in the Paediatric Emergency Centre (PEC) of Hamad General Hospital in Qatar - estimated completion 2023
Participants	• Infants aged ≤ 3 months presenting to the unit for treatment of viral bronchiolitis with positive RSV test will be eligible for the study
Interventions	• Patients will be randomised into either the HHHFNC group or the standard therapy + rescue HHHFNC group • Early HHHFNC group will be treated by using heated humidified high flow oxygen/air via nasal cannula; investigators will keep the patient on HHHFNC until he/she becomes clinically ready for discharge • Standard therapy and rescue HHHFNC group will receive standard therapy, defined in their study as low flow nasal cannula oxygen therapy up to 2 L/min to maintain $SpO_2 \geq 92\%$. Those who deteriorate will then receive HHHFNC before admission to the ICU.
Outcomes	• Primary outcome: the rate of PICU admissions • Secondary outcomes: hospital length of stay; Bronchiolitis Severity Score (BSS); transcutaneous partial pressure of carbon dioxide; percentage of patients who are on the standard therapy arm and required ICU admission, but improved after the rescue HHHFNC; percentage of revisit 2 weeks post discharge
Starting date	August 2018
Contact information	Dr Khalid Alansari, MD Email: kalansari1@hamad.qa
Notes	Recruitment status: currently recruiting - estimated study completion 2023

NCT03505814

Study name	Interest of high flow nasal cannula oxygen therapy in paediatric intensive care unit
Methods	• Single-centre RCT in the paediatric ward of the Benioff Children's Hospital Oakland, United States • Study period: March 2017 - unknown (estimated completion Feb 2019)
Participants	• Patients aged between 0 and 45 days needing mechanical ventilation with tracheal intubation • Inclusion criteria: need for mechanical ventilation, tracheal intubation, surgical intensive care admission, availability of extubation criteria • Exclusion criteria: prior extubation and mechanical ventilation to the actual episode, weaning failure due to neurological status
Interventions	• Experimental: HFNC Group - high flow (6 L/min), humidified oxygen administered into nasal cannula for post extubation newborn ventilated patients • Active comparator: conventional oxygen therapy for post extubation care

NCT03505814 *(Continued)*

Outcomes	• Primary outcome: reintubation rate 72 hours following extubation • Secondary outcomes: incidence of post-extubation respiratory failure, time to reintubate, weaning time from oxygen, BP, HR, RR, SpO_2, FiO_2
Starting date	1 March 2017
Contact information	Sonia Ben Khalifa Email: benkhalifa_sonia@yahoo.fr
Notes	Status: estimated completion 2019. No results posted. We attempted to contact the responsible party for further information on when results will be published. However, we did not receive a reply.

BP: blood pressure
FiO_2: fraction of inspired oxygen
HHHFNC: heated, humidified, high flow nasal cannula
HR: heart rate
L/kg/min: litres per kilogram per minute
$PaCO_2$: partial pressures of carbon dioxide
PEWS: Paediatric Early Warning Score
PICU: paediatric intensive care unit
RCT: randomised controlled trial
RR: respiratory rate
RSV: respiratory syncytial virus
SpO_2: peripheral oxygen saturation
WOB: work of breathing

RISK OF BIAS

Legend:	✓ Low risk of bias	✗ High risk of bias	~ Some concerns

Risk of bias for analysis 1.2 Treatment failure

	Bias					
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Cesar 2020	✓	✓	✓	✓	✓	✓
Manley 2019	✓	✓	✓	✓	✓	✓
Milesi 2017	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.4 Duration of any form of respiratory support (hours/days)

	Bias					
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Cesar 2020	✓	✓	✓	✓	✓	✓
Gao 2017	~	✓	✓	✓	✓	~
Manley 2019	✓	✓	✓	✓	✓	✓
Milesi 2017	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.5 Length of stay at intensive care unit (days)

	Bias					
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Cesar 2020	✓	✓	✓	✓	✓	✓
Manley 2019	✓	✓	✓	✓	✓	✓
Milesi 2017	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.6 Hospital length of stay (days)

	Bias					
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Cesar 2020	✓	✓	✓	✓	✓	✓
Gao 2017	~	✓	✓	✓	✓	~
Manley 2019	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.7 Adverse events - air leak syndrome

Study			Bias			
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Gao 2017	〜	✓	✓	✓	✓	〜
Manley 2019	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.8 Adverse events - nasal trauma

Study			Bias			
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Gao 2017	〜	✓	✓	✓	✓	〜

Risk of bias for analysis 1.9 Adverse events - abdominal overdistension

Study			Bias			
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Gao 2017	〜	✓	✓	✓	✓	〜

Risk of bias for analysis 2.2 Treatment failure

Study			Bias			
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Franklin 2018	✓	✓	✓	✓	✓	✓
Kepreotes 2017	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.4 Duration of any form of respiratory support (hours/days)

