High-flow nasal cannula therapy for infants with bronchiolitis (Review)

Beggs S, Wong ZH, Kaul S, Ogden KJ, Walters JAE

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[Intervention Review]

High-flow nasal cannula therapy for infants with bronchiolitis

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New, published in Issue 1, 2014.
Review content assessed as up-to-date: 15 May 2013.

Citation: 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.

ABSTRACT

Background

Bronchiolitis is a common lower respiratory tract illness, usually of viral aetiology, affecting infants younger than 24 months of age and is a frequent cause of hospitalisation. It causes airway inflammation, mucus production and mucous plugging, resulting in airway obstruction. Effective pharmacotherapy is lacking and bronchiolitis is a major cause of morbidity and mortality.

Conventional treatment consists of supportive therapy in the form of fluids, supplemental oxygen and respiratory support. Traditionally oxygen delivery is as a dry gas at 100% concentration via low-flow nasal prongs. However, the use of heated, humidified, high-flow nasal cannula (HFNC) therapy enables delivery of higher inspired gas flows of an air/oxygen blend, up to 12 L/min in infants and 30 L/min in children. Its use provides some level of continuous positive airway pressure to improve ventilation in a minimally invasive manner. This may reduce the need for invasive respiratory support thus potentially lowering costs, with clinical advantages and fewer adverse effects.

Objectives

To assess the effects of HFNC therapy compared with conventional respiratory support in the treatment of infants with bronchiolitis.

Search methods

We searched CENTRAL (2013, Issue 4), MEDLINE (1946 to May week 1, 2013), EMBASE (January 2010 to May 2013), CINAHL (1981 to May 2013), LILACS (1982 to May 2013) and Web of Science (1985 to May 2013). In addition we consulted ongoing trial registers and experts in the field to identify ongoing studies, checked reference lists of relevant articles and searched conference abstracts.

Selection criteria

We included randomised controlled trials (RCTs) or quasi-RCTs which assessed the effects of HFNC (delivering oxygen or oxygen/room air blend at flow rates greater than 4 L/min) compared to conventional treatment in infants (< 24 months) with a clinical diagnosis of bronchiolitis.

Data collection and analysis

Two review authors independently used a standard template to assess trials for inclusion and extract data on study characteristics, 'Risk of bias' elements and outcomes. We contacted trial authors to request missing data. Outcome measures included the need for invasive respiratory support and time until discharge, clinical severity measures, oxygen saturation, duration of oxygen therapy and adverse events.

Main results

We included one RCT which was a pilot study with 19 participants that compared HFNC therapy with oxygen delivery via a head box. In this study, we judged the risk of selection, attrition and reporting bias to be low, and we judged the risk of performance and detection bias to be unclear due to lack of blinding. The median oxygen saturation (SpO_2) was higher in the HFNC group at eight hours (100% versus 96%, P = 0.04) and at 12 hours (99% versus 96%, P = 0.04) but similar at 24 hours. There was no clear evidence of a difference in total duration of oxygen therapy, time to discharge or total length of stay between groups. No adverse events were reported in either group and no participants in either group required further respiratory support. Five ongoing trials were identified but no data were available in May 2013. We were not able to perform a meta-analysis.

Authors' conclusions

There is insufficient evidence to determine the effectiveness of HFNC therapy for treating infants with bronchiolitis. The current evidence in this review is of low quality, from one small study with uncertainty about the estimates of effect and an unclear risk of performance and detection bias. The included study provides some indication that HFNC therapy is feasible and well tolerated. Further research is required to determine the role of HFNC in the management of bronchiolitis in infants. The results of the ongoing studies identified will contribute to the evidence in future updates of this review.

PLAIN LANGUAGE SUMMARY

High-flow nasal cannula (tube) therapy for infants with bronchiolitis

Bronchiolitis is a common illness affecting the lower (smaller) respiratory airways in infants (younger than 24 months of age). Usually caused by a viral infection, it results in breathing problems, including cough, fast breathing, wheezing and can cause poor feeding. It is a major cause of hospitalisation in infants. Current treatment involves supporting infants to breath until the infection clears. An emerging method to support breathing is using blended, heated, humidified air and oxygen, through nasal cannulae (tubes) at flow rates higher than two litres per minute, which is the maximum for conventional dry oxygen delivery. This is known as high-flow nasal cannula therapy and it allows the comfortable delivery of high flow rates of an air/oxygen blend which may improve ventilation. This may lead to a reduced need for invasive respiratory support (e.g. intubation) and may have a clinical advantage over other treatments by preventing drying of the upper airway. This review assessed the effects of high-flow nasal cannula therapy, compared with other respiratory support, in the treatment of infants with bronchiolitis.

One study (19 participants) met our inclusion criteria. It showed that high-flow nasal cannula therapy is well tolerated as a treatment for bronchiolitis. Oxygen saturations (blood oxygen levels) were better at eight and 12 hours in participants receiving high-flow nasal cannula therapy than in those receiving oxygen therapy via a head box, but were similar between groups at 24 hours, although this may have been due to higher oxygen flow rates in the high-flow nasal cannula group. There was no clear evidence of a difference between the two groups in the duration of oxygen therapy, length of hospitalisation and time to discharge. No adverse events were reported in either group.

There is insufficient evidence to determine the effectiveness of high-flow nasal cannula therapy for treating bronchiolitis in infants. The included study provides some indication that HFNC therapy is feasible and well tolerated. However, our evidence is based on one low-quality, small study with uncertainty about the effects and some possibility of bias arising from the study methods. Further research is required to determine the role of high-flow nasal cannula therapy in the management of bronchiolitis in infants. The results of six ongoing studies identified will contribute to the evidence in future updates of this review.

The evidence is current to May 2013.

BACKGROUND

Description of the condition

Bronchiolitis is one of the most common and serious lower respi-

ratory tract illnesses in infants, causing breathlessness, coughing and wheezing (AAPS 2006). It is a major cause of morbidity and mortality in this age group and a leading cause of infant hospitalisation, with annual hospitalisation rates of 17 per 1000 children under six months of age and 3 per 1000 children under five years of age, mostly in children without coexisting illnesses (Hall 2009). It has been associated with increasing morbidity and health costs over recent decades (AAPS 2006; Hall 2009; Pelletier 2006; Shay 1999).

