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Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia (Review)

Bamat N, Fierro J, Wang Y, Millar D, Kirpalani H

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Cochrane Database of Systematic Reviews 2019, Issue 2. Art. No.: CD004500.

DOI: 10.1002/14651858.CD004500.pub3.

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	6
OBJECTIVES	7
METHODS	7
Figure 1.	9
RESULTS	11
Figure 2.	13
Figure 3.	14
Figure 4.	16
Figure 5.	16
Figure 6.	16
Figure 7.	17
Figure 8.	17
Figure 9.	18
Figure 10.	18
Figure 11.	19
Figure 12.	19
Figure 13.	20
Figure 14.	20
Figure 15.	21
DISCUSSION	21
AUTHORS' CONCLUSIONS	23
ACKNOWLEDGEMENTS	23
REFERENCES	23
CHARACTERISTICS OF STUDIES	26
DATA AND ANALYSES	34
Analysis 1.1. Comparison 1 Low PEEP (less than 5 cmH ₂ O) versus high PEEP (5 cmH ₂ O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 1 Oxygenation measures: various, combined with standardized mean differences.	35
Analysis 1.2. Comparison 1 Low PEEP (less than 5 cmH ₂ O) versus high PEEP (5 cmH ₂ O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 2 Oxygenation measures: alveolar to arterial oxygen tension difference.	36
Analysis 1.3. Comparison 1 Low PEEP (less than 5 cmH ₂ O) versus high PEEP (5 cmH ₂ O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 3 Oxygenation measures: fraction of inspired oxygen administered.	37
Analysis 1.4. Comparison 1 Low PEEP (less than 5 cmH ₂ O) versus high PEEP (5 cmH ₂ O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 4 Arterial or transcutaneous carbon dioxide pressure, combined with standardized mean differences.	38
Analysis 1.5. Comparison 1 Low PEEP (less than 5 cmH ₂ O) versus high PEEP (5 cmH ₂ O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 5 Arterial carbon dioxide pressure.	39
Analysis 1.6. Comparison 1 Low PEEP (less than 5 cmH ₂ O) versus high PEEP (5 cmH ₂ O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 6 Transcutaneous carbon dioxide pressure.	40
Analysis 1.7. Comparison 1 Low PEEP (less than 5 cmH ₂ O) versus high PEEP (5 cmH ₂ O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 7 Cardiac output: left ventricular output, as measured on echocardiogram.	41

Analysis 2.1. Comparison 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 1 Mortality by hospital discharge.	42
Analysis 2.2. Comparison 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 2 Bronchopulmonary dysplasia.	43
Analysis 2.3. Comparison 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 3 Duration of invasive ventilatory support.	44
Analysis 2.4. Comparison 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 4 Oxygenation measures: lowest fraction of inspired oxygen administered in the first 12 hours of life.	45
Analysis 2.5. Comparison 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 5 Oxygenation measures: arterial/alveolar oxygen ratio at end of LRM.	46
ADDITIONAL TABLES	46
APPENDICES	48
WHAT'S NEW	52
CONTRIBUTIONS OF AUTHORS	52
DECLARATIONS OF INTEREST	53
SOURCES OF SUPPORT	53
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	53
INDEX TERMS	53

Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

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Editorial group: Cochrane Neonatal Group.

Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 2, 2019.

Citation: Bamat N, Fierro J, Wang Y, Millar D, Kirpalani H. Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia. *Cochrane Database of Systematic Reviews* 2019, Issue 2. Art. No.: CD004500. DOI: 10.1002/14651858.CD004500.pub3.

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ABSTRACT

Background

Conventional mechanical ventilation (CMV) is a common therapy for neonatal respiratory failure. While CMV facilitates gas exchange, it may simultaneously injure the lungs. Positive end-expiratory pressure (PEEP) has received less attention than other ventilation parameters when considering this benefit-risk balance. While an appropriate PEEP level may result in clinical benefits, both inappropriately low or high levels may cause harm. An appropriate PEEP level may also be best achieved by an individualized approach.

Objectives

1. To compare the effects of PEEP levels in preterm infants requiring CMV for respiratory distress syndrome (RDS). We compare both: zero end-expiratory pressure (ZEEP) (0 cm H₂O) versus any PEEP and low (< 5 cm H₂O) vs high (≥ 5 cm H₂O) PEEP.
2. To compare the effects of PEEP levels in preterm infants requiring CMV for bronchopulmonary dysplasia (BPD). We compare both: ZEEP (0 cm H₂O) vs any PEEP and low (< 5 cm H₂O) versus high (≥ 5 cm H₂O) PEEP.
3. To compare the effects of different methods for individualizing PEEP to an optimal level in preterm newborn infants requiring CMV for RDS.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials, MEDLINE via PubMed, Embase, and CINAHL to 14 February 2018. We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials.

Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia (Review)

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Selection criteria

We included all randomized or quasi-randomized controlled trials studying preterm infants born at less than 37 weeks' gestational age, requiring CMV and undergoing randomization to either different PEEP levels (RDS or BPD); or, two or more alternative methods for individualizing PEEP levels (RDS only). We included cross-over trials but limited outcomes to those from the first cross-over period.

Data collection and analysis

We performed data collection and analysis according to the recommendations of the Cochrane Neonatal Review Group. We used the GRADE approach to assess the quality of evidence for prespecified key clinically relevant outcomes.

Main results

Four trials met the inclusion criteria. Two cross-over trials with 28 participants compared different PEEP levels in infants with RDS. Meta-analysis was limited to short-term measures of pulmonary gas exchange and showed no differences between low and high PEEP.

We identified no trials comparing PEEP levels in infants with BPD.

Two trials enrolling 44 participants compared different methods for individualizing PEEP in infants with RDS. Both trials compared an oxygenation-guided lung-recruitment maneuver (LRM) with gradual PEEP level titrations for individualizing PEEP to routine care (control). Meta-analysis showed no difference between LRM and control on mortality by hospital discharge (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.17 to 5.77); there was no statistically significant difference on BPD, with an effect estimate favoring LRM (RR 0.25, 95% CI 0.03 to 2.07); and a statistically significant difference favoring LRM for the outcome of duration of ventilatory support (mean difference -1.06 days, 95% CI -1.85 to -0.26; moderate heterogeneity, $I^2 = 67\%$). Short-term oxygenation measures also favored LRM. We graded the quality of the evidence as low for all key outcomes due to risk of bias and imprecision of the effect estimates.

Authors' conclusions

There continues to be insufficient evidence to guide PEEP level selection for preterm infants on CMV for RDS or BPD. Low-quality data suggests that selecting PEEP levels through the application of an oxygenation-guided LRM may result in clinical benefit. Well-conducted randomized trials, particularly to further evaluate the potential benefits of oxygenation-guided LRMs, are needed.

PLAIN LANGUAGE SUMMARY

Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Review question: how do different positive end-expiratory pressure (PEEP) levels, or different approaches for selecting PEEP levels, compare on their effects in preterm infants with respiratory distress syndrome (RDS) or bronchopulmonary dysplasia (BPD)?

Background: infants born preterm (before 37 weeks' gestational age) often have respiratory failure and require medical support to achieve adequate pulmonary gas exchange (removing carbon dioxide from the blood and replenishing it with oxygen). RDS and BPD are complications of premature babies that describe early (RDS) and late (BPD) respiratory failure as a result of preterm birth. Conventional mechanical ventilation (the use of a breathing machine) following endotracheal intubation (placement of a breathing tube in the windpipe) is a commonly used therapy for both complications. While this therapy can improve pulmonary gas exchange and lead to benefits, it may simultaneously injure the lungs and cause harms. Gas exchange is achieved by several ventilator settings that help cycle heated, humidified and (sometimes) oxygen-enriched air in and out of the lungs. One of these settings is called PEEP, which is a continuous distending pressure applied throughout the respiratory cycle. It plays an important role in keeping the lungs open, enabling all areas of the lungs to undergo gas exchange. While the use of PEEP is generally accepted, it is not clear which PEEP levels maximize benefits while minimizing possible harms. An appropriate PEEP level may also be best achieved by an individualized approach in which a good PEEP level is determined on a patient-to-patient basis.

Study characteristics: we organized our study to compare the effect of low versus high PEEP levels, which we defined as: less than 5 cmH₂O (low) versus 5 cmH₂O or greater (high). Our primary outcomes were death by hospital discharge (for RDS) or two years of age (for BPD) and neurodevelopmental impairment (problems with growth and development of the brain or central nervous system) at two years of age. We identified four trials. Two trials with 28 infants compared different PEEP levels in infants with RDS. Two trials with 44 infants compared approaches for individually selecting PEEP levels. The compared approaches were: routine, typical practice

(control) versus a “lung-recruitment maneuver.” With this maneuver, investigators slowly increased and then decreased PEEP levels while monitoring for improvements in oxygenation to guide PEEP level selection. The evidence is up to date to 14 February 2018.

Key results: two trials comparing different PEEP levels in RDS did not report on any patient important outcomes. They compared the short-term effect of different PEEP levels on pulmonary gas exchange, and found no differences between low and high PEEP levels. The two trials comparing the lung-recruitment maneuver to control reported survival to hospital discharge or the development of BPD and found no clear difference between groups. However, they did suggest that an infant receiving the maneuver may have required less time on conventional mechanical ventilation and had better oxygenation for a period after the maneuver. The quality of the evidence for these results was low because they were small studies and vulnerable to bias from limitations in the study methods.