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
			Bias			
Franklin 2018	✔	✔	✔	✔	✔	✔

Risk of bias for analysis 2.5 Length of stay at intensive care unit (days)

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
			Bias			
Franklin 2018	✔	✔	✔	✔	✔	✔

Risk of bias for analysis 2.6 Hospital length of stay (days)

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
			Bias			
Franklin 2018	✔	✔	✔	✔	✔	✔
Kepreotes 2017	✔	✔	✔	✔	✔	✔

Risk of bias for analysis 2.7 Adverse events

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
			Bias			
Franklin 2018	✔	✔	✔	✔	✔	✔
Kepreotes 2017	✔	✔	✔	✔	✔	✔

DATA AND ANALYSES

Comparison 1.   HFNC versus CPAP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death	2	439	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.01, 0.01]
1.2 Treatment failure	3	452	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.47, 2.04]
1.3 Chronic lung disease (need for supplemental oxygen at 28 days of life)	1	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.4 Duration of any form of respiratory support (hours/days)	4	530	Mean Difference (IV, Random, 95% CI)	0.17 [-0.28, 0.61]
1.5 Length of stay at intensive care unit (days)	3	452	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.31, 2.12]
1.6 Hospital length of stay (days)	3	466	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.52, 0.74]
1.7 Adverse events - air leak syndrome	2	453	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.41, 1.36]
1.8 Adverse events - nasal trauma	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.04, 0.66]
1.9 Adverse events - abdominal overdistension	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.07, 0.71]

Analysis 1.1. Comparison 1: HFNC versus CPAP, Outcome 1: Death

Study or Subgroup	HFNC Events	HFNC Total	CPAP Events	CPAP Total	Weight	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI
Manley 2019	0	196	0	179	85.5%	0.00 [-0.01 , 0.01]	
Milesi 2017	0	29	0	35	14.5%	0.00 [-0.06 , 0.06]	
Total (95% CI)		225		214	100.0%	0.00 [-0.01 , 0.01]	
Total events:	0		0				

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

-100 -50 0 50 100
Favours HFNC   Favours CPAP

Analysis 1.2. Comparison 1: HFNC versus CPAP, Outcome 2: Treatment failure
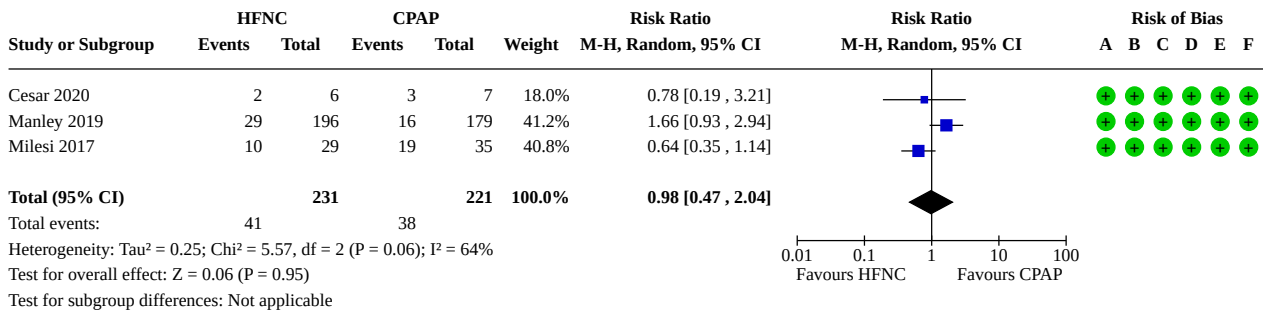
Study or Subgroup	HFNC Events	HFNC Total	CPAP Events	CPAP Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Cesar 2020	2	6	3	7	18.0%	0.78 [0.19 , 3.21]		+ + + + + +
Manley 2019	29	196	16	179	41.2%	1.66 [0.93 , 2.94]		+ + + + + +
Milesi 2017	10	29	19	35	40.8%	0.64 [0.35 , 1.14]		+ + + + + +
Total (95% CI)		231		221	100.0%	0.98 [0.47 , 2.04]		
Total events:	41		38					

Heterogeneity: Tau² = 0.25; Chi² = 5.57, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours HFNC   Favours CPAP

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: HFNC versus CPAP, Outcome 3: Chronic lung disease (need for supplemental oxygen at 28 days of life)

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	CPAP Mean	CPAP SD	CPAP Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Manley 2019	0	0	196	0	0	179		Not estimable	
Total (95% CI)			0			0		Not estimable	