The pathological features of bronchiolitis primarily involve airway inflammation, excess mucus production and mucous plugging, which results in airway obstruction. Bronchiolitis in infants is a clinical diagnosis, which is defined as an episode of acute wheezing associated with rhinorrhoea, sneezing, cough and fever or tachypnoea in infants less than 24 months of age, with the majority of cases occurring in the first year of life. Most cases have a viral aetiology with respiratory syncytial virus (RSV) being the commonest virus isolated (Vicencio 2010). Other commonly associated viruses include parainfluenza viruses, human metapneumovirus and rhinovirus (Hall 2009; Kusel 2006).

Supportive therapy, in the form of supplemental oxygen, fluid therapy and respiratory support, remains the mainstay of treatment due to the lack of effective pharmacotherapies (Fernandes 2013; Gadomski 2010; Hartling 2011; Spurling 2011).

Description of the intervention

Heated, humidified, high-flow nasal cannula (HFNC) therapy allows the delivery of high inspired gas flows (up to 12 L/min in infants and 30 L/min in older children) of an air/oxygen blend (Spentzas 2009). The inspired oxygen concentration can be varied from 21% to 100% (De Klerk 2008), therefore giving greater ability to titrate the concentration of oxygen delivered. Traditionally oxygen (O_2) is provided at 100% concentration via low-flow nasal prongs as a dry gas, which is not heated or humidified. The lack of humidification and warming limits the flow rate that can be delivered comfortably. Recently devices that can effectively heat and humidify inspired gas at high-flow rates have been developed and are increasingly being used (Dysart 2009; Lee 2012). HFNC therapy has been used in children with bronchiolitis to deliver O_2/air blends at flow rates of 2 L/min to 10 L/min (McKiernan 2010; Schibler 2011). HFNC therapy has been shown to be a well-tolerated intervention (Lee 2012; Spentzas 2009).

How the intervention might work

There are a number of proposed mechanisms for why the delivery of respiratory gas via HFNC may be superior to standard therapy. Using heated, humidified gas should reduce the damage to the upper airway mucosa thereby preventing inflammatory reactions and reflex naso-pulmonary bronchoconstriction induced by cold dry air (Spentzas 2009). Another proposed mechanism is through washout of nasopharyngeal dead space thus resulting in alveolar ventilation as a greater fraction of minute ventilation. Reduction of upper-airway resistance, which constitutes 50% of total airway resistance, is also proposed as a possible mechanism (Dysart 2009). It is also suggested that the HFNC system provides a degree of continuous positive airway pressure (CPAP) thus assisting in keeping the child's small airways open and improving ventilation. The exact level generated depends on the flow delivered relative to the size of the patient and on the anatomical leak that is always present in HFNC systems, which is due to factors such as leak around the nasal cannulae and mouth opening (Kubicka 2008; Lampland 2009; Lee 2012). Flows of three L/min to five L/min in term and preterm infants have been shown to generate CPAP measured as intrapharyngeal pressure of 1.7 cm H_2O to 4.8 cm H_2O (Spence 2007), while flow rates equal to or greater than two L/kg/min have recently been shown to generate a clinically relevant pharyngeal pressure in infants under six months with RSV bronchiolitis (Milesi 2013). HFNC is a less invasive way of providing CPAP than conventional nasopharyngeal or nasal CPAP and as such its use could lead to a reduced need for invasive respiratory support.

Why it is important to do this review

Bronchiolitis is an illness for which there are very limited proven treatment options. To establish HFNC therapy as an effective and safe intervention in bronchiolitis has significant clinical implications. This intervention may provide an effective form of respiratory support that is less invasive and potentially has lower costs and fewer adverse events than conventional non-invasive ventilation therapy.

OBJECTIVES

To assess the effects of high-flow nasal cannula (HFNC) therapy compared with conventional respiratory support in the treatment of infants with bronchiolitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and we would also have accepted quasi-RCTs using a systematic method of allocation, such as alternation, assignment based on date of birth,

case record number and date of presentation. We included studies reported in abstract form and contacted trial authors for data on study design and results to include in meta-analysis if data were lacking.

Types of participants

We included infants under the age of 24 months, with an established clinical diagnosis of bronchiolitis, as defined by the trial authors. We excluded studies of infants with established significant cardiorespiratory disorders.

Types of interventions

We compared HFNC therapy to alternative forms of respiratory support, that could include:

- clinical and oxygen saturation monitoring;
- oxygen delivered by head box, mask or tent;
- oxygen delivered by low-flow nasal cannulae (flow rate equal to or less than 4 L/min);
- continuous positive airway pressure (CPAP);
- non-invasive intermittent positive pressure ventilation (nIPPV); and
- invasive intermittent positive pressure ventilation (IPPV).

For the purpose of this review, HFNC therapy was defined as delivery of oxygen or an oxygen/room air blend at flow rates greater than 4 L/min via nasal cannulae.

Types of outcome measures

Primary outcomes

1. Need for IPPV or CPAP.
2. Length of hospital stay or time until ready for discharge.

Secondary outcomes

1. Clinical severity score.
2. Duration of oxygen therapy or any other form of respiratory support.
3. Oxygen saturation.
4. Respiratory rate.
5. Heart rate.
6. Adverse events.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 4, part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 15 May 2013), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1946 to May week 1, 2013), EMBASE (January 2010 to May 2013), CINAHL (1981 to May 2013), LILACS (1982 to May 2013) and Web of Science (1985 to May 2013).

We used the search strategy in Appendix 1 to search CENTRAL and MEDLINE. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search EMBASE (Appendix 2), CINAHL (Appendix 3), LILACS (Appendix 4) and Web of Science (Appendix 5). No date, language or publication restrictions were imposed.

Searching other resources

We consulted national and international trial registers and experts in this field to identify ongoing studies. We checked conference abstracts for unpublished studies. We checked reference lists of all relevant articles to identify other relevant studies. We contacted authors of any identified abstracts or unpublished studies to ascertain the nature of the study design and outcome measures. We only included abstracts and unpublished studies with sufficient information on the study design and outcome measures in meta-analyses.

Data collection and analysis

Selection of studies

Two review authors (WZH, SK) independently identified studies and assessed whether they met the inclusion criteria. We resolved any discrepancies by discussion with other review authors (SB, JW, KO). The review authors identified studies for full assessment based on the abstract. We retrieved the full-text articles if there was insufficient information in the abstract.

Data extraction and management

Two review authors (WZH, KO) independently performed data extraction using a standardised data extraction form. We collected data on the following criteria.