Conclusions: evidence-based guidance for PEEP level selection in preterm infants continues to be limited. We are unable to make recommendations for clinical practice based on our findings. This review should raise awareness of the lack of high-quality research evidence guiding the selection of PEEP levels in preterm infants and encourage further research. Additional research evaluating lung-recruitment maneuvers as an approach for individually selecting PEEP levels would be particularly valuable, given our findings of possible but uncertain benefit with this approach.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Oxygen-guided lung-recruitment maneuver compared to routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome (objective 3)						
Patient or population: preterm infants < 37 weeks' gestational age requiring conventional mechanical ventilation for respiratory distress syndrome Setting: neonatal intensive care unit Intervention: positive end-expiratory pressure level titration with an oxygenation-guided lung-recruitment maneuver Comparison: routine care						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with routine care	Risk with an oxygenation-guided lung-recruitment maneuver				
Mortality by hospital discharge	Study population		RR 1.00 (0.17 to 5.77)	44 (2 studies)	Low ^a	-
	91 per 1000	91 per 1000 (15 to 525)				
Bronchopulmonary dysplasia	Study population		RR 0.25 (0.03 to 2.07)	44 (2 study)	Low ^a	-
	136 per 1000	34 per 1000 (4 to 282)				
Duration of invasive ventilatory support	-	MD 1.06 lower (1.85 lower to 0.26 lower)	-	44 (2 study)	Low ^b	-
*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

^aDowngraded for risk of bias and imprecision.

^bDowngraded for risk of bias and imprecision. Moderate heterogeneity, $I^2 = 67\%$, $\text{Chi}^2 = 3.07$; $P = 0.08$.

BACKGROUND

Description of the condition

Respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) describe the early and late clinical manifestations of respiratory failure in preterm infants. They are common causes of mortality and long-term morbidity in this population (Schmidt 2003; Patel 2015).

Respiratory failure occurs in part because preterm infants are born with lungs that tend to collapse (Gregory 1971). This is the result of several anatomic and physiologic factors. Immature neurologic control results in periodic breathing and central apnea (Martin 1977). A compliant chest wall and the relative shape and position of the diaphragm, ribs, and chest wall contribute to inefficient respiratory mechanics, requiring additional work to inflate the lungs (Muller 1979). Both surfactant quantity and quality are decreased (Ueda 1994). These factors and others contribute to atelectasis and inadequate pulmonary gas exchange.

Description of the intervention

Positive end-expiratory pressure (PEEP) is a continuous distending airway pressure (CDP) applied through an endotracheal tube and maintained throughout the respiratory cycle during conventional mechanical ventilation (CMV). CMV is a common intervention for neonatal respiratory failure. Heated, humidified gas is driven into the lungs for a set period (inspiratory time) at a given pressure (peak inspiratory pressure (PIP)), followed by an expiratory phase of set duration (expiratory time) where PEEP is maintained. This cycle is repeated several times each minute, giving a respiratory rate or frequency. "Mean airway pressure" conveniently summarizes these parameters as a single pressure level (Boros 1979). However, the clinical effects of different mean airway pressure levels may vary as a function of the specific parameter (e.g. PIP versus PEEP) changed.

While CMV provides benefit by facilitating pulmonary gas exchange, it simultaneously carries the risk of lung damage - ventilator-induced lung injury (VILI) (Slutsky 2013). In newborns, most attention has focused on the potentially damaging effects of PIP and associated peak volumes (Klingenberg 2017). Although acknowledged, the contribution of PEEP on this benefit-risk balance is less well studied (Monkman 2003). As with other ventilator parameters, providers choose how much PEEP (commonly measured in centimeters of water (cmH₂O)) to apply. This review focuses on the impact of different PEEP levels on morbidity and mortality in infants born preterm.

How the intervention might work

PEEP helps offset the factors contributing to lung collapse and inadequate gas exchange in preterm infants. Both Corbridge 1990 and Froese 1993 demonstrated in animal models that the absence of PEEP, or zero end-expiratory pressure (ZEEP), is deleterious. The use of some amount of PEEP is standard of care for preterm infants receiving CMV.

However, it is uncertain how much PEEP should be used. If the PEEP level is too low, alveolar collapse will persist, with impaired pulmonary mechanics, gas exchange, and risk for further lung injury from atelectrauma (Froese 1993). Higher PEEP levels may increase lung volumes and improve pulmonary mechanics and gas exchange in under-recruited lungs (Gregory 1971; Richardson 1978; Thome 1998). But, excessive distending pressure may result in overdistension and worsen respiratory mechanics and gas exchange, while causing lung injury through air leak syndromes and volutrauma (Greenough 1992; Bartholomew 1994). Overdistension may also impair venous return and cardiovascular performance (Hausdorf 1987).

For the comparisons in this review, we considered PEEP levels of less than 5 cmH₂O to comprise 'low PEEP' and 5 cmH₂O or greater to comprise 'high PEEP.' We acknowledge this dichotomy is arbitrary. However, da Silva 1994 demonstrated useful increases in functional residual capacity when increasing PEEP from levels of 2 cmH₂O to 5 cmH₂O, and at 5 cmH₂O the mean functional residual capacity values were similar to the normal values of healthy term infants. A further pragmatic consideration is that 5 cmH₂O is a commonly selected initial PEEP level (Bamat 2018).

Identification of an 'optimal' PEEP level that minimizes harm from either insufficient or excessive distension may require an individualized approach. Individualized, optimal PEEP levels that vary between infants would reflect differences in underlying disease type and severity, and likely change over time in the same infant. In fact, determination of optimal individualized levels by monitoring esophageal pressures and gas exchange was suggested in one of the earliest applications of CDP therapy in preterm infants (Bonta 1977). Other investigators have advocated monitoring pulmonary mechanics to identify best levels. For example, Mathe and colleagues proposed examining individual pressure-volume curves to identify the lower inflection point of the inspiratory limb as the point of 'appropriate PEEP' (Mathe 1987). Controlled trials in newborn animal models suggest that setting PEEP levels above this level may provide an individualized technique to minimize lung damage (Monkman 2004). This review compares not only different PEEP levels, but also methods for individualizing PEEP therapy.

Why it is important to do this review

Respiratory failure and VILI remains a common source of harm in preterm infants. Systematic reviews comparing the preferential use of non-invasive respiratory support strategies such as nasal continuous positive airway pressure (nCPAP) over mechanical ventila-

tion suggest an improvement in BPD-free survival (Fischer 2013; Schmölzer 2013). This benefit is likely mediated, at least in part, through avoidance of VILI. However, the magnitude of the benefit is modest, with a number needed to treat for an additional beneficial outcome of 25 (Schmölzer 2013) or 35 (Fischer 2013). Consistent with this limited benefit are trial data that report non-invasive support failure requiring mechanical ventilation in 46% to 83% of preterm infants randomized to preferential nCPAP (Morley 2008; SUPPORT 2010). Likewise, non-invasive respiratory support failure is common after extubation (Danan 2008). As such, preterm infants are commonly exposed to CMV and are at risk for VILI despite the increased adoption of non-invasive respiratory support strategies.

This updates a review published in 2012 (Bamat 2012). At that time, we identified one study reporting short-term pulmonary gas exchange outcomes in 12 participants (Aufrecht 1995), and concluded insufficient evidence for practice recommendation. One published study identified notable practice variation in PEEP level selection between centers despite adjustment for infant characteristics in extremely low birth weight infants (Bamat 2018). This variation likely reflects the absence of existing evidence-based guidance. In contrast, in adults with acute RDS, one systematic review of PEEP level selection included seven randomized controlled trials (RCTs) enrolling 2565 participants (Santa Cruz 2013). This evidence disparity between adults and preterm infants highlights that PEEP level selection is a relevant clinical consideration and the relative paucity of data contributing to an evidence-base in preterm infants.

OBJECTIVES

1. To compare the effects of PEEP levels in preterm infants requiring CMV for respiratory distress syndrome (RDS). We compare both: zero end-expiratory pressure (ZEEP) (0 cm H₂O) versus any PEEP and low (< 5 cm H₂O) vs high (≥ 5 cm H₂O) PEEP.

2. To compare the effects of PEEP levels in preterm infants requiring CMV for bronchopulmonary dysplasia (BPD). We compare both: ZEEP (0 cm H₂O) vs any PEEP and low (< 5 cm H₂O) versus high (≥ 5 cm H₂O) PEEP.

3. To compare the effects of different methods for individualizing PEEP to an optimal level in preterm newborn infants requiring CMV for RDS.

For each objective, the effects of intervention were compared for various prespecified outcomes. A full list of eligible comparisons, organized by the objectives above, is provided in Table 1.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs and quasi-RCTs. We included randomized cross-over designs.

Types of participants

Preterm infants born at less than 37 weeks' gestational age (GA) and requiring CMV with endotracheal intubation for RDS or BPD. We included preterm infants evaluated in the first two weeks of life when a diagnosis of RDS was not explicitly addressed.

For the determination of the effects of PEEP levels in preterm infants requiring CMV for RDS (objective 1), we planned subgroup analyses based on GA (less than 28 weeks' GA, 28 to 31 weeks' GA, 32 weeks' GA or greater) and for presurfactant versus postsurfactant therapy.

Types of interventions

Randomization to different PEEP levels in infants requiring CMV for RDS or BPD. As this review focused on CMV, we excluded trials of high-frequency oscillatory ventilation or high-frequency jet ventilation.

Interventions for comparison included randomization to either:

- different PEEP levels in infants requiring CMV for RDS or BPD, including comparisons of both ZEEP versus (any) PEEP and comparisons of low versus high PEEP;

or

- two or more alternative methods for individualizing PEEP in infants requiring CMV for RDS.

Types of outcome measures

Eligible outcomes varied slightly between the three objectives. Outcomes from cross-over trials were limited to those measured at the end of the first cross-over period.

For comparisons within objectives (1): different levels of PEEP and (3) different methods to individualize PEEP, in RDS

Primary outcomes

- Mortality by hospital discharge.
- Neurodevelopmental impairment at approximately two years' corrected age.