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

-100 -50 0 50 100
Favours HFNC   Favours CPAP
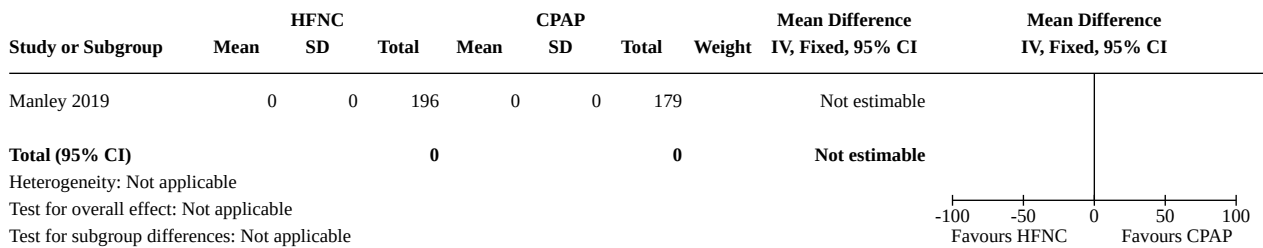
Analysis 1.4. Comparison 1: HFNC versus CPAP, Outcome 4: Duration of any form of respiratory support (hours/days)

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	CPAP Mean	CPAP SD	CPAP Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Cesar 2020	2.17	2.17	6	1.17	1.11	7	4.9%	1.00 [-0.92 , 2.92]		+ + + + + +
Gao 2017	4	0.71	40	4.17	0.54	38	45.3%	-0.17 [-0.45 , 0.11]		? + + + + ?
Manley 2019	1.15	1.48	196	0.83	1.11	179	46.2%	0.32 [0.06 , 0.58]		+ + + + + +
Milesi 2017	5.29	5.83	29	4	2.71	35	3.5%	1.29 [-1.01 , 3.59]		+ + + + ? ?
Total (95% CI)			271			259	100.0%	0.17 [-0.28 , 0.61]		

Heterogeneity: Tau² = 0.09; Chi² = 8.14, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable

-100 -50 0 50 100
Favours HFNC   Favours CPAP

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: HFNC versus CPAP, Outcome 5: Length of stay at intensive care unit (days)
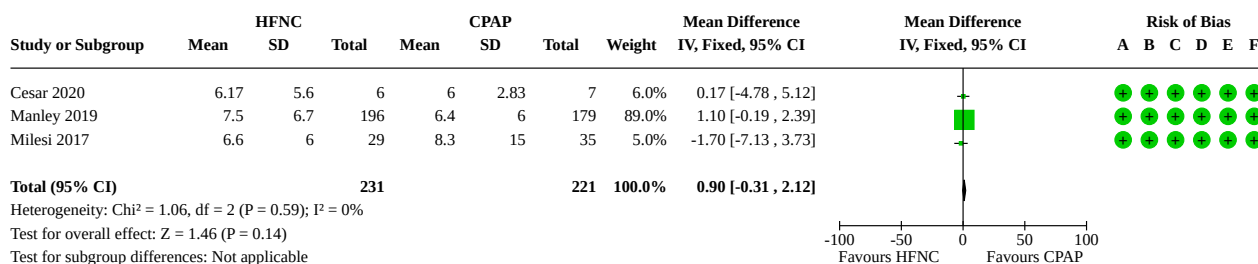
Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	CPAP Mean	CPAP SD	CPAP Total	Weight	Mean Difference IV, Fixed, 95% CI
Cesar 2020	6.17	5.6	6	6	2.83	7	6.0%	0.17 [-4.78, 5.12]
Manley 2019	7.5	6.7	196	6.4	6	179	89.0%	1.10 [-0.19, 2.39]
Milesi 2017	6.6	6	29	8.3	15	35	5.0%	-1.70 [-7.13, 3.73]
Total (95% CI)			**231**			**221**	**100.0%**	**0.90 [-0.31, 2.12]**

Heterogeneity: Chi² = 1.06, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable

Mean Difference IV, Fixed, 95% CI — Favours HFNC / Favours CPAP (-100, -50, 0, 50, 100)

Risk of Bias: A B C D E F

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: HFNC versus CPAP, Outcome 6: Hospital length of stay (days)

Study or Subgroup	HFNC Mean	HFNC SD	HFNC Total	CPAP Mean	CPAP SD	CPAP Total	Weight	Mean Difference IV, Fixed, 95% CI
Cesar 2020	9.67	2.73	6	9.29	3.09	7	3.9%	0.38 [-2.78, 3.54]
Gao 2017	16.1	1.9	40	16.5	1.8	38	58.2%	-0.40 [-1.22, 0.42]
Manley 2019	5.76	6.29	196	4.89	3.49	179	37.9%	0.87 [-0.15, 1.89]
Total (95% CI)			**242**			**224**	**100.0%**	**0.11 [-0.52, 0.74]**

Heterogeneity: Chi² = 3.65, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable

Mean Difference IV, Fixed, 95% CI — Favours HFNC / Favours CPAP (-100, -50, 0, 50, 100)