1. Study details: title, names of authors, publication status and year of publication.
2. Study eligibility and characteristics: study type, participant characteristics, diagnostic criteria of bronchiolitis, interventions, controls and outcomes.

3. Methodological quality: method of sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data, selective reporting and intention-to-treat (ITT) analysis.

4. Outcomes: we extracted the mean, standard deviation (SD) and the number of participants studied in each group for continuous outcomes. We extracted the total number of participants per group and number of participants experiencing the event for dichotomous outcomes.

We entered the extracted data into RevMan 5.2 (RevMan 2012), The Cochrane Collaboration's software program.

Assessment of risk of bias in included studies

Two review authors (WZH, KO) independently assessed the methodological quality and performed 'Risk of bias' assessment of all included studies using The Cochrane Collaboration's tool for assessing 'Risk of bias' (Higgins 2011), for the following domains.

1. Sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessors.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other sources of bias.

Measures of treatment effect

If data for more than one included trial were available, we would have calculated treatment effects using a fixed-effect mean difference (MD), with 95% confidence intervals (CIs) for continuous variables. We would have calculated standardised mean differences (SMD) with 95% CIs if an outcome was measured on different scales. The SMD is a statistic which expresses the difference in means between treatment groups in units of the pooled SD.

We would have used the risk ratio (RR) with 95% CIs for dichotomous outcomes unless the event rate was very low. We would have used the Peto odds ratio (OR) method if the case of an event rate was below 1%. We would have calculated the fixed-effect generic inverse variance outcome in a meta-analysis for time-to-event outcomes such as log hazard ratios (log HRs) to give a weighted average of the effect estimates of separate studies (Higgins 2011). The number needed to treat for an additional beneficial outcome (NNTB) would have been calculated using the risk difference (RD). This is defined as the expected number who need to receive the intervention rather than the control treatment for one additional person to either incur or avoid an event in a given time frame.

Dealing with missing data

We contacted trial authors directly to request additional information if data were missing in trial publications.

Assessment of heterogeneity

If sufficient studies were available, heterogeneity for outcomes would be assessed using the Chi^2 test in RevMan 2012 with the null hypothesis being no heterogeneity for treatment effect (Higgins 2011). The Chi^2 test measures the deviation of observed effect sizes from an underlying overall effect. This test has low power to detect true heterogeneity when studies have small sample sizes or are few in number, hence the P value of 0.10 is used (Deeks 2011). The I^2 statistic assesses the impact of heterogeneity in the meta-analysis. The magnitude is roughly interpreted as (Deeks 2011):

1. 0% to 40%: may be unimportant;
2. 30% to 60%: represents moderate heterogeneity;
3. 50% to 90%: represents substantial heterogeneity; and
4. 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

With sufficient included studies we intended to use funnel plot symmetry to detect publication bias.

Data synthesis

We entered data and intended to calculate summary treatment effects using RevMan 2012. A summary of findings table according to recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* will be presented for the primary outcomes, adverse effects and patient-important outcomes (clinical severity score, duration of oxygen therapy, oxygen saturation, respiratory rate) when data are available from a full study/studies.

Subgroup analysis and investigation of heterogeneity

We planned to conduct prespecified subgroup analyses by participants' age and weight.

Sensitivity analysis

We prespecified sensitivity analyses for methodological quality using the 'Risk of bias' domains. Additional sensitivity analysis using random-effects versus fixed-effect models were intended if significant heterogeneity was detected.

RESULTS

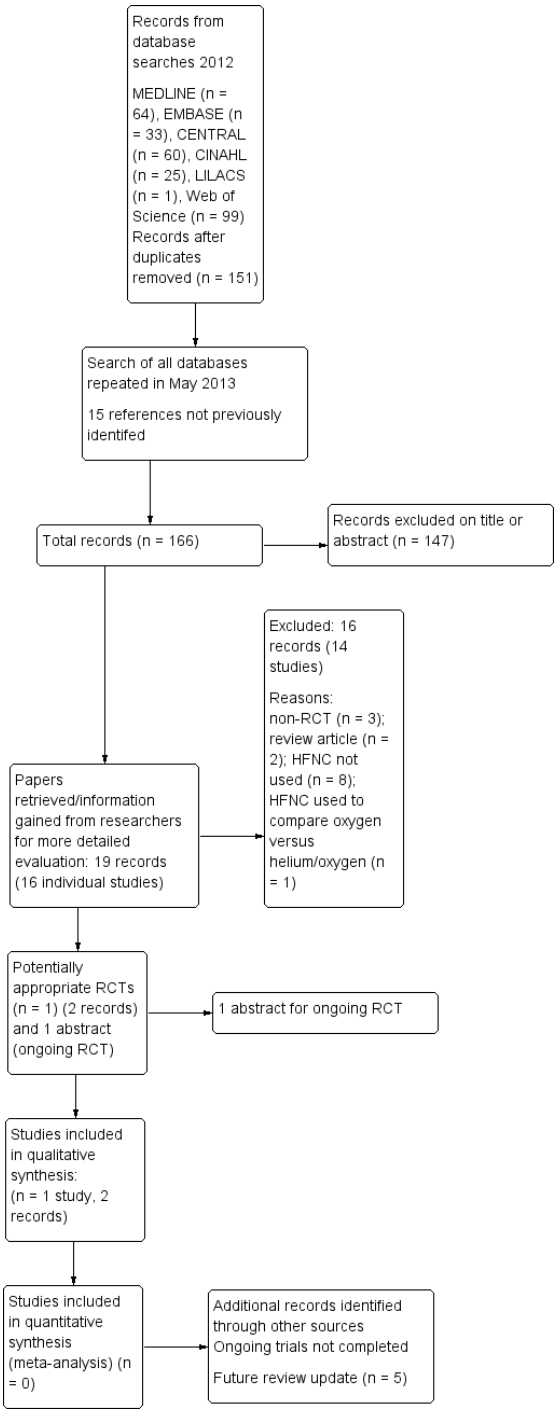
Description of studies

Results of the search

The search of the electronic databases identified 151 records after duplicates were removed. Records retrieved from individual databases included 67 records from MEDLINE, 39 records from EMBASE, 60 records from CENTRAL, 26 records from CINAHL, one record from LILACS and 106 records from Web of Science. A repeat search between August 2012 to 15 May 2013 located 15 additional records not previously identified.