Secondary outcomes

- Incidence of BPD (defined as requiring oxygen supplementation at 36 weeks' postmenstrual age, when available).
- Incidence of air leak syndromes; specifically, pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, and pneumopericardium.
- Duration of invasive ventilatory support.
- Fraction of inspired oxygen (FiO₂) needed to maintain target arterial gas or oxygen saturation levels, or other measures of oxygenation.
- Arterial carbon dioxide pressure (PaCO₂) or transcutaneous carbon dioxide levels.
- Direct measures of cardiac output, or surrogate markers of cardiac output, if these became apparent during analysis of the data.
- Blood pressure measurements, requirement for fluid boluses or inotropic support.
- Brain injury, defined as the incidence of grade III to IV intraventricular hemorrhage, periventricular leukomalacia, or both, as identified by neuroimaging with cranial ultrasound (Papile 1978).
- Functional residual capacity.

For comparisons within objective (2): different levels of PEEP in BPD

Primary outcomes

- Mortality by two years of age.
- Neurodevelopmental impairment at approximately two years' corrected age.

Secondary outcomes

- Incidence of air leak syndromes; specifically, pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, and pneumopericardium.
- Duration of invasive ventilatory support.
- FiO₂ needed to maintain target arterial gas or oxygen saturation levels, or other measures of oxygenation.
- PaCO₂ or transcutaneous carbon dioxide levels.
- Direct measures of cardiac output, or surrogate markers of cardiac output, if these became apparent during analysis of the data.
- Blood pressure measurements, requirement for fluid boluses or inotropic support.
- Brain injury, defined as the incidence of grade III to IV intraventricular hemorrhage, periventricular leukomalacia, or both, as identified by neuroimaging with cranial ultrasound (Papile 1978).
- Functional residual capacity.

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal [search strategy](#) for specialized register).

Electronic searches

For this update, we conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 1) in the Cochrane Library; MEDLINE via PubMed (1966 to 14 February 2018); Embase (1980 to 14 February 2018); and CINAHL (1982 to 14 February 2018) using the following search terms: (respiratory distress syndrome OR RDS OR hyaline membrane disease OR bronchopulmonary dysplasia OR BPD OR chronic lung disease OR CLD) AND (positive pressure respiration OR positive pressure ventilation OR PEEP OR positive end expiratory pressure), plus database-specific limiters for RCTs and neonates (see [Appendix 1](#) for the full search strategies for each database). We applied no language restrictions.

We searched clinical trial registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform www.who.int/ictrp/search/en/, and the [ISRCTN Registry](#)). The search strategy was executed centrally through the support of Cochrane Neonatal. The search strategy for the original review is provided in [Appendix 2](#). In the original review, two review authors independently executed the search strategy, resolving any discrepancies by discussion and resolution mediated by a third review author.

Searching other resources

We searched the reference lists of any articles selected for inclusion in this review. Additionally, we relied on the review authors' existing knowledge of potentially relevant studies to identify potentially eligible trials.

Data collection and analysis

Selection of studies

For this update, we exported records of the electronic database search results to Covidence to facilitate title and abstract screening (www.covidence.org). We ensured single inclusion of duplicate data from the same study identified in multiple reports. Two review authors (JF and either YW or NB) independently reviewed the search results by titles and abstract, and excluded studies clearly not meeting the inclusion criteria. We obtained the full-text articles of potentially relevant studies. After assessing these articles, we listed all studies excluded after full-text assessment and the reasons for exclusion in the [Characteristics of excluded studies](#) table. A third review author (NB or HK) resolved differences and uncertainties

when present. We display the study selection process in a PRISMA diagram in [Figure 1](#).

Figure 1. Study flow diagram: review update.

Data extraction and management

Extraction of relevant data eligible for analysis was guided by a standardized and previously prepared data extraction form. Original data were taken from published reports of trials. Two review authors (NB, JF) independently extracted data with identical results then confirmed. We used Review Manager 5 for data entry, and construction of comparison tables and graphs ([Review Manager 2014](#)).

When we required additional information to determine study inclusion or analyze data in a manner consistent with our protocol, we attempted to contact the corresponding study authors directly. Any potentially recoverable or unexplained missing data triggered an author inquiry. We made a minimum of three separate attempts at correspondence. We described any studies excluded due to an inability to obtain additional information in our review results.

Assessment of risk of bias in included studies

Two review authors (JF, NB) independently assessed the risk of bias (low, high, or unclear) of all included studies using the Cochrane 'Risk of bias' tool for the following domains ([Higgins 2011](#)):

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- or other bias.

Any disagreements were resolved by discussion or by a third review author (HK). See [Appendix 3](#) for a more detailed description of risk of bias for each domain.

Measures of treatment effect

For continuous data, we presented treatment effects as the mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals (CIs) for individual studies and pooled estimates, using an inverse-variance fixed-effect approach for meta-analysis (see [Data synthesis](#)).

For dichotomous categorical data, we presented treatment effect as risk ratio (RR), risk difference (RD) and, for statistically significant comparisons, and the number needed to treat for an additional beneficial outcome (NNTB) or additional harmful outcome (NNTH) with 95% CIs for individual studies and pooled estimates. We used a Mantel-Haenszel fixed-effect approach for meta-analysis.

Unit of analysis issues

For cross-over studies, we restricted outcome data to the first period given concerns for bias from carry-over. These concerns stem from uncertainty related to the duration of time required for equilibration of lung volumes following a PEEP level change and the plausibility of lung-recruitment maneuvers (LRMs; from PEEP level increases) resulting in persistent physiologic changes despite subsequent PEEP level decrements. For studies including repeated measures over time, particularly for physiologic outcomes such as measures of gas exchange, we used the repeated measure furthest from the intervention, so long as we judged the measure plausibly remaining a reflection of the PEEP level change.

Dealing with missing data

Our approach to missing data was as follows. First, we contacted the study investigators to inquire if any missing data were available. For studies using imputation to account for missing data, our primary analysis would only analyze available data (ignoring the imputed, missing data) and subsequently perform a sensitivity analysis including the imputed data. We planned to discuss the likelihood that data were 'missing at random' or 'not missing at random,' assumptions of methods used by study authors to deal with missing data, and address the potential impact of missing data on bias and the findings of the review.

Assessment of heterogeneity

See the [Subgroup analysis and investigation of heterogeneity](#) section which outlines the steps we planned to limit aggregation and meta-analysis of data at risk of excess heterogeneity and to facilitate assessment of heterogeneity within overall results. When we pursued meta-analysis, when applicable, we planned to perform posterior assessments of heterogeneity through:

- identification of studies contributing 'outlying' effect estimates. We would assess these studies for unanticipated clinical and methodologic characteristics plausibly explaining the observed heterogeneity. Identification of such characteristics would not result in exclusion from the pooled estimates of the primary analysis, but would result in exclusion from a secondary sensitivity analyses (see [Sensitivity analysis](#));
- quantifying the degree of heterogeneity by applying the I^2 statistic together with a χ^2 test as a measure of corresponding statistical significance, using a conservative P value of 0.10 for statistical significance. We used the following I^2 statistic thresholds as a guide to help interpret the degree of heterogeneity:

- 25%: none;

- 25% to 49%: low;
- 50% to 74%: moderate;
- 75% to 100%: high.

Assessment of reporting biases

We assessed reporting bias through visual inspection of funnel plots of effect estimates using Review Manager 5, when applicable ([Review Manager 2014](#)).

Data synthesis

When possible, we extracted consistent units of analysis for studies that reported the same outcome measure, or transformed units of analysis to achieve consistency (e.g. converting hours to days or days to weeks). When transforming units, we applied the same transformation to the corresponding measures of variance. When combining outcome measures from studies using different measurement scales to report the same outcome, we used the SMD as a summary measure of treatment effect. This is particularly relevant to short-term physiologic outcomes for which a variety of measures may be used to describe a similar process (e.g. oxygenation measures).

We used the following approaches for data synthesis and meta-analysis: for continuous data, we used an inverse-variance fixed-effect approach for meta-analysis. For dichotomous categorical data, we will use a Mantel-Haenszel fixed-effect approach for meta-analysis.

Quality of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook ([Schünemann 2013](#)), to assess the quality of evidence. For objectives 1 and 3, we assessed the following (clinically relevant) outcomes listed above: mortality by hospital discharge, neurodevelopmental impairment at approximately two years' corrected age, incidence of BPD, incidence of air leak syndromes, and duration of invasive ventilatory support. For objective 2, we assessed: mortality at two years of age, neurodevelopmental impairment at approximately two years' corrected age, incidence of air leak syndromes, and duration of ventilatory support.

Two review authors (NB and JF) independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from RCTs as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the [GRADEpro](#) GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.

- Moderate: 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: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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

Subgroup analysis and investigation of heterogeneity

We adopted a cautious approach to aggregation and meta-analysis of data at risk of excess heterogeneity, erring on the side of avoidance when there was uncertainty. Two review authors (NB and JF) independently made this decision, and resolved any disagreements through discussion or resolution by a third review author (HK). For objective 1, we planned to limited heterogeneity, in part, through the a priori application of several subgroup analyses stratified on key clinical characteristics, as follows.

Planned subgroups analyses

When possible, we performed planned subgroup analyses stratified based on:

- GA (less than 28 weeks' GA, 28 to 31 weeks' GA, 32 weeks' GA or greater);
- presurfactant versus postsurfactant therapy.

Sensitivity analysis

We planned the following sensitivity analyses a priori:

- excluding studies assessed as 'high' for overall risk of bias;
- excluding studies that contributed 'outlying' effect estimates that can be plausibly attributed to unanticipated study characteristics following review as described; in the [Assessment of heterogeneity](#) section;
- including data obtained following imputation of missing data.

RESULTS

Description of studies

Results of the search

In the original review, our search strategy resulted in 888 articles for screening ([Bamat 2012](#)). We identified 10 studies for potential

inclusion and excluded nine upon full review (see: [Characteristics of excluded studies](#) table). One study met the inclusion criteria ([Aufrecht 1995](#)).