Risk of Bias: A B C D E F

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.7. Comparison 1: HFNC versus CPAP, Outcome 7: Adverse events - air leak syndrome

Study or Subgroup	HFNC Events	HFNC Total	CPAP Events	CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gao 2017	0	40	2	38	11.4%	0.19 [0.01, 3.84]
Manley 2019	17	196	19	179	88.6%	0.82 [0.44, 1.52]
Total (95% CI)		**236**		**217**	**100.0%**	**0.75 [0.41, 1.36]**
Total events:	17		21			

Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Fixed, 95% CI — Favours HFNC / Favours CPAP (0.01, 0.1, 1, 10, 100)
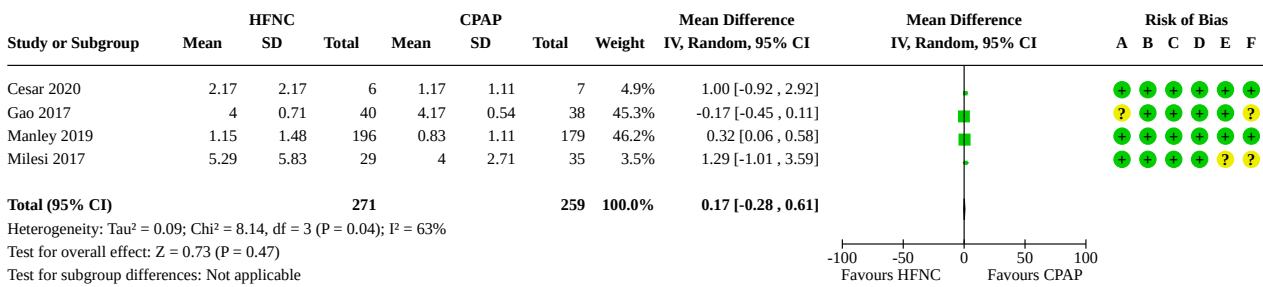
Risk of Bias: A B C D E F

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.8. Comparison 1: HFNC versus CPAP, Outcome 8: Adverse events - nasal trauma

Study or Subgroup	HFNC Events	HFNC Total	CPAP Events	CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Gao 2017	2	40	12	38	100.0%	0.16 [0.04 , 0.66]		? + + + + ?
Total (95% CI)		**40**		**38**	**100.0%**	**0.16 [0.04 , 0.66]**		
Total events:	2		12					

Heterogeneity: Not applicable
Test for overall effect: Z = 2.53 (P = 0.01)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.9. Comparison 1: HFNC versus CPAP, Outcome 9: Adverse events - abdominal overdistension

Study or Subgroup	HFNC Events	HFNC Total	CPAP Events	CPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Gao 2017	3	40	13	38	100.0%	0.22 [0.07 , 0.71]		? + + + + ?
Total (95% CI)		**40**		**38**	**100.0%**	**0.22 [0.07 , 0.71]**		
Total events:	3		13					

Heterogeneity: Not applicable
Test for overall effect: Z = 2.53 (P = 0.01)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
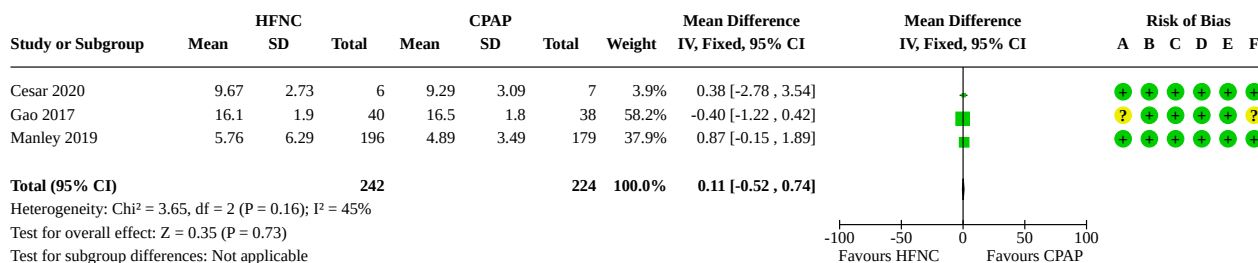(E) Bias in selection of the reported result
(F) Overall bias