We excluded 147 records based on the title or abstract. We assessed the full papers of 19 records, of which we excluded 16 records that related to 14 studies. Two records were related to one study that met our inclusion criteria (Hilliard 2012). One reference was in the form of a conference abstract and the other in the form of a letter to the editor (Figure 1). We contacted the authors of this study and they provided an unpublished manuscript. We requested raw data but these were not provided. An abstract for an ongoing RCT was identified (Sood 2012) and we contacted the authors regarding publication and availability of data. The study was not completed at the time of this review. Another four ongoing trials were identified from clinical trials registries, all of which were relevant (Kepreotes 2012; Milner 2012; Seear 2011; Whitehall 2012). We contacted the authors of the ongoing trials and all responded. However, data were not available for inclusion at the time of writing this review as studies are still ongoing. They are described in the Characteristics of ongoing studies table.

Figure 1. Study flow diagram.



Included studies

Hilliard 2012 conducted a randomised pilot study of 19 infants aged less than 12 months admitted to a general paediatric ward with a clinical diagnosis of moderately severe bronchiolitis. Eleven participants received oxygen delivered by HFNC therapy (via the Vapotherm 2000i device) at 4 L/min increasing to 8 L/min if tolerated. The control group of seven patients were treated with headbox oxygen therapy. Baseline characteristics of the two groups were comparable. A range of outcomes were reported. The primary outcome was blood oxygen saturation (SpO_2) at eight hours post randomisation. Other outcomes measured were SpO_2, heart rate, respiratory rate, blood pressure, fraction of inspired oxygen (FiO_2) and a combined bronchiolitis severity score at 4, 8, 12, 24, 36 and 48 hours post randomisation, length of time to dry oxygen, length of time receiving oxygen therapy, total length of time on oxygen, time to enteral feeds, time to discharge and total length of stay in hospital.

Excluded studies

The reasons for exclusion of studies were: HFNC not forming an intervention arm (n = 8), the study not conforming to a randomised or pseudo-randomised methodology (n = 2), review articles only (n = 2) and one study which compared two different methods for delivering HFNC (Characteristics of excluded studies).

Risk of bias in included studies

Allocation

The one included trial used a randomised design but the risk of bias was unclear as the method used to generate the sequence was not given. There was an adequate attempt to conceal allocation using sealed envelopes, which has a low risk of bias.

Blinding

There was no attempt to blind participants or those documenting outcomes due to the nature of the intervention. Given the largely objective nature of the outcomes the potential for this to cause bias is unclear and not addressed by the authors.

Incomplete outcome data

There was no loss to follow-up and thus a low risk of attrition bias.

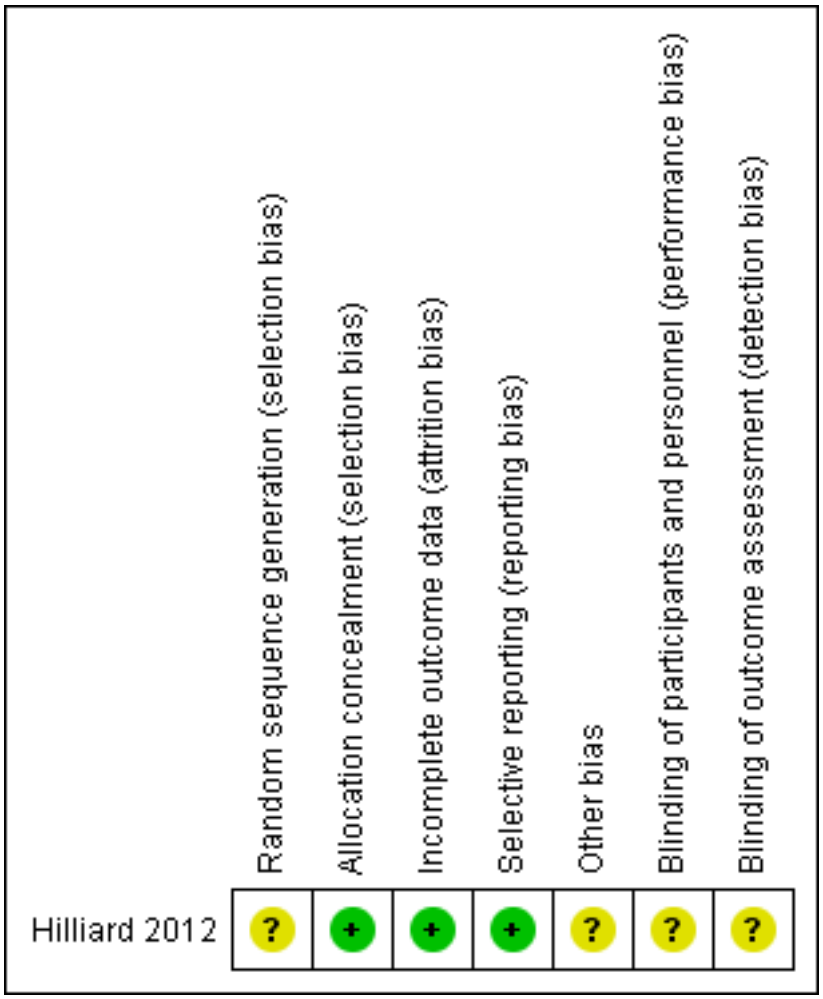
Selective reporting

There was no evidence of selective reporting of outcomes with data on all prespecified outcomes available.

Other potential sources of bias

One participant was changed from the control to the intervention group for 'clinical reasons' at 24 hours; the clinical reason was not detailed. This has the potential to bias data after the 24-hour point. However, data were not presented beyond 24 hours. Time to switch to dry nasal cannula was measured. However, this was subject to potential bias due to the differing weaning protocols for the two interventions, with weaning from HFNC following a more rigid and potentially slower protocol. In the HFNC group weaning began after 24 hours and may have contributed to FiO_2 being higher in the intervention group, thus potentially biasing the result for SpO_2. Differences in weaning protocols could also have biased the time to discharge measurement (Figure 2).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

Primary outcomes

The only comparison possible was HFNC therapy versus head-box oxygen for the treatment of bronchiolitis in infants < 24 months of age in one study (Hilliard 2012). Treatment effects in this study were analyzed using Mann-Whitney tests to compare results between groups.

1. Need for IPPV or CPAP

No infant required additional respiratory support.

2. Length of hospital stay or time until ready for discharge

There was no significant difference in length of hospital stay between the two groups (median time for HFNC = 162 hours (range 96 to 300) versus 164 hours (range 84 to 233), P = 0.7).