[Figure 1](#) displays the search results for this update. The updated search identified an additional 1026 records following removal of duplicate records. We identified five studies for potential inclusion and excluded two upon full review (see: [Characteristics of excluded studies](#) table). Three additional studies met inclusion criteria ([Castoldi 2011](#); [Fajardo 2014](#); [Wu 2014](#)).

Included studies

See: [Characteristics of included studies](#) for further details of included studies.

Four studies met the inclusion criteria ([Aufrecht 1995](#); [Castoldi 2011](#); [Fajardo 2014](#); [Wu 2014](#)). All were single-center studies enrolling between 13 and 24 participants.

[Aufrecht 1995](#) and [Fajardo 2014](#) met inclusion for objective 1, to compare the effects of different PEEP levels in preterm infants requiring CMV for RDS. Both were cross-over trials. Isolation of outcomes following the first cross-over period was possible due to either the provision of individual participant data in the published manuscript ([Aufrecht 1995](#)), or through correspondence with the study authors ([Fajardo 2014](#)).

[Castoldi 2011](#) and [Wu 2014](#) met inclusion for objective 3, to compare the effects of different methods for individualizing PEEP to an optimal level in preterm newborn infants requiring CMV for RDS. Both were single-center RCTs.

Participants

The included studies enrolled 73 participants. In our original review, we excluded one participant from [Aufrecht 1995](#) receiving a deliberate hyperventilation strategy as this directly biased the study outcomes eligible for inclusion in this review (measures of pulmonary gas exchange). Of the remaining 72 participants, 28 corresponded to objective 1 and 44 corresponded to objective 3. Most participants were preterm infants of GA less than 32 weeks, including all participants in [Castoldi 2011](#) (GA less than 28 weeks), [Fajardo 2014](#) (GA less than 32 weeks), and [Wu 2014](#) (GA 28 to 30 weeks). Participants in [Aufrecht 1995](#) were of mean GA 30.8 (standard deviation (SD) 2.6) weeks, but no GA-based inclusion criteria were specified. [Fajardo 2014](#) (less than 2000 g) and [Wu 2014](#) (1000 g to 1500 g) additionally specified birth weight inclusion criteria. Most participants were studied in the first week of life. In [Castoldi 2011](#) and [Wu 2014](#), all interventions occurred within four hours of life. The age at intervention was both older and more variable in [Aufrecht 1995](#) (mean 1.5 (SD 0.6) days) and particularly in [Fajardo 2014](#) (mean 6 (range 2 to 71) days).

Three studies specified a diagnosis of RDS ([Aufrecht 1995](#); [Castoldi 2011](#); [Wu 2014](#)). All studies had an inclusion criterion of use of CMV, although specific modalities and settings varied between studies. Three studies provided ventilatory parameter details

([Aufrecht 1995](#); [Castoldi 2011](#); [Wu 2014](#)). Details are included in the [Characteristics of included studies](#) table. [Aufrecht 1995](#) did not administer surfactant to any participants, [Castoldi 2011](#) and [Wu 2014](#) administered surfactant to all participants immediately following endotracheal intubation, and [Fajardo 2014](#) did not discuss surfactant.

Other notable inclusion and exclusion criteria were: the presence of a patent ductus arteriosus as an inclusion criterion for [Fajardo 2014](#), in which the primary objective was to evaluate the impact of PEEP level changes on the degree of left to right ductal shunting; and [Castoldi 2011](#) and [Wu 2014](#) specified major congenital anomalies and intraventricular hemorrhage greater than grade 2 as additional exclusion criteria.

Interventions

[Aufrecht 1995](#) and [Fajardo 2014](#) were both three-period cross-over trials evaluating between-participant changes in various short-term physiologic outcomes following PEEP level changes.

[Aufrecht 1995](#) evaluated participants at PEEP levels of 2 cmH₂O, 4 cmH₂O, and 6 cmH₂O, with allocation sequence selected in random order. To align with the objectives of this review, we restricted outcomes to those measured after the first cross-over period and combined 2 cmH₂O and 4 cmH₂O as low PEEP versus 6 cmH₂O as high PEEP. Infants remained at each level for 30 minutes, at which time outcomes were ascertained and the participants were crossed over to the next PEEP level intervention in the allocation sequence.

[Fajardo 2014](#) evaluated participants at PEEP levels of baseline, +3 cmH₂O relative to baseline and -3 cmH₂O relative to baseline, with allocation sequence selected in random order. As baseline PEEP were 5 cmH₂O for all but one participant (with baseline 4 cmH₂O), all but one participant were assessed at levels of 2 cmH₂O, 5 cmH₂O, and 8 cmH₂O. The corresponding author provided individual participant data. To align with the objectives of this review, we restricted outcomes to those measured after the first cross-over period and combined 2 cmH₂O and 4 cmH₂O as low PEEP versus 5 cmH₂O and 8 cmH₂O as high PEEP. Infants remained at each level for 10 to 20 minutes before being crossed over to the next PEEP level intervention in the allocation sequence. Outcomes were ascertained beginning at 10 minutes after a PEEP level change.

[Castoldi 2011](#) and [Wu 2014](#) were both two-arm parallel-group RCTs comparing the effects of PEEP level selection through the application of an oxygen-guided LRM versus control participants who received standard care without an LRM. The study methods were nearly identical, with [Wu 2014](#) basing their intervention on [Castoldi 2011](#). In short, the LRM was initiated at a PEEP of 5 cmH₂O, with repeated PEEP level increments by 0.2 cmH₂O every five minutes while evaluating for improvements in oxygenation by monitoring peripheral oxygen saturation (SpO₂) levels and FiO₂ requirements. PEEP was progressively increased if oxygena-

tion improved. If FiO_2 reached 0.25, PEEP levels were then reduced in a gradual stepwise manner until oxygenation worsened. Then, PEEP was again increased until “stable oxygenation was achieved and the FiO_2 level reached levels prior to the fall in oxygenation” (during the PEEP reduction phase). The intervention differed between [Castoldi 2011](#) (83% to 93%) and [Wu 2014](#) (85% to 93%) only with respect to SpO_2 targets.

Outcomes

The primary outcomes of each study, as well as the details of outcome measures eligible for and included in this review can be found in the [Characteristics of included studies](#) table. In short, eligible outcomes included: mortality by hospital discharge ([Castoldi 2011](#); [Wu 2014](#)); incidence of BPD ([Castoldi 2011](#); [Wu 2014](#)); duration of invasive ventilatory support ([Castoldi 2011](#); [Wu 2014](#)); and various measures of pulmonary gas exchange (all four studies) and cardiac output ([Fajardo 2014](#)).

Excluded studies

See [Characteristics of excluded studies](#) table for additional information regarding excluded studies.

We excluded 10 studies evaluated for potential inclusion following detailed assessment.

Six of the studies did not meet inclusion criteria upon further review or correspondence with study authors ([Belenky 1976](#); [Durbin 1976](#); [Stewart 1981](#); [Hausdorf 1987](#); [Finer 2004](#); [Jauncey-Cooke 2012](#)). [Stewart 1981](#) and [Durbin 1976](#) were not RCTs, [Belenky 1976](#) and [Finer 2004](#) did not randomize participants requiring CMV to different PEEP levels, and [Jauncey-Cooke 2012](#) did not evaluate the eligible population. Four studies required further information to determine classification ([Dimitriou 1999](#); [Herman 1973](#); [Simbruner 1989](#); [Dinger 2001](#)). Correspondence with the authors of [Dimitriou 1999](#) established that while the study methods were eligible, the necessary original data were no longer available. For the remaining three studies, we could not secure the study information or data needed to further evaluate for potential inclusion, or both.

Risk of bias in included studies

All included studies had high or uncertain risk of bias for at least one criterion. See [Figure 2](#) for a summary representation of the risk of bias across the review by criteria, and [Figure 3](#) for risk of bias per criteria for each study. Further, a ‘Risk of bias’ table with additional details is included study within the [Characteristics of included studies](#) table.

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aufricht 1995						
Castoldi 2011						
Fajardo 2014						
Wu 2014						

Allocation

Three studies reported adequate random sequence generation methods (low risk of bias; [Aufrecht 1995](#); [Castoldi 2011](#); [Wu 2014](#)). One study did not specify random sequence generation methods (unclear risk of bias; [Fajardo 2014](#)). Two studies described adequate allocation concealment (low risk of bias; [Castoldi 2011](#); [Wu 2014](#)), and two studies did not specify concealment methods (unclear risk of bias; [Aufrecht 1995](#); [Fajardo 2014](#)).

Blinding

None of the included studies described attempts at blinding the investigators, clinical staff, or families to any aspect of the interventions. We judged that the lack of blinding was unlikely to influence the short-term physiologic outcomes reported in [Aufrecht 1995](#) and [Fajardo 2014](#). However, the risk of influencing some of the eligible outcomes in [Castoldi 2011](#) and [Wu 2014](#) (such as duration of invasive ventilatory support) was plausible, resulting in an unclear risk of bias judgment for these latter two.

Incomplete outcome data

All four included studies had complete outcome ascertainment and reporting.

Selective reporting

Protocol registrations or publications were not available for any of the four included studies.

Other potential sources of bias

One selected participant in [Aufrecht 1995](#) underwent a deliberate hyperventilation technique, resulting in a high risk of bias for the pulmonary gas exchange outcomes eligible for this review. As individual participant data was available for [Aufrecht 1995](#), we excluded this participant from our analyses. For [Fajardo 2014](#), a comparison of data restricted to the first-cross over period when applying the low/high PEEP dichotomy prespecified in this review to summary data collapsed across the three cross-over periods of the

original study suggested the possibility of chance randomization imbalance between low and high PEEP groups with respect to the mean FiO_2 and left ventricular output (LVO) values. This is further described in the [Discussion](#) section.