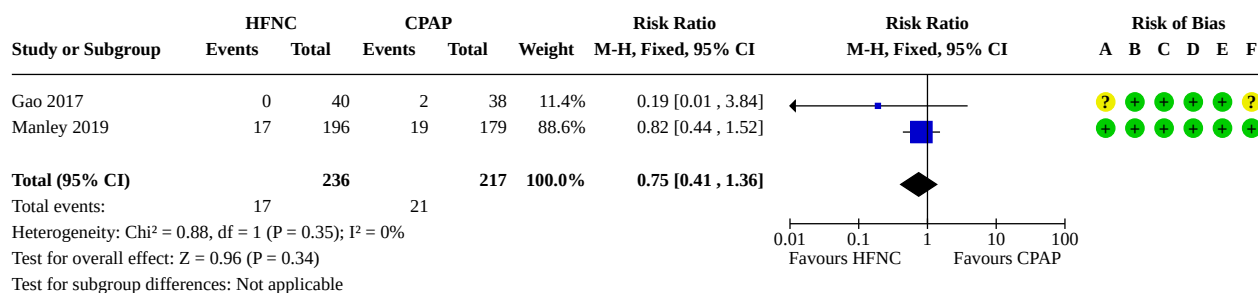## Comparison 2. HFNC versus LFNC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Death	2	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Treatment failure	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.21, 0.92]
2.3 Chronic lung disease (need for supplemental oxygen at 28 days of life)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.4 Duration of any form of respiratory support (hours/days)	1	74	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.83, 0.69]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.5 Length of stay at intensive care unit (days)	1	74	Mean Difference (IV, Fixed, 95% CI)	0.49 [-0.83, 1.81]
2.6 Hospital length of stay (days)	2	95	Mean Difference (IV, Random, 95% CI)	-0.60 [-2.07, 0.86]
2.7 Adverse events	2	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 2.1. Comparison 2: HFNC versus LFNC, Outcome 1: Death

Study or Subgroup	HFNC Events	HFNC Total	LFNC Events	LFNC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Franklin 2018	0	46	0	28		Not estimable
Kepreotes 2017	0	11	0	10		Not estimable
Total (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

Risk Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours HFNC   Favours LFNC

Analysis 2.2. Comparison 2: HFNC versus LFNC, Outcome 2: Treatment failure

Study or Subgroup	HFNC Events	HFNC Total	LFNC Events	LFNC Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Franklin 2018	7	46	9	28	68.1%	0.47 [0.20, 1.13]	+ + + + + +
Kepreotes 2017	2	11	5	10	31.9%	0.36 [0.09, 1.47]	+ + + + + +
Total (95% CI)		**57**		**38**	**100.0%**	**0.44 [0.21, 0.92]**	
Total events:	9		14				

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.19 (P = 0.03)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Fixed, 95% CI
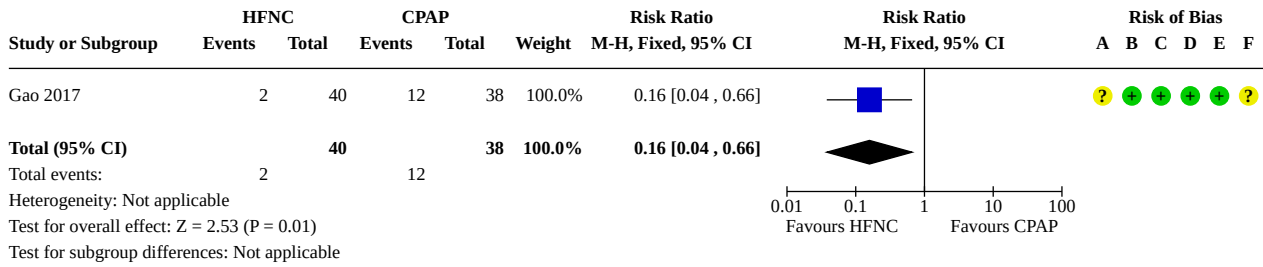0.01 0.1 1 10 100
Favours HFNC   Favours LFNC

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
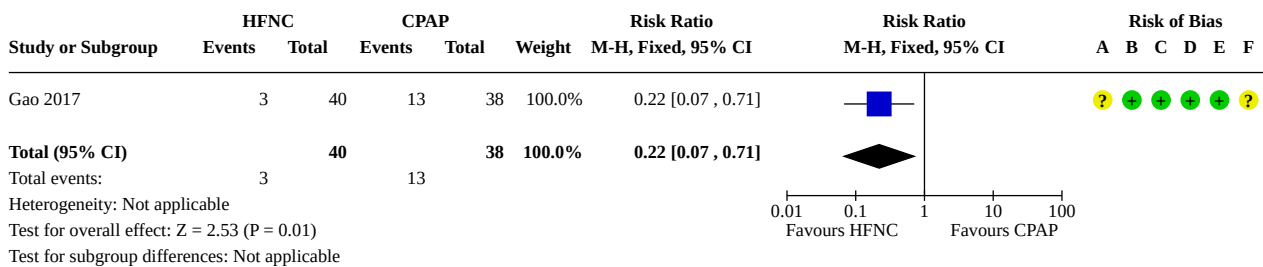(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: HFNC versus LFNC, Outcome 3: Chronic lung disease (need for supplemental oxygen at 28 days of life)