Secondary outcomes

1. Clinical severity score

Clinical outcomes were reported as not being significantly different. However, data for clinical indicators and severity scores were not available.

2. Duration of oxygen therapy or any other form of respiratory support

Time to dry oxygen was significantly greater in the HFNC group (median time for HFNC = 86 hours (range 53 to 149) versus 46 hours (range 4 to 164), P = 0.06) and there was no statistically significant difference in total duration of oxygen therapy (median time for HFNC = 117 (range 64 to 220) hours versus 80 hours (range 4 to 180), P = 0.32). However, these measurements were subject to potential bias as discussed in Risk of bias in included studies.

3. Oxygen saturation

Median SpO_2 was significantly higher in the HFNC group at eight hours (100% (range 94 to 100) versus 96% (range 93 to 100), P = 0.04) and 12 hours (99% (range 96 to 100) versus 96% (range 93 to 99), P = 0.05), with no significant difference at 24 hours. However, FiO_2 was also significantly higher in the HFNC group at 8, 12 and 24 hours and in this group weaning only began after 24 hours, according to the protocol.

4. Respiratory rate

Not reported.

5. Heart rate

Not reported.

6. Adverse events

All participants in the HFNC group tolerated the treatment well.

DISCUSSION

Summary of main results

The results in this review are based on one study (Hilliard 2012) described as a pilot study comparing infants treated with HFNC therapy to a control group treated with conventional head-box oxygen therapy. The primary outcome of the study was SpO_2 recorded at multiple time points, where a statistically significant increase in median SpO_2 was reported in the HFNC group at the eight and 12-hour mark after randomisation but returned back to similar levels between groups at the 24-hour mark. However, it was also reported that the titrated FiO_2 was higher in the HFNC group at all three time points. A higher FiO_2 could potentially account for a higher median SpO_2. Nevertheless, it was noted that all participants fell within or above the target SpO_2, which brings into question the clinical relevance of these study findings.

There were no significant secondary outcome differences between groups. Of note is that time to discharge is similar between groups. However, a slower weaning protocol was adopted for the HFNC group as compared to the control group. This has the potential to bias this outcome towards a longer time to discharge for patients on HFNC which may have, in this study, masked any benefit for the HFNC group.

Overall completeness and applicability of evidence

Only one study (Hilliard 2012) met the selection criteria and was included in the analysis. However, at the time of analysis, our search of ongoing clinical trial registers showed that this is a clinical question of increasing importance with the existence of four ongoing trials (Kepreotes 2012; Milner 2012; Seear 2011; Whitehall 2012) and one trial, published as an abstract but without any data on results (Sood 2012), potentially meeting the selection criteria. The included study is a small but reasonably designed study consisting of 19 participants randomised to either the HFNC group or control group. However, the control group treatment is not one that is widely used. Consequently, the clinical relevance of the findings from this analysis is limited. As a pilot study, it was not powered to detect a difference in the requirement for respiratory support.

Safety and tolerability of HFNC

An important outcome of this study is that all participants randomised to the HFNC group tolerated it well. No participants randomised to HFNC were required to be switched back to conventional therapy due to failure to maintain SpO_2 or clinical deterioration. No adverse events were reported in either group. No participants in either group required further respiratory support.

Quality of the evidence

The single included study was a pilot study that did not achieve the sample size necessary for detecting the prespecified difference in SpO_2 eight hours post randomisation. We assessed the strength of evidence using the GRADE Working Group method (Guyatt 2008). No data contributed to the primary outcomes, the need for intermittent positive pressure ventilation (IPPV) or continuous positive airway pressure (CPAP). We judged the strength of evidence for the effect on length of stay and time to discharge as low (limitations in study methods in the single included study, imprecision in the result with CIs for the effect not excluding a null effect or harm). For the secondary outcome SpO_2 we graded the evidence as low (limitations in study methods in the single included study, imprecision in the results at different time periods that did not exclude a null effect or harm).

Potential biases in the review process

We did not identify any potential biases in the review process.

Agreements and disagreements with other studies or reviews

There are no relevant reviews for comparison. However, two retrospective chart reviews of HFNC for infants admitted to paediatric intensive care unit (PICU) with bronchiolitis were found (Abboud 2012; McKiernan 2010). These reported HFNC failure or non response rates of 9% and 18%, defined as the need for intubation. This is in contrast to the included study where no patients required intubation. However, the patients in both these retrospective studies are likely to represent sicker infants as they both took place in a paediatric intensive care unit (PICU), as opposed to a general paediatric ward which was the case for the included RCT. Neither of the retrospective reviews described any adverse events while only one (McKiernan 2010) specifically reported that no complications were seen and that HFNC was well tolerated.

AUTHORS' CONCLUSIONS

Implications for practice

At this point in time there is insufficient evidence of the effectiveness of HFNC therapy for bronchiolitis in infants. While HFNC therapy appears a safe and feasible therapy in infants with moderately severe bronchiolitis in the one included trial in this review, the strength of the evidence for the outcomes that were assessed was low and there were no data on important outcomes, including the need for intensive respiratory support.

Implications for research

Further evidence of effectiveness and safety is required. The evidence in this systematic review will be strengthened by inclusion of the results from the ongoing trials in future updates.

ACKNOWLEDGEMENTS

We wish to thank the following people for commenting on the draft protocol: Peter Morris, Jean-Michel Liet, Gilles Cambonie, Anne Lyddiat, Robert Ware and Christophe Milési. We wish to thank the trialists we contacted for further information about studies who responded to queries: Dr T. Hilliard, Dr E. Kepreotes, Dr M Seear, Dr D. Milner and Dr M Rowin. Finally we wish to thank the following people for commenting on the draft of this review: Anne Lyddiat, Gilles Cambonie, Jean-Michel Liet, Robert Ware and Peter Morris.

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Donna M. Milner, Emergency Department Children's Hospitals and Clinics of Minnesota, 345 North Smith AveSt. Paul, MN, 55102, USA.