Effects of interventions

See: [Summary of findings for the main comparison Oxygen-guided lung-recruitment maneuver compared to routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome \(objective 3\)](#)

All outcomes considered for comparison for the three objectives of this review are listed in [Table 1](#). Below, we detail all comparisons for which any data were available, omitting comparisons for which there were no data. In instances in which various specific measurements were provided for the same outcome (e.g. oxygenation measures), we displayed results with and without aggregate meta-analysis. In turn, we did not conduct subgroup or sensitivity analyses as planned because we felt there was insufficient data to undertake meaningful analyses of this nature. As no meta-analysis included more than two trials at this time, sensitivity analyses would have simply reported the results of individual trials.

Comparison 1. Low PEEP versus high PEEP in preterm infants requiring CMV for RDS (objective 1)

Two studies enrolling 28 participants compared high versus low PEEP in preterm infants requiring CMV for RDS ([Aufrecht 1995](#); [Fajardo 2014](#)).

Oxygenation measures: various, combined with standardized mean differences

We combined the outcomes of alveolar to arterial oxygen tension difference (AaDO_2) in [Aufrecht 1995](#) with FiO_2 to meet (unspecified) SpO_2 targets in [Fajardo 2014](#) in a meta-analysis of oxygenation measures using SMDs. We found no statistically significant difference between low and high PEEP levels (SMD -0.31, 95% CI -1.12 to 0.50; participants = 28; studies = 2; $I^2 = 0\%$; [Analysis 1.1](#); [Figure 4](#)).

Figure 4. Forest plot of comparison: I Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: I.1 Oxygenation measures: various, combined with standardized mean differences.

Oxygenation measures: alveolar to arterial oxygen tension difference

One study measured AaDO₂ (Aufricht 1995). The effect estimate from this study found no statistically significant difference between low and high PEEP levels (MD -61.90 mmHg, 95% CI -189.06 to 65.26; participants = 12; studies = 1; I² = 0%; Analysis 1.2; Figure 5).

Figure 5. Forest plot of comparison: I Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: I.2 Oxygenation measures: alveolar to arterial oxygen tension difference.

Oxygenation measures: fraction of inspired oxygen administered

One study measured administered FiO₂ to meet (unspecified) SpO₂ targets (Fajardo 2014). The effect estimate from this study found no statistically significant difference between low and high PEEP levels (MD -2.80%, 95% CI -11.87% to 6.27%; participants = 16; studies = 1; I² = 0%; Analysis 1.3; Figure 6).

Figure 6. Forest plot of comparison: I Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: I.3 Oxygenation measures: fraction of inspired oxygen administered.

Arterial or transcutaneous carbon dioxide pressure, combined with standardized mean differences

We combined the outcomes of PaCO₂ (Aufricht 1995) and transcutaneous CO₂ (Fajardo 2014) in a meta-analysis using SMDs. We found no statistically significant difference between low and high PEEP levels (SMD -0.04, 95% CI -0.84 to 0.76; participants = 28; studies = 2; I² = 0%; Analysis 1.4; Figure 7).

Figure 7. Forest plot of comparison: I Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: I.4 Arterial or transcutaneous carbon dioxide pressure, combined with standardized mean differences.

Arterial carbon dioxide pressure

One study measured PaCO₂ (Aufricht 1995). The effect estimate from this study found no statistically significant difference between low and high PEEP levels (MD -1.80 mmHg, 95% CI -16.56 to 12.96; participants = 12; studies = 1; I² = 0%; Analysis 1.5; Figure 8).

Figure 8. Forest plot of comparison: I Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: I.5 Arterial carbon dioxide pressure).

Transcutaneous carbon dioxide pressure

One study measured transcutaneous CO₂ (Fajardo 2014). The effect estimate from this study found no statistically significant difference between low and high PEEP levels (MD 0.70 mmHg, 95% CI -13.62 to 15.02; participants = 16; studies = 1; I² = 0%; Analysis 1.6; Figure 9).

Figure 9. Forest plot of comparison: I Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: I.6 Transcutaneous carbon dioxide pressure.

Cardiac output: left ventricular output, as measured on echocardiogram

One study measured the outcome of cardiac output, as LVO measured on echocardiogram (Fajardo 2014). The effect estimate from this study showed a statistically significant difference; low PEEP levels were associated with lower LVO than high PEEP levels (MD -126.00 mL/kg/minute, 95% CI -201.58 to -50.42; participants = 16; studies = 1; I² = 0%; Analysis 1.7; Figure 10).

Figure 10. Forest plot of comparison: I Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: I.7 Cardiac output: left ventricular output, as measured on echocardiogram.

Comparison 2. Oxygenation-guided LRM versus routine care for individualizing PEEP to an optimal level in preterm infants requiring CMV for RDS

Two studies enrolling 44 participants compared an oxygen-guided LRM versus routine care for individualizing PEEP to an optimal level in preterm infants requiring CMV for RDS (Castoldi 2011;

Wu 2014). Both studies contributed data to the following five outcomes.

Mortality by hospital discharge

The meta-analysis found no difference between an oxygen-guided LRM and routine care on the outcome of mortality by hospital discharge (RR 1.00, 95% CI 0.17 to 5.77; participants = 44;

studies = 2; $I^2 = 0\%$; [Analysis 2.1](#); [Figure 11](#)). We graded the quality of the evidence as low, due to risk of bias and imprecision of the estimate.

Figure 11. Forest plot of comparison: 2 Oxygenation-guided lung-recruitment maneuver versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: 2.1 Mortality by hospital discharge.

Bronchopulmonary dysplasia

The meta-analysis found no statistically significant difference between an oxygen-guided LRM and routine care on the outcome of BPD. The effect estimate favored an oxygen-guided LRM (RR 0.25, 95% CI 0.03 to 2.07; participants = 44; studies = 2; $I^2 = 0\%$; [Analysis 2.2](#); [Figure 12](#)). We graded the quality of the evidence as low, due to risk of bias and imprecision of the estimate.

Figure 12. Forest plot of comparison: 2 Oxygenation-guided lung-recruitment maneuver versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: 2.2 Bronchopulmonary dysplasia.

Duration of invasive ventilatory support

The meta-analysis found a statistically significant difference between an oxygen-guided LRM and routine care on the outcome of duration of ventilatory support, with the effect estimate favoring an oxygen-guided LRM (MD -1.06 days, 95% CI -1.85 to -0.26; participants = 44; studies = 2; $I^2 = 67\%$; moderate heterogeneity, $\text{Chi}^2 = 3.07$; $P = 0.08$). We graded the quality of the evidence as low, due to risk of bias and imprecision of the estimate ([Analysis 2.3](#); [Figure 13](#)).

Figure 13. Forest plot of comparison: 2 Oxygenation-guided lung-recruitment maneuver versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: 2.3 Duration of invasive ventilatory support.

Oxygenation measures: lowest fraction of inspired oxygen administered in the first 12 hours of life

The meta-analysis showed a statistically significant difference between an oxygen-guided LRM and routine care on the outcome of lowest FiO_2 administered in the first 12 hours of life to meet SpO_2 target (83% to 93% in [Castoldi 2011](#), 85% to 93% in [Wu 2014](#)), with the effect estimate favoring an oxygen-guided LRM (MD -3.94 %, 95% CI -5.51 to -2.36; participants = 44; studies = 2; $I^2 = 96\%$; [Analysis 2.4](#); [Figure 14](#)).

Figure 14. Forest plot of comparison: 2 Oxygenation-guided lung-recruitment maneuver versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: 2.4 Oxygenation measures: lowest fraction of inspired oxygen administered in the first 12 hours of life.

Oxygenation measures: arterial/alveolar oxygen ratio at end of lung-recruitment maneuver

The meta-analysis showed a statistically significant difference between an oxygen-guided LRM and routine care on the outcome of arterial/alveolar oxygen ratio at the end of the maneuver, with the effect estimate favoring an oxygen-guided LRM (MD 0.11, 95% CI 0.06 to 0.17; participants = 44; studies = 2; $I^2 = 0\%$; [Analysis 2.5](#); [Figure 15](#)). It is unclear how the timing of this measure was selected for participants in the control groups.

Figure 15. Forest plot of comparison: 2 Oxygenation-guided lung-recruitment maneuver versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, outcome: 2.5 Oxygenation measures: arterial/alveolar oxygen ratio at end of lung-recruitment maneuver.

tervention on patient-important outcomes are warranted. We do not believe that our current findings have implications for clinical practice.

DISCUSSION

Summary of main results

Evidence-based guidance for PEEP level selection in preterm infants continues to be limited. With this update, we identified four eligible trials contributing data to two of the three objectives of this review. To date, we have identified no eligible data addressing the effects of different PEEP levels in preterm infants with BPD on CMV (objective 2). We identified no data addressing our primary outcomes of mortality by hospital discharge and neurodevelopmental impairment - or any other clinically important outcomes - following the application of different PEEP levels in preterm infants with RDS on CMV (objective 1). Data from two small trials enrolling 28 participants compared the effects of different PEEP levels on pulmonary gas exchange measures and found no statistically or clinically significant difference between low and high PEEP levels. With this update, we identified data from two small trials enrolling 44 participants for the primary outcome of mortality by hospital discharge for objective 3, comparing the effects of different methods to individualize PEEP (in this case, an oxygen-guided LRM with gradual PEEP level titrations versus routine care) for infants with RDS on CMV. There was no difference in mortality between groups and the effect estimate was imprecise. Additional data from these two trials provided an imprecise, statistically insignificant effect estimate favoring the LRM for the outcome of BPD and effect estimates favoring the LRM on the outcomes of duration of invasive ventilatory support and oxygenation in the first 12 hours of life. We a priori judged the outcomes of mortality, BPD, and duration of invasive ventilatory support to be clinically important and included them in our [Summary of findings for the main comparison](#). These objective 3 findings are intriguing and suggest that an early LRM may be beneficial in preterm infants with RDS requiring CMV. We opine that larger trials to confirm these findings and more precisely measure the effect of this in-

Overall completeness and applicability of evidence

Our overall findings continue to be insufficiently complete to meaningfully address the objectives of this systematic review or to merit clinical practice recommendations. The overall findings are imprecise due to the small number of participants eligible for inclusion and except for objective 3, fail to address clinically important outcomes.