Study or Subgroup	HFNC Mean	SD	Total	LFNC Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Total (95% CI)			**0**			**0**		**Not estimable**	

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

-100 -50 0 50 100
Favours HFNC   Favours LFNC

Analysis 2.4. Comparison 2: HFNC versus LFNC, Outcome 4: Duration of any form of respiratory support (hours/days)

Study or Subgroup	HFNC Mean	SD	Total	LFNC Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Franklin 2018	2.38	1.68	46	2.45	1.59	28	100.0%	-0.07 [-0.83 , 0.69]		+ + + + + +
Total (95% CI)			**46**			**28**	**100.0%**	**-0.07 [-0.83 , 0.69]**		

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable

-100 -50 0 50 100
Favours HFNC   Favours LFNC

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.5. Comparison 2: HFNC versus LFNC, Outcome 5: Length of stay at intensive care unit (days)

Study or Subgroup	HFNC Mean	SD	Total	LFNC Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Franklin 2018	4.31	2.78	46	3.82	2.83	28	100.0%	0.49 [-0.83 , 1.81]		+ + + + + +
Total (95% CI)			**46**			**28**	**100.0%**	**0.49 [-0.83 , 1.81]**		

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable

-100 -50 0 50 100
Favours HFNC   Favours LFNC

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.6. Comparison 2: HFNC versus LFNC, Outcome 6: Hospital length of stay (days)

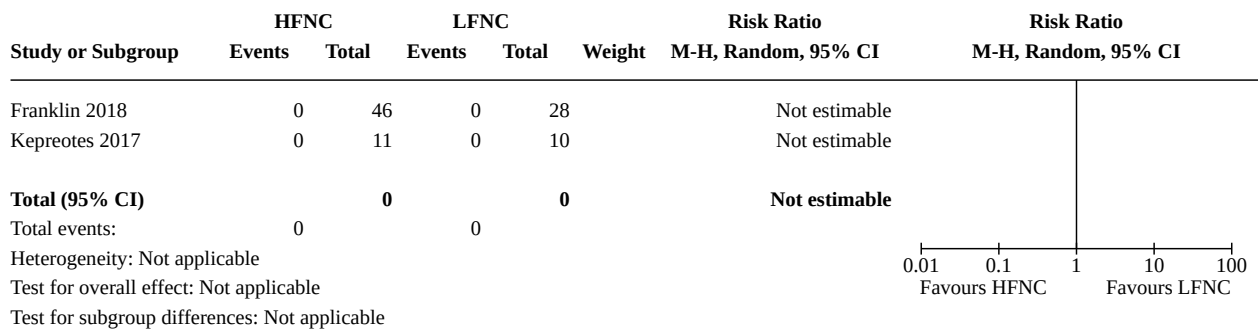| Study or Subgroup	HFNC Mean	SD	Total	LFNC Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Franklin 2018	3.8	2	46	3.78	1.83	28	58.9%	0.02 [-0.87 , 0.91]	
Kepreotes 2017	2.1	1	11	3.6	2.3	10	41.1%	-1.50 [-3.04 , 0.04]	
Total (95% CI)			**57**			**38**	**100.0%**	**-0.60 [-2.07 , 0.86]**	

Heterogeneity: Tau² = 0.74; Chi² = 2.80, df = 1 (P = 0.09); I² = 64%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable

-100   -50   0   50   100
Favours HFNC   Favours LFNC

Analysis 2.7. Comparison 2: HFNC versus LFNC, Outcome 7: Adverse events

Study or Subgroup	HFNC Events	Total	LFNC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Franklin 2018	0	46	0	28		Not estimable	
Kepreotes 2017	0	11	0	10		Not estimable	
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

0.01   0.1   1   10   100
Favours HFNC   Favours LFNC

A P P E N D I C E S

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials

Searched 11 November 2020 (710 records)
Searched 10 November 2021 (70 additional records)
Searched 13 December 2022 (49 additional records)
((infant* OR neonat* OR neo-nat* OR newborn* OR new-born* OR new NEXT born* OR newly NEXT born* OR baby* or babies) NOT (preterm OR pre-term OR prematur*)):ti,ab,kw OR MeSH descriptor: [Infant, Newborn] explode all trees)

AND

((nasal NEXT cannula* OR nasal NEXT prong* OR "high-flow nasal" OR "high flow nasal" OR HFNC OR respiratory NEXT support* OR "artificial respiration")):ti,ab,kw OR MeSH descriptor: [Cannula] explode all trees

CINAHL via EBSCOhost

Searched 11 November 2020 (382 records)
Searched 10 November 2021 (42 additional records)
Searched 12 December 2022 (23 additional records)
TI (infant* OR neonat* OR neo-nat* OR newborn* OR new-born* OR "new born*" OR "newly born*" OR baby* OR babies) OR AB (infant* OR neonat* OR neo-nat* OR newborn* OR new-born* OR "new born*" OR "newly born*" OR baby* OR babies)OR (MH "Infant, Newborn")