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A/Prof Andreas Schibler, Mater Children's Hospital Paediatric Intensive Care Unit, Stanely Street, South Brisbane, 4101, QLD, Australia.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Hilliard 2012

Methods	Prospective, randomised, pilot study, single centre in UK
Participants	Infants with a clinical diagnosis of bronchiolitis admitted to Bristol Children's Hospital Department of Paediatric Respiratory Medicine Recruited: 21 infants (1 excluded with onset of apnoea, 1 excluded with fall in oxygen requirement) Randomised: 19 infants, median age 3.0 months, range 0.3 to 11.3 months Intervention group: 11 infants. Age in days: median 49 (range 8 to 334) Control group: 8 infants. Age in days: median 125 (range 12 to 343) Inclusion criteria: infants aged less than 12 months admitted to a general paediatric ward with a clinical diagnosis of bronchiolitis (cough, tachypnoea, chest retraction and crackles on auscultation); moderately severe disease defined as a head-box oxygen requirement of at least 35%, moderate to severe tachypnoea, increased effort of breathing and in whom feeding had been discontinued Exclusion criteria: congenital cyanotic heart disease, repeated severe apnoeas or severe hypercapnia with acidosis on blood gas analysis of pH < 7.2
Interventions	High-flow nasal cannula therapy via Vapotherm 2000i device, with a 1 to 8 L/min paediatric cartridge and infant-sized nasal cannulae (VT), started at a flow of 4 L/min with 100% oxygen, at 37 °C and flow rate increased by 0.5 L every 5 minutes up to 8 L/min if tolerated to achieve target SpO_2 for 24 hours. If clinically stable, FiO_2 decreased in steps of 10% at 4-hourly intervals, with same target SpO_2 Control: conventional therapy head-box oxygen (HBO)
Outcomes	Primary: SpO_2 at 8 hours post randomisation Heart rate, respiratory rate, blood pressure, FiO_2, combined bronchiolitis severity score (maximum of 7) Outcomes recorded: 4, 8, 12, 24, 36, 48 hours Additional outcomes recorded: - length of time to switch to dry oxygen - length of time receiving oxygen therapy after randomisation - total length of time of oxygen therapy - time until enteral feeds were started, time to discharge - total length of stay in hospital Outcomes reported: - SpO_2 at 8 hours, FiO_2 at 8 hours, SpO_2 at 12 hours, FiO_2 at 12 hours, SpO_2 at 24 hours, FiO_2 at 24 hours - Time to dry O_2 (hours) - Total time in O_2 (hours) - Time to feed (hours) - Time to discharge (hours) - Total length of stay (hours)

Notes	Study protocol supplied by authors To detect a difference between groups in the main outcome measure of one standard deviation, at a significance level of 5% and a power of 80%, the study required 16 infants in each group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no information on method for randomisation schedule
Allocation concealment (selection bias)	Low risk	Numbered, sealed envelopes used for allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals noted
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported either in data form or text form
Other bias	Unclear risk	One participant was changed from Vapotherm to head-box oxygen for clinical reasons, which was not expanded on. It was not specified if the infant not adhering to the allocated group was analyzed in the allocated group Different weaning protocols may have affected the time to ceasing treatment measurements, in the direction of Vapotherm being longer FiO_2 was a titration and hence may affect SpO_2. However, both data sets were recorded and reported for comparison Insufficient information to identify this as a source of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were not blinded due to the nature of the intervention. Personnel followed standardised protocols. Likelihood of lack of blinding influencing outcome was not reported and is unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome was documented by unblinded nursing staff caring for participants. However, impact on bias is unclear given the objective nature of the outcome measurements

FiO_2: fraction of inspired oxygen
HBO: head-box oxygen
SpO_2: oxygen saturation
VT: vapotherm

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

Study	Reason for exclusion
Bajaj 2006	High-flow nasal cannula therapy not an intervention arm
Balanzat 2006	High-flow nasal cannula therapy not an intervention arm
Blyth 2003	High-flow nasal cannula therapy not an intervention arm
Donlan 2011	Review article
Figueruelo 2011	Not RCT/out of age range
Hough 2011	Not RCT
Kim 2011	Not examining HFNC therapy versus other treatment - instead examining HFNC therapy with helium/oxygen and with oxygen alone
Martinon-Torres 2003	Not RCT
Martinon-Torres 2008	High-flow nasal cannula therapy not an intervention arm
Martinón-Torres 2002	Review article
Milesi 2010	High-flow nasal cannula therapy not an intervention arm
Smith 1993	High-flow nasal cannula therapy not an intervention arm
Tie 2009	High-flow nasal cannula therapy not an intervention arm
Unger 2008	High-flow nasal cannula therapy not an intervention arm

HFNC: high-flow nasal cannula
RCT: randomised controlled trial

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

Kepreotes 2012

Trial name or title	Pilot randomised control trial of highflow nasal prong warm, humidified oxygen (HFNP WHO) compared to standard oxygen therapy in the management of moderate bronchiolitis in infants aged < 24 months in the Emergency Department and Children's Medical Ward of a tertiary referral hospital in Australia
Methods	Single site, open, 2-arm, pilot, randomised controlled trial of highflow nasal prong with warm, humidified oxygen compared to standard oxygen therapy in the management of moderate bronchiolitis in infants aged < 24 months
Participants	Infants 0 to 24 months old
Interventions	Highflow, nasal prong with warmed, humidified oxygen plus supplemental oxygen if necessary
Outcomes	Primary: time to weaning off supplemental oxygen Secondary: treatment failure, change in baseline vital observations and respiratory distress score, length of stay, adverse events, severity score, parents assessment, biomarkers and imaging
Starting date	July 2012
Contact information	elizabeth.kepreotes@hnehealth.nsw.gov.au
Notes	ACTRN12612000685819. Recruited n = 18 at 22 August 2012; anticipate completion of recruitment by end of 2013

Milner 2012

Trial name or title	Heated High Flow Oxygen Use in Infants With Bronchiolitis and Hypoxia (HHFNC) inpatients in Children's Hospitals and Clinics of Minnesota
Methods	Prospective randomised study comparing clinical severity score and Pediatric Early Warning System scores of infants who receive oxygen by standard flow nasal cannula to those who receive oxygen via humidified, highflow nasal cannula
Participants	Children 3 to 18 months old with a clinical diagnosis of bronchiolitis and hypoxia, and a CSS showing moderate distress > 4
Interventions	Oxygen delivered via humidified high-flow nasal cannula (HHFNC) or oxygen received by standard flow nasal cannula
Outcomes	Primary: clinical severity score Secondary: Pediatric Early Warning System score
Starting date	August 2012
Contact information	donna.milner@childrensMN.org

Milner 2012 (*Continued*)