The data available for objective 1 have limited applicability to current practice. [Aufrecht 1995](#) was published 23 years ago and evaluated participants with a mean GA of nearly 31 completed weeks. Participants did not receive surfactant despite endotracheal intubation for RDS and 5/12 participants were sedated and paralyzed. In our experience, preterm infants with RDS undergoing CMV are now typically of a lower GA, routinely receive surfactant therapy, and are uncommonly sedated and paralyzed during CMV. Although we chose to include [Fajardo 2014](#) in objective 1, we recognize limitations in the applicability of data from this trial for these comparisons. The objective of [Fajardo 2014](#) was to assess the impact of PEEP level changes on right-to-left shunting through a patent ductus arteriosus (PDA); all participants had this complication of prematurity. The authors did not specify RDS in the inclusion criteria and enrolled some participants with a broader postnatal age than is consistent with RDS (2 to 71 days). This specific instance highlights broader concerns regarding the explicit inclusion of RDS in defining a population of interest for neonatal interventions. Although the incidence of RDS increases with decreasing GA ([Stoll 2010](#)), modern trials of early respiratory interventions in extremely preterm infants often do not list RDS among inclusion criteria. Rather, they base inclusion on GA, weight, postnatal age, respiratory support requirement, or a combination of these ([Morley 2008](#); [SUPPORT 2010](#)). We considered that restricting inclusion to trials explicitly specifying a diagnosis of RDS could exclude many participants in the intended popula-

tion: infants undergoing CMV for respiratory failure in the early postnatal period. Therefore, we amended the [Types of participants](#) eligible in this update, allowing studies that predominantly included preterm infants evaluated in the first two weeks of life when a diagnosis of RDS was not addressed. Nonetheless, it could be argued that infants requiring CMV in the setting of a PDA may differ in their response to different PEEP levels than infants on CMV for respiratory failure stemming from prematurity in the absence of a PDA. Thus, the contribution of data from [Fajardo 2014](#) should be interpreted with these limitations with respect to applicability in mind.

The data available for objective 3 are largely applicable to current practice. Both studies were published after 2010, enrolled participants commonly requiring CMV, and applied therapies consistent with modern practice, such as surfactant therapy and attempts to limit invasive ventilatory support. The only major discrepancy, perhaps, is the lower SpO₂ targets chosen by the study investigators (83% to 93%, 85% to 93%) than are now sometimes preferred following findings from the various trials of the NeOPRoM (Neonatal Oxygenation Prospective Meta-analysis) Collaboration ([Askie 2018](#)). While applying higher oxygen saturation targets could have influenced quantitative aspects of the LRM in each study (such as the FiO₂ or PEEP required to meet goal SpO₂ targets), we judged the overall rationale and process applied in these studies remains pertinent to modern practice.

Quality of the evidence

We graded the overall quality of the evidence for the three objective 3 comparisons listed in the [Summary of findings for the main comparison](#) to be low based on the GRADE approach, consistent with a limited confidence in the effect estimate ([Schünemann 2013](#)). For each, we arrived at this conclusion by starting with a default of 'high-quality' based on study design (RCT) and downgrading for both potential bias and imprecision. With respect to bias, we judged trials contributing data to have unclear risk with respect to performance and detection bias given no description of attempts at blinding and reporting bias given the lack of published or registered protocols ([Castoldi 2011](#); [Wu 2014](#)). Although it is uncertain and perhaps even unlikely that these limitations influenced the outcomes reported in [Summary of findings for the main comparison](#), we erred on the side of caution. Imprecision is a problem as the comparisons resulted from two small trials. For mortality to discharge and BPD, comparisons were based on a small number of events, contributing to wide CIs around the effect estimates. While the effect estimates for duration of invasive ventilatory support and oxygenation measures favoring an oxygen-guided LRM for PEEP level selection were statistically significant, they nonetheless reflect data from 44 participants and should be interpreted cautiously.

Potential biases in the review process

This review was limited by several potential sources of bias.

The electronic search strategies used in the original review and for this update were created a priori with a deliberate effort to maximize the sensitivity for identifying relevant trials. However, in the original review, only six of the 10 studies ultimately considered for inclusion resulted from the original electronic search. Of the four remaining articles, three were known and provided by one of our senior authors and one was identified through a search of the reference section of an article being considered for inclusion. For this update, one of included studies was similarly missed by the search strategy ([Fajardo 2014](#)), and identified based on our existing awareness of this publication. This suggests that our search strategies potentially lacked the sensitivity to identify all relevant studies that may contribute data to the objectives of this review.

A barrier to the inclusion of studies in this review was the restriction of data to the first period of cross-over studies. Generally, the effects of interventions in preceding cross-over periods may influence a measured outcome in subsequent cross-over periods, so called 'carry-over' or residual effects. We chose to restrict data to the first cross-over period given uncertainty related to the duration of time required for equilibration of lung volumes following a PEEP level change and the plausibility of LRMs (from PEEP increases) causing persistent physiologic changes despite subsequent PEEP level decrements. Indeed, the findings from [Castoldi 2011](#) and [Wu 2014](#) support the latter concern as valid. Several of the identified studies employed cross-over designs to assess the within-participant effects of different PEEP levels in infants with RDS on CMV ([Herman 1973](#); [Aufrecht 1995](#); [Dimitriou 1999](#); [Dinger 2001](#); [Fajardo 2014](#)). Of these studies, we were only able to restrict data to the first cross-over period for [Aufrecht 1995](#) and [Fajardo 2014](#). This criterion of restricting data to the first cross-over period may have excluded valuable data from this review. Further, in the included studies, relatively small samples were randomized to three possible initial PEEP levels, making randomization imbalance in baseline characteristics plausible. For [Fajardo 2014](#), a comparison of low and high PEEP groups as prespecified for this review resulted in a lower point estimate for FiO₂ and LVO in the low-PEEP group following the first cross-over period. In contrast, summary data collapsed across the three cross-over periods of the original study suggest a slight increase in FiO₂ at lower PEEP levels, while LVO was lower at PEEP 8 cmH₂O in comparison to 5 cmH₂O (although not in comparison to 2 cmH₂O). This may reflect chance randomization in the first cross-over period allocations.

For the purpose of this review, we created a dichotomy that defines low PEEP as less than 5 cmH₂O and high PEEP as 5 cmH₂O or greater. Although there are some data to suggest 5 cmH₂O is an appropriate cut-off value ([da Silva 1994](#)), and this level is commonly selected as an initial PEEP level in practice ([Bamat 2018](#)), this dichotomy is by necessity arbitrary. Both studies included in objective 1 assessed the effect of three separate PEEP

levels (Aufricht 1995; Fajardo 2014), applying a cross-over trial with random sequence allocation. As specified a priori, outcomes obtained at various PEEP levels were combined to create low PEEP (2 cmH₂O and 4 cmH₂O) and high PEEP (5 cmH₂O, 6 cmH₂O and 8 cmH₂O) groups for comparison. As the pressure difference in PEEP level between infants assigned to, for example, 5 cmH₂O and 8 cmH₂O (both high PEEP group) is quantitatively greater than the difference between, for example, 4 cmH₂O and 5 cmH₂O (one low, one high PEEP group) the limitations of our arbitrary dichotomy are highlighted by the data available from these trials.

Agreements and disagreements with other studies or reviews

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

AUTHORS' CONCLUSIONS

Implications for practice

Evidence-based guidance for positive end-expiratory pressure (PEEP) level selection in preterm infants continues to be limited. We are unable to make recommendations for clinical practice based on the results of this review.

Implications for research

The findings of this review should raise awareness of the lack of evidence guiding the selection of PEEP levels in preterm infants undergoing conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia and encourage further well-designed trials.

The findings of this review suggest that an individualized approach to PEEP level selection that applies gradual PEEP level titrations during an oxygenation-guided lung-recruitment maneuver may result in improved oxygenation and a shorter duration of invasive ventilatory support. Larger studies to confirm these findings and more precisely measure the effect of this intervention on patient-important outcomes are warranted.

ACKNOWLEDGEMENTS

We wish to acknowledge Drs Gabriel Dimitriou, George Simbruner, Nelson Claire, and Jacqueline Jauncey-Cooke for their helpful responses to our inquiries. We acknowledge Dr Sanghee Suh for her important contributions to the original review. We are immensely grateful to Colleen Ovelman, Jennifer Spano, and Dr Roger Soll of Cochrane Neonatal for their technical assistance and guidance in the preparation of this review update.