AND
TI ("nasal cannula*" OR "nasal prong*" OR "high-flow nasal" OR "high flow nasal" OR HFNC OR "respiratory support*" OR "artificial respiration") OR AB ("nasal cannula*" OR "nasal prong*" OR "high-flow nasal" OR "high flow nasal" OR HFNC OR "respiratory support*" OR "artificial respiration") OR (MH "Nasal Cannula")

AND

"randomized controlled trial" OR "controlled clinical trial" OR random* OR placebo OR "clinical trials" OR trial OR PT clinical trial

PubMed

Searched 11 November 2020 (366 records)
Searched 10 November 2021 (48 additional records)
Searched 13 December 2022 (21 additional records)
infant*[Title/Abstract] OR neonat*[Title/Abstract] OR neo-nat*[Title/Abstract] OR newborn*[Title/Abstract] OR new-born*[Title/Abstract] OR "new born*"[Title/Abstract] OR "new borns"[Title/Abstract] OR "newly born*"[Title/Abstract] OR baby*[Title/Abstract] OR babies[Title/Abstract]

OR ("infant, newborn"[MeSH Terms])

AND

"nasal cannula*"[Title/Abstract] OR "nasal prong*"[Title/Abstract] OR "high-flow nasal"[Title/Abstract] OR "high flow nasal"[Title/Abstract] OR HFNC[Title/Abstract] OR "respiratory support*"[Title/Abstract] OR "artificial respiration"[Title/Abstract]

OR ("cannula"[MeSH Terms])

AND ((clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])

LILACS via Virtual Health Library

Searched 11 November 2020 (66 records)
Searched 10 November 2021 (1 additional records)
Searched 13 December 2022 (2 additional records)
Title, abstract, subject: (infant$ OR neonat$ OR neo-nat$ OR newborn$ OR new-born$ OR "new born" OR "new borns" OR "newly born" OR "newly borns" OR baby$ OR babies)

AND

("nasal cannula" OR "nasal cannulas" OR "nasal cannulae" OR "nasal prong" OR "nasal prongs" OR "high-flow nasal" OR "high flow nasal" OR HFNC OR "respiratory support" OR "artificial respiration" OR cannula$)

AND (controlled clinical trial [Filter])

Scopus

Searched 11 November 2020 (1104 records)
Searched 11 November 2021 (145 additional records)
Searched 12 December 2022 (148 additional records)
TITLE-ABS-KEY (infant* OR neonat* OR neo-nat* OR newborn* OR new-born* OR "new born*" OR "newly born*" OR baby* OR babies)

AND

TITLE-ABS-KEY ("nasal cannula*" OR "nasal prong*" OR "high-flow nasal" OR"high flow nasal" OR HFNC OR "respiratory support*" OR "artificial respiration")

AND

(TITLE-ABS-KEY(("controlled trial" OR "clinical trial" OR random* OR placebo OR trial*)))

Web of Science

Searched 11 November 2020 (2400 records)
Searched 12 November 2021 (370 additional records)
Searched 12 December 2022 (286 additional records)
((TI=(infant* OR neonat* OR neo-nat* OR newborn* OR new-born* OR "new born*" OR "newly born*" OR baby* OR babies)) OR AB=(infant* OR neonat* OR neo-nat* OR newborn* OR new-born* OR "new born*" OR "newly born*" OR baby* OR babies))

AND

(TI=("nasal cannula*" OR "nasal prong*" OR "high-flow nasal" OR "high flow nasal" OR HFNC OR "respiratory support*" OR "artificial respiration")) OR AB=("nasal cannula*" OR "nasal prong*" OR "high-flow nasal" OR "high flow nasal" OR HFNC OR "respiratory support*" OR "artificial respiration")

Embase via Ovid

Searched 11 November 2020 (804 records)

Searched 10 November 2021 (94 additional records)
Searched 12 December 2022 (111 additional records)

((infant* or neonat* or neo-nat* or newborn* or new-born* or "new born*" or "newly born*" or baby* or babies) not (preterm or pre-term or prematur*)).ti. or ((infant* or neonat* or neo-nat* or newborn* or new-born* or "new born*" or "newly born*" or baby* or babies) not (preterm or pre-term or prematur*)).ab.

OR newborn/

AND

("nasal cannula*" or "nasal prong*" or "high-flow nasal" or "high flow nasal" or HFNC or "respiratory support*" or "artificial respiration").ti. or ("nasal cannula*" or "nasal prong*" or "high-flow nasal" or "high flow nasal" or HFNC or "respiratory support*" or "artificial respiration").ab.