Notes	ClinicalTrials.gov Identifier: NCT01662544

Schibler 2013

Trial name or title	High Flow Nasal Cannula Treatment for Viral Bronchiolitis in Infants, a Randomised Controlled Trial
Methods	Randomised controlled trial to be conducted in New South Wales and Queensland, Australia. Randomisation on ED admission using central online randomisation allocation concealment
Participants	Infants with bronchiolitis less than 12 months of age Oxygen requirement with SpO_2 < 94% in room air
Interventions	High flow nasal cannula oxygen delivery at a rate of 2 L/kg/min for the duration of oxygen requirement
Outcomes	Primary: reduction in transfer rate from regional hospital to tertiary centre Secondary: reduction in intubation rate, hospital length of stay
Starting date	1 July 2013
Contact information	icuch5@mater.org.au
Notes	ACTRN12613000388718

Seear 2011

Trial name or title	Study of High-flow Oxygen Therapy Against Standard Therapy in Bronchiolitis (Hi-Flo) 2 centre study
Methods	Prospective, open, randomised study comparing standard ward management with high-flow nasal cannula oxygen therapy
Participants	0 to 18 months old
Interventions	High-flow nasal cannula oxygen therapy
Outcomes	Primary: length of hospital stay Secondary: ICU admission, work of breathing
Starting date	December 2011
Contact information	mseear@cw.bc.ca
Notes	ClinicalTrials.gov Identifier: NCT01498094. To be conducted in British Columbia Children's Hospital, Vancouver, British Columbia, Canada and Sydney Children's Hospital, New South Wales, Australia. At 23 August 2012 recruitment was not complete; possible target date January 2013

Sood 2012

Trial name or title	Randomised controlled IRB-approved prospective, multicenter study in USA
Methods	Participants randomised into 1 of 3 groups from December 2010 through March 2011 at 2 children's hospitals
Participants	Infants admitted to PICU with the diagnosis of RSV bronchiolitis
Interventions	1. Conventional nasal cannula (NC) with 100% oxygen and flow rate of < 2 litres/min (LPM) 2. High-flow high-humidity (HFHH) therapy with 30% oxygen, flow of 4 LPM 3. HFHH therapy with 30% oxygen, flow of 8 LPM All other therapies identical between groups
Outcomes	Serial data collected on pre/post therapy blood gases, respiratory rates (RR), validated work of breathing (WOB) scores, days on oxygen, length of hospital stay and treatment failures
Starting date	December 2010
Contact information	Mark Rowin, Associate Professor of Pediatrics, University of Tennessee Medical College-Chattanooga
Notes	Data in abstract Sood 2012 represented the first year of a multi-year prospective study. 3 years of the study completed by May 2013, preliminary data analysis commencing in July 2013

Whitehall 2012

Trial name or title	Trial of high flow nasal prong (HFNP) oxygen therapy for viral bronchiolitis in children's wards of southwest Sydney, NSW, Australia
Methods	Open, randomised controlled trial comparing high-flow nasal prong oxygen therapy with standard care on rate of intubation and requirements for intensive care in children with viral bronchiolitis
Participants	Infants 0 to 24 months old
Interventions	High-flow nasal prong therapy (HFNP) providing humidified oxygen and warmed to 37 degrees. Flow rate, set to optimise oxygen saturation, will be up to 8 L/min depending on patient comfort. Duration of HFNP will vary depending on severity of the bronchiolitis. Breaks for nasal care or mobilisation permitted. Other treatments such as drug therapy will be given according to standard protocols Control: respiratory therapy presently available in the participating hospitals, i.e. supplemental oxygen up to 2 L/min provided by lowflow normal nasal prongs with unheated humidifier. Other treatments such as drug therapy will be given according to standard protocols
Outcomes	Primary: decrease in intubation and intensive care requirement Secondary: reduction in transfer to children's hospital
Starting date	November 2011
Contact information	john.whitehall@uws.edu.au

Whitehall 2012 (*Continued*)

Notes	ACTRN12611001016921. Not recruiting at 1 November 2011 Australian hospitals listed: Campbelltown Hospital and Mount Druitt Hospital, NSW

CSS: clinical severity score
ED: emergency department
HFHH: high-flow high-humidity
HFNP: high-flow nasal prong therapy
ICU: intensive care unit
IRB: Institutional Review Board
LPM: litres/minute
PICU: paediatric intensive care unit
RSV: respiratory syncytial virus
SpO_2: oxygen saturation

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. CENTRAL and MEDLINE search strategies

1 exp Bronchiolitis/
2 bronchiolit*.tw.
3 bronchopneumon*.tw.
4 Respiratory Syncytial Virus Infections/
5 respiratory syncytial viruses/ or respiratory syncytial virus, human/
6 (respiratory syncytial virus* or rsv).tw.
7 ((viral or virus*) adj5 wheez*).tw.
8 or/1-7
9 positive-pressure respiration/ or continuous positive airway pressure/
10 (continuous positive airway pressure* or cpap or ncpap).tw.
11 ((non-invasive or non invasive or noninvasive) adj5 (respirat* or ventilat*)).tw.
12 (nppv or nippv).tw.
13 Oxygen Inhalation Therapy/
14 (oxygen adj1 (inhal* or therap* or deliver* or supplement*)).tw.
15 (nasal adj1 (prong* or cannul*)).tw.
16 ((high frequency or high flow) adj5 nasal).tw.
17 (hfnc or hfnp or hhfnox).tw.
18 or/9-17
19 8 and 18

Appendix 2. Embase.com search strategy

#23 #19 AND #22
#22 #20 OR #21
#21 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti
#20 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#19 #8 AND #18
#18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#17 hfnc:ab,ti OR hfnp:ab,ti OR hhfnox:ab,ti
#16 (('high frequency' OR 'high flow') NEAR/5 nasal):ab,ti
#15 (nasal NEAR/1 (prong* OR cannul*)):ab,ti
#14 (oxygen NEAR/1 (inhal* OR therap* OR deliver* OR supplement*)):ab,ti
#13 'oxygen therapy'/de
#12 nppv:ab,ti OR nippv:ab,ti
#11 (('non invasive' OR 'non-invasive' OR noninvasive) NEAR/3 (ventilat* OR respirat*)):ab,ti
#10 'continuous positive airway pressure':ab,ti OR cpap:ab,ti
#9 'positive end expiratory pressure'/de
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#7 ((viral OR virus*) NEAR/5 wheez*):ab,ti
#6 'respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti

#5 'respiratory syncytial virus infection'/de OR 'respiratory syncytial pneumovirus'/de
#4 bronchopneumon*:ab,ti
#3 'bronchopneumonia'/de
#2 bronchiolit*:ab,ti
#1 'bronchiolitis'/exp