REFERENCES

References to studies included in this review

Aufricht 1995 {published data only}

Aufricht C, Frenzel K, Votava F, Simbruner G. Quasistatic volume-pressure curve to predict the effects of positive end-expiratory pressure on lung mechanics and gas exchange in neonates ventilated for respiratory distress syndrome. *American Journal of Perinatology* 1995;**12**(1):67–72. DOI: 10.1055/s-2007-994405; PUBMED: 7710583

Castoldi 2011 {published data only}

Castoldi F, Daniele I, Fontana P, Cavigioli F, Lupo E, Lista G. Lung recruitment maneuver during volume guarantee ventilation of preterm infants with acute respiratory distress syndrome. *American Journal of Perinatology* 2011;**28**(7): 521–27. DOI: 10.1055/s-0031-1272970; PUBMED: 21380992

Fajardo 2014 {published and unpublished data}

Fajardo MF, Claire N, Swaminathan S, Sattar S, Vazquez A, D'Ugard C, et al. Effect of positive end-expiratory pressure on ductal shunting and systemic blood flow in preterm infants with patent ductus arteriosus. *Neonatology* 2014;**105**:9–13. DOI: 10.1159/000355146; PUBMED: 2961141

Wu 2014 {published data only}

Wu R, Li SB, Tian ZF, Li N, Zheng GF, Zhao YX, et al. Lung recruitment maneuver during proportional assist ventilation of preterm infants with acute respiratory distress syndrome. *Journal of Perinatology* 2014;**34**:524–7. DOI: 10.1038/jp.2014.53; PUBMED: 24699217

References to studies excluded from this review

Belenky 1976 {published data only}

Belenky DA, Orr RJ, Woodrum DE, Hodson WA. Is continuous transpulmonary pressure better than conventional respiratory management of hyaline membrane disease? A controlled study. *Pediatrics* 1976;**58**(6):800–8. PUBMED: 792789]

Dimitriou 1999 {published data only (unpublished sought but not used)}

Dimitriou G, Greenough A, Laubscher B. Appropriate positive end expiratory pressure level in surfactant-treated preterm infant. *European Journal of Pediatrics* 1999;**158** (11):888–91. PUBMED: 10541942]

Dinger 2001 {published data only (unpublished sought but not used)}

Dinger J, Topfer A, Schaller P, Schwarze R. Effect of positive end expiratory pressure on functional residual capacity and

- compliance in surfactant treated preterm infants. *Journal of Perinatal Medicine* 2001;**29**(2):137–43. DOI: 10.1515/JPM.2001.018; PUBMED: 11344672
- Durbin 1976** *[published data only]*
Durbin GM, Hunter NJ, McIntosh N, Reynolds EO, Wimberley PD. Controlled trial of continuous inflating pressure for hyaline membrane disease. *Archives of Disease in Childhood* 1976;**51**(3):163–9. PUBMED: 782375]
- Finer 2004** *[published data only]*
Finer NN, Carlo WA, Duara S, Fanaroff AA, Donovan EF, Wright LL, et al. Delivery room continuous positive airway pressure/positive end expiratory pressure in extremely low birth weight infants: a feasibility trial. *Pediatrics* 2004;**114**(3):651–7. DOI: 10.1542/peds.2004-0394; PUBMED: 15342835
- Hausdorf 1987** *[published data only]*
Hausdorf G, Hellwege HH. Influence of positive end-expiratory pressure on cardiac performance in premature infants: a Doppler-echocardiographic study. *Critical Care Medicine* 1987;**15**(7):661–4. PUBMED: 3297490]
- Herman 1973** *[published data only (unpublished sought but not used)]*
Herman S, Reynolds EO. Methods for improving oxygenation in infants mechanically ventilated for severe hyaline membrane disease. *Archives of Disease in Childhood* 1973;**48**(8):612–7. PUBMED: 4783001]
- Jauncey-Cooke 2012** *[published and unpublished data]*
Jauncey-Cook J, Pham T, Grant CA, Bogossian F, East CE, Schibler A. Lung recruitment by manipulating peep following endotracheal suction improves end expiratory lung volume and oxygenation. *Australian Critical Care* 2012;**25**(2):127. DOI: doi.org/10.1016/j.aucc.2011.12.018
- Simbruner 1989** *[published data only (unpublished sought but not used)]*
Simbruner G, Popow C, Aufricht C. The effect of PEEP in lung mechanics and blood gases in mechanically ventilated newborn infants. *Pediatric Research* 1989;**26**:508. DOI: doi.org/10.1203/00006450-198911000-00051
- Stewart 1981** *[published data only (unpublished sought but not used)]*
Stewart AR, Finer NN, Peters KL. Effects of alterations of inspiratory and expiratory pressures and inspiratory/expiratory ratios on mean airway pressure, blood gases and intracranial pressure. *Pediatrics* 1981;**67**(4):474–81. PUBMED: 6789294]
- Additional references**
- Askie 2018**
Askie LM, Darlow BA, Finer N, Schmidt B, Stenson B, Tarnow-Mordi W, et al. Association between oxygen saturation targeting and death or disability in extremely preterm infants in the neonatal oxygenation prospective meta-analysis collaboration. *JAMA* 2018;**319**(21):2190–201. DOI: 10.1001/jama.2018.5725.; PUBMED: 29872859
- Bamat 2018**
Bamat NA, Guevara JP, Bryan M, Roberts RS, Yoder BA, Lemyre B, et al. Variation in positive end-expiratory pressure levels for mechanically ventilated extremely low birth weight infants. *Journal of Pediatrics* 2018;**194**:28–33. DOI: dx.doi.org/10.1016/j.jpeds.2017.10.065; PUBMED: 29275926
- Bartholomew 1994**
Bartholomew KM, Brownlee KG, Snowden S, Dear PR. To PEEP or not to PEEP?. *Archives of Disease in Childhood* 1994;**70**:F209–12. DOI: dx.doi.org/10.1136/fn.70.3.F209
- Bonta 1977**
Bonta BW, Uauy R, Warshaw JB, Motoyama EK. Determination of optimal continuous positive airway pressure for the treatment of IRDS by measurement of esophageal pressure. *Journal of Pediatrics* 1977;**91**(3):449–54. [PUBMED: 330831]
- Boros 1979**
Boros SJ. Variations in inspiratory:expiratory ratio and airways pressures wave form during mechanical ventilation: the significance of mean airways pressure. *Journal of Pediatrics* 1979;**94**(1):114–7. [PUBMED: 758387]
- Corbridge 1990**
Corbridge TC, Wood LD, Crawford GP, Chudoba MJ, Yanos J, Sznajder JL. Adverse effects of large tidal volume and low PEEP in canine acid aspiration. *American Review of Respiratory Disease* 1990;**142**(2):311–5. DOI: 10.1164/ajrccm/142.2.311; PUBMED: 2200314
- da Silva 1994**
da Silva WJ, Abbasi S, Pereira G, Bhutani VK. Role of positive end-expiratory pressure changes on functional residual capacity in surfactant treated preterm infants. *Pediatric Pulmonology* 1994;**18**(2):89–92. [PUBMED: 7970924]
- Danan 2008**
Danan C, Durrmeyer X, Brochard L, Decobert F, Benani M, Dassieu G. A randomized trial of delayed extubation for the reduction of reintubation in extremely preterm infants. *Pediatric Pulmonology* 2008;**43**(2):117–24. DOI: 10.1002/ppul.20726; PUBMED: 18092355
- Fischer 2013**
Fischer HS, Bühner C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2013;**132**(5):e1351–60. DOI: 10.1542/peds.2013-1880; PUBMED: 24144716
- Froese 1993**
Froese AB, McMulloch PR, Sugiura M, Vaclavik S, Possmayer F, Moller F. Optimizing alveolar expansion prolongs the effectiveness of exogenous surfactant therapy in the adult rabbit. *American Review of Respiratory Disease* 1993;**148**(3):569–77. DOI: 10.1164/ajrccm/148.3.569; PUBMED: 8368625
- GRADEpro [Computer program]**
McMaster University (developed by Evidence Prime). GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.
- Greenough 1992**
Greenough A, Chan V, Hird MF. Positive end expiratory pressure in acute and chronic respiratory distress. *Archives*

- of Disease in Childhood 1992;**67**(3):320–3. [PUBMED: 1575557]
- Gregory 1971**
Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory distress syndrome with continuous positive airways pressure. *New England Journal of Medicine* 1971;**284**(24):1333–40. DOI: 10.1056/NEJM197106172842401; PUBMED: 4930602
- Higgins 2011**
Higgins JP, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.
- Klingenberg 2017**
Klingenberg C, Wheeler KI, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in neonates. *Cochrane Database of Systematic Reviews* 2017, Issue 10. DOI: 10.1002/14651858.CD003666.pub4
- Martin 1977**
Martin RJ, Nearman HS, Katona PG, Klaus MH. Effect of a low continuous positive airway pressure on reflex control of respiration in preterm infant. *Journal of Pediatrics* 1977; **90**(6):976–81. [PUBMED: 323448]
- Mathe 1987**
Mathe JC, Clement A, Chevalier JY, Gaultier C, Costil J. Use of total inspiratory pressure-volume curves for determination of appropriate positive end expiratory pressure in newborns with hyaline membrane disease. *Intensive Care Medicine* 1987;**13**(5):332–6. [PUBMED: 3308991]
- Monkman 2003**
Monkman S, Kirpalani H. PEEP - a “cheap” and effective lung protection. *Paediatric Respiratory Reviews* 2003;**4**(1): 15–20.
- Monkman 2004**
Monkman SL, Andersen CC, Nahmias C, Ghaffer H, Bourgeois JM, Roberts RS, et al. Positive end expiratory pressure above lower inflection point minimizes influx of activated neutrophils into lung. *Critical Care Medicine* 2004;**32**(12):2471–5. [PUBMED: 15599153]
- Morley 2008**
Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, et al. Nasal CPAP or intubation at birth for very preterm infants. *New England Journal of Medicine* 2008;**358** (7):700–8. DOI: 10.1056/NEJMx080008
- Muller 1979**
Muller NL, Bryan AC. Chest wall mechanics and respiratory muscles in infants. *Pediatric Clinics of North America* 1979; **26**(3):503–16. [PUBMED: doi.org/10.1016/S0031–3955 (16)33745–2]
- Papile 1978**
Papile L, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *Journal of Pediatrics* 1978;**92**(4):529–34. [PUBMED: 305471]
- Patel 2015**
Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, et al. Causes and timing of death in extremely premature infants from 2000 through 2011. *New England Journal of Medicine* 2015;**372**(4):331–40. DOI: 10.1056/NEJMoa1403489; PUBMED: 25607427
- Review Manager 2014 [Computer program]**
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- Richardson 1978**
Richardson CP, Jung AL. Effects of continuous positive airway pressure on pulmonary function and blood gases of infants with respiratory distress syndrome. *Pediatric Research* 1978;**12**(7):771–4. DOI: 10.1203/00006450-197807000-00006; PUBMED: 358112
- Santa Cruz 2013**
Santa Cruz R, Rojas JI, Nervi R, Heredia R, Ciapponi A. High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2013, Issue 6. DOI: 10.1002/14651858.CD009098.pub2
- Schmidt 2003**
Schmidt B, Asztalos EV, Roberts RS, Robertson CMT, Sauve RS, Whitfield MF, et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months, results from the trial of Indomethacin prophylaxis in preterms. *JAMA* 2003;**289**(9):1124–9. [PUBMED: 12622582]
- Schmölzer 2013**
Schmölzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. *BMJ* 2013;**347**:f5980. DOI: 10.1136/bmj.f5980; PUBMED: 24136633
- Schünemann 2013**
Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s), GRADE Working Group. 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/app/handbook/handbook.html.
- Slutsky 2013**
Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *New England Journal of Medicine* 2013;**369**(22):2126–36. DOI: 10.1056/NEJMra1208707; PUBMED: 24283226
- Stoll 2010**
Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely

preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 2010;**126**(3):443–56. DOI: 10.1542/peds.2009-2959; PUBMED: 20732945

SUPPORT 2010

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, et al. Early CPAP versus surfactant in extremely preterm infants. *New England Journal of Medicine* 2010;**362**(21):1970–9. DOI: 10.1056/NEJMoa0911783; PUBMED: 20472939

Thome 1998

Thome U, Topfer A, Schaller P, Pohlandt F. The effect of positive end expiratory pressure, peak inspiratory pressure and inspiratory time on functional residual capacity in mechanically ventilated preterm infants. *European Journal of Pediatrics* 1998;**157**(10):831–7. [PUBMED: 9809824]

Ueda 1994

Ueda T, Ikegami M, Jobe AH. Developmental changes of sheep surfactant: in vivo function and in vitro subtype conversion. *Journal of Applied Physiology* 1994;**76**(6):2701–6. DOI: 10.1152/jappl.1994.76.6.2701; PUBMED: 7928903

References to other published versions of this review

Bamat 2012

Bamat N, Millar D, Suh S, Kirpalani H. Positive end expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia. *Cochrane Database of Systematic Reviews* 2012, Issue 1. DOI: 10.1002/14651858.CD004500.pub2

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Aufricht 1995

Methods	3 period cross-over trial with random sequence allocation Randomization to intervention sequence via random tables, no blinding of intervention or outcome ascertainment, follow-up complete	
Participants	13 infants from 1 center in Vienna, Austria with RDS diagnosed based on clinical, radiologic, and blood gas findings Inclusion criteria: none stated Exclusion criteria: none stated Infants with mean GA of 30.8 (SD 2.6) weeks were randomized at 1.5 (SD 0.6) days of life. Participants did not receive surfactant. All infants intubated with uncuffed endotracheal tubes and received CMV with Drager Babylog ventilator. Infants were sedated with chloral hydrate and paralyzed with pancuronium and ventilated with controlled ventilation (n = 5 infants); sedated with chloral hydrate and hyperventilated to PaCO ₂ < 35 mmHg with controlled ventilation (n = 1); or received no sedation while spontaneously breathing on CMV (n = 7)	
Interventions	Initially randomized to PEEP levels of 2 cmH ₂ O (n = 4), 4 cmH ₂ O (n = 6), or 6 (n = 3) cmH ₂ O from unspecified baseline. Maintained at PEEP level for 30 minutes prior to being crossed over to next level in random allocation sequence	
Outcomes	<ul style="list-style-type: none">Primary study outcome/objective: to determine if characteristics of the baseline pressure/volume curve could predict the responses of lung compliance and oxygenation following PEEP level changes.Outcomes eligible for this review: PaCO₂; AaDO₂, both obtained through arterial blood sampling.Outcomes measured following maintenance at specified PEEP level for 30 minutes.	
Notes	Qualified for objective 1: to compare the effects of different levels of PEEP in preterm infants requiring CMV for RDS <ul style="list-style-type: none">Data and results provided for each infant after each cross-over period, allowing isolation of data after first cross-over period and inclusion in study.For review, we combined 2 cmH₂O and 4 cmH₂O as 'low PEEP' vs 6 cmH₂O as 'high PEEP.' Quote: "Peak pressures were simultaneously altered to keep inflation pressures (peak pressure, PEEP) constant. Other respiratory settings were not changed."	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence determined by random tables.

Allocation concealment (selection bias)	Unclear risk	Not addressed
Blinding (performance bias and detection bias) All outcomes	Low risk	Not addressed, but unlikely given nature of intervention and methods. Unlikely to influence outcomes reported in this review
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome ascertainment complete
Selective reporting (reporting bias)	Unclear risk	Protocol registration not addressed in manuscript
Other bias	High risk	For 1 infant, PaCO ₂ provided as measured outcome result despite ventilation technique which deliberately hyperventilated infant to achieve prespecified PaCO ₂ goal. Participant excluded from analysis.

Castoldi 2011

Methods	2-arm, parallel-group RCT Randomization via sequentially numbered, sealed, opaque envelopes. Blinding of intervention or outcome ascertainment not addressed, follow-up complete
Participants	20 infants from 1 center in Milan, Italy with RDS diagnosed based on clinical and radiologic findings and exclusion of other causes of respiratory failure Inclusion criteria: GA < 27 weeks, ≥ 1 course of prenatal corticosteroids and requirement of endotracheal intubation and CMV within the first hour of life Exclusion criteria: lethal congenital anomalies and IVH > grade 2 All participants received surfactant immediately after endotracheal intubation. CMV provided with assist/control ventilation + volume guarantee (Babylog 8000 plus, Dräger) with starting parameters of: Tv 6 mL/kg, Ti 0.3 seconds, respiratory rate 60/minute, PIP 25 cmH ₂ O, PEEP 5 cmH ₂ O. Randomization and intervention occurred within the first 3 hours of life
Interventions	Randomized to either receive LRM or no LRM. LRM consisted of a starting PEEP of 5 cmH ₂ O, followed by repeated increments by 0.2 cmH ₂ O every 5 minutes while evaluating for improvements in oxygenation by monitoring SpO ₂ levels (target 83-93%) and FiO ₂ requirement. PEEP progressively increased if oxygenation improved. If FiO ₂ reached 0.25, a slow stepwise PEEP reduction was started until oxygenation worsened. This was followed by a re-increase in PEEP until "stable oxygenation was achieved and the FiO ₂ level reached levels prior to the fall in oxygenation." The mean baseline PEEP level was 5 (SD 0.2) cmH ₂ O in both groups, reached a mean maximal level of 6.1 (SD 0.3) cmH ₂ O in the LRM group vs 5.3 (SD 0.3) cmH ₂ O in the control group and a mean final PEEP of 5.0 (SD 0.3) cmH ₂ O in the LRM group vs 5.1 (SD 0.3) cmH ₂ O in the control group.

Outcomes	<ul style="list-style-type: none"> Primary study outcome/objective: not explicitly stated, but hypothesis was that (LRM) “would lead to a shorter need for FiO₂ and a more rapid achievement of better oxygenation.” Outcomes eligible for this review: mortality by hospital discharge; incidence of BPD (NIH consensus criteria referenced, reported as “moderate/severe” BPD, composite of death or BPD not provided but “we calculated BPD in survivors”); duration of invasive ventilatory support (unclear if this referred to total postnatal days or duration of initial ventilatory course); measures of oxygenation (lowest FiO₂ to maintain SpO₂ targets in the first 12 hours of life and arterial/alveolar oxygen ratio, seemingly at conclusion of LRM, but unclear).
Notes	Qualified for objective 3: to compare the effects of different methods for individualizing PEEP to an optimal level in preterm newborn infants requiring CMV for RDS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequentially numbered randomly selected envelopes
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not addressed, but unlikely given nature of intervention and methods and could have influenced some eligible outcomes, such as duration of ventilatory support
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome ascertainment complete
Selective reporting (reporting bias)	Unclear risk	Protocol registration not addressed in manuscript
Other bias	Low risk	

Fajardo 2014

Methods	3 period cross-over trial with random sequence allocation Intervention sequence “determined at random” (no further details provided). Blinding of intervention or outcome ascertainment not addressed. Follow-up complete
Participants	16 infants from 1 center in Miami, US RDS diagnosis not addressed Inclusion criteria: GA < 32 weeks, BW < 2 kg, requirement of CMV, presence of patent ductus arteriosus Exclusion criteria: not specified

	Presence or absence of surfactant administration and ventilation modes or parameters not addressed Mean GA of 26 (range 23-30) weeks; aged 6 (range 2-71) day	
Interventions	Evaluated at PEEP levels of: baseline (5 cmH ₂ O for all but 1 participant with baseline 4 cmH ₂ O); - 3 cmH ₂ O from baseline; and + 3 cmH ₂ O from baseline; therefore, typically 2 cmH ₂ O, 5 cmH ₂ O, and 8 cmH ₂ O, in random order. PIP levels adjusted to maintain the difference between PIP and PEEP constant. Maintained at each PEEP level for 10-20 minutes	
Outcomes	<ul style="list-style-type: none">• Primary study outcome/objective: evaluate impact of PEEP level changes on left-to-right shunting through the patent ductus arteriosus, as measured by LVO, SVC flow and the LVO/SVC flow ratio.• Outcomes eligible and obtained for this review were: measures of oxygenation (FiO₂ to maintain unspecified SpO₂