OR nasal cannula/ OR nasal prong/ OR oxygen nasal cannula/

AND

("controlled trial" or "clinical trial" or random* or placebo or trial*).ab. or ("controlled trial" or "clinical trial" or random* or placebo or trial*).ti.

Google Scholar

Searched 13 November 2020 (6820 results) (23 new records identified in screening process)*
Searched 02 Jan 2022 (0 new records identified in screening)*
Searched 13 Jan 2022 (0 new records identified in screening)*

* For our Google Scholar supplementary searches, the results were screened in Google Scholar, and the screening approach was to stop when 5 pages of Google Scolar search results (or 50 results) yielded nothing relevant. Since Google Scolar results are relevancy ranked, the probability of another relevant article then drops to less than 1 in 50 (Griffith University 2017).

Google Scholar search terms:
infants "nasal cannula" OR "nasal prong" OR "high flow nasal" OR "high flow nasal" OR HFNC OR "respiratory support" OR "artificial respiration" "randomised controlled trial"

H I S T O R Y

Protocol first published: Issue 3, 2014

C O N T R I B U T I O N S   O F   A U T H O R S

Conceiving the review: Sara Mayfield (not involved in the subsequent review process), Jacqueline Jauncey-Cooke (not involved in the subsequent review process), Andreas Schibler (not involved in the subsequent review process), Judith Hough (JH), and Fiona Bogossian (FB)

Co-ordinating the review: Alex Dopper (AD)

Undertaking manual searches: AD and Judith Hough (JH)

Screening search results: AD and JH

Organising retrieval of papers: AD and JH

Screening retrieved papers against inclusion criteria: AD and JH

Appraising quality of papers: AD, JH, and Michael Steele (MS)

Abstracting data from papers: AD and JH

Writing to authors of papers for additional information: AD

Providing additional data about papers: AD

Obtaining and screening data on unpublished studies: AD

Data management for the review: AD, JH, MS, FB

Entering data into RevMan Web: AD

RevMan statistical data: AD, JH, MS

Other statistical analysis not using RevMan: MS

Interpretation of data: AD, JH, MS, FB

Statistical inferences: AD, JH, MS, FB

Writing the review: AD

Securing funding for the review: n/a

Performing previous work that was the foundation of the present study: n/a

Guarantor for the review (one author): JH

Person responsible for reading and checking review before submission: AD, JH, MS, FB

DECLARATIONS OF INTEREST

Alex Dopper has no interest to declare.

Michael Steele has no interest to declare.

Judith L Hough has no interest to declare.

Fiona Bogossian has no interest to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied, Other

  No sources of support supplied

External sources

- Vermont Oxford Network, USA

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes from the published protocol (Mayfield 2014b).

- The Background was modified from the protocol to include updated literature.
- We updated our eligibility criteria to include RCT data available only in conference abstract form.
- We are no longer including quasi-randomised controlled trials since their methods of allocating participants to groups are not truly random.
- Search sources:
  - Additional databases were utilised in our review search strategy (PubMed, Scopus). We also performed a search of a non-database resource (Google Scholar).
  - We used PubMed to search MEDLINE versus searching via the OVID interface.
  - We omitted independent searches of trial registries based on advice (given in 2019) from Cochrane Neonatal; the rationale was that Cochrane CENTRAL includes trial registry records. We have since been advised that independent searches of trial registries are advisable and will do so for updates of this review.
- We incorporated RoB 2 rather than RoB 1 to assess the risk of bias in the included studies.
- We updated the selection of studies section to include the use of Covidence and RevMan Web.
- We updated the measures of treatment effect section to include the methods described in Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* for calculating the number needed to treat for an additional beneficial outcome (NNTB) from the risk ratio (RR) (Higgins 2022).
- In accordance with Cochrane guidelines, we incorporated the use of the GRADE approach to assess the certainty of evidence for outcomes.

- In clarifying the role of outcomes as inclusion criteria for this review, we are aware that outcome measures should not always form part of the criteria for including studies in a review (as per the MECIR standard C8 in the *Cochrane Handbook for Systematic Reviews of Interventions* Section 3, 3.2.4.1. (Higgins 2022)). However, some reviews do legitimately restrict eligibility to specific outcomes. For example, the same intervention may be studied in the same population for different purposes. We believe this is the case for high flow nasal cannula oxygen therapy, and we examined the relevant trial registrations and protocols of any studies excluded on the basis of outcomes to confirm that our review outcomes were not measured or reported.
- Dr Sara Mayfield, Dr Jacqueline Jauncey-Cooke, and Dr Andreas Schibler were credited for their contributions to the original review protocol, however they were not involved in the subsequent review process.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cannula; Continuous Positive Airway Pressure [adverse effects]; *Lung Diseases [etiology]; Oxygen; Respiration, Artificial

MeSH check words

Humans; Infant; Infant, Newborn