Appendix 3. CINAHL (Ebsco) search strategy

S32 S21 and S31
S31 S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
S30 (MH "Quantitative Studies")
S29 TI placebo* OR AB placebo*
S28 (MH "Placebos")
S27 TI random* OR AB random*
S26 (MH "Random Assignment")
S25 TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*))
S24 TI clinic* trial* OR AB clinic* trial*
S23 PT clinical trial
S22 (MH "Clinical Trials+")
S21 S9 and S20
S20 S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19
S19 TI (hfnc or hfnp or hhfnox) OR AB (hfnc or hfnp or hhfnox)
S18 TI ((high frequency or high flow) W5 nasal) OR AB ((high frequency or high flow) W5 nasal)
S17 TI (nasal W1 (cannul* or prong*)) OR AB (nasal W1 (cannul* or prong*))
S16 (MH "Nasal Cannula")
S15 TI (oxygen W1 (inhal* or therap* or deliver* or supplement*)) OR AB (oxygen W1 (inhal* or therap* or deliver* or supplement*))
S14 (MH "Oxygen Therapy")
S13 TI (nppv or nippv) OR AB (nppv or nippv)
S12 TI ((noninvasive or non-invasive or non invasive) W5 (respirat* or ventilat*)) OR AB ((noninvasive or non-invasive or non invasive) W5 (respirat* or ventilat*))
S11 TI (continuous positive airway pressure* or cpap or ncpap) OR AB (continuous positive airway pressure* or cpap or ncpap)
S10 (MH "Positive Pressure Ventilation") OR (MH "Continuous Positive Airway Pressure") OR (MH "Positive End-Expiratory Pressure")
S9 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8
S8 TI ((viral or virus*) W5 wheez*) OR AB ((viral or virus*) W5 wheez*)
S7 TI (respiratory syncytial virus* or rsv) OR AB (respiratory syncytial virus* or rsv)
S6 (MH "Respiratory Syncytial Virus Infections")
S5 (MH "Respiratory Syncytial Viruses")
S4 TI bronchopneumon* OR AB bronchopneumon*
S3 (MH "Bronchopneumonia")
S2 TI bronchiolit* OR AB bronchiolit*
S1 (MH "Bronchiolitis+")

Appendix 4. LILACS (BIREME - VHL) search strategy

> Search > (MH:Bronchiolitis OR bronchiolit$ OR Bronquiolitis OR Bronquiolite OR MH:C08.127.446.135$ OR MH:C08.381.495.146.135$ OR C08.730.099.135$ OR MH:Bronchopneumonia OR bronchopneumon$ OR Bronconeumonía OR MH:"Respiratory Syncytial Virus Infections" OR "Infecciones por Virus Sincitial Respiratorio" OR "Infecções por Vírus Respiratório Sincicial" OR MH:C02.782.580.600.620.750 OR "respiratory syncytial virus" OR "respiratory syncytial viruses" OR rsv OR MH:"Respiratory Syncytial Viruses" OR "Virus Sincitiales Respiratorios" OR "Vírus Sinciciais Respiratórios" OR "Virus Sincitial Respiratorio" OR MH:B04.820.455.600.670.600.750 OR MH:B04.909.777.455.600.670.600.750 OR MH:"Respiratory Syncytial Virus, Human" OR "Virus Sincitial Respiratorio Humano" OR "Vírus Sincicial Respiratório Humano" OR MH:B04.820.455.600.670.600.750.730 OR MH:B04.909.777.455.600.670.600.750.730 OR Sibilancias OR wheez$ OR Sibiação) AND (MH:"Positive-Pressure Respiration" OR "Respiración con Presión Positiva" OR "Respiração com Pressão Positiva" OR MH:E02.041.625.790 OR MH:E02.880.820.790 OR "Respiración por Presión Positiva Continua" OR "Respiração por Pressão Positiva Contínua" OR "continuous positive airway pressure" OR cpap OR ncpap OR nppv OR nippv OR "non-invasive respiration" OR "non-invasive ventilation" OR MH:"Oxygen Inhalation Therapy" OR "Terapia por Inhalación de Oxígeno" OR Oxigenoterapia OR "oxygen inhalation" OR "oxygen delivery" OR "nasal prong" OR "nasal prongs" OR "nasal cannula" OR "nasal cannulae" OR "high flow" OR hfnc OR hfnp OR hhfnox) > clinical˙trials

Appendix 5. Web of Science (Thomson ISI) search strategy

Topic=(bronchiolit* or bronchopneumon* or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or (viral NEAR/5 wheez*) or (virus* NEAR/5 wheez*)) AND Topic=("positive pressure respiration" or "coninuous positive airway pressure" or cpap or ncpap or ("non-invasive" NEAR/5 (respirat* or ventilat*)) or nppv or nippv or (oxygen NEAR/1 (inhal* or deliver* or therap* or supplement*)) or (nasal NEAR/1 (prong* or cannul*)) or (nasal NEAR/5 ("high flow" or "high frequency")) or hfnc or hfnp or hhfnox)
Refined by: Topic=(random* or placebo* or ((control* or clinic*) NEAR/2 (trial* or stud*)) or ((singl* or doubl*) NEAR/1 blind*))
Timespan=1985-2012. Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC.
Lemmatization=On

CONTRIBUTIONS OF AUTHORS

Sean Beggs, Zee Hame Wong, Sheena Kaul, Kathryn Ogden and Julia Walters collaborated on writing the protocol for this review.

Searches of ongoing trials registers were performed by Zee Hame Wong.

Study selection was by Zee Hame Wong, Sheena Kaul and Julia Walters.

'Risk of bias' assessment and data extraction for the included study was performed by Zee Hame Wong and Kathryn Ogden.

Zee Hame Wong and Julia Walters provided details of the included studies and ongoing trials.

Zee Hame Wong, Julia Walters and Sean Beggs wrote the initial results and discussion.

All authors contributed to the preparation of the final draft manuscript.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- University of Tasmania, Australia.

Logistic and administration

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We specified the presentation of a summary of findings table according to recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* for the primary outcomes, adverse effects and patient-important outcomes (clinical severity score, duration of oxygen therapy, oxygen saturation, respiratory rate) when data are available from a full study/studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Bronchiolitis [*therapy]; Oxygen Inhalation Therapy [*methods]; Pilot Projects; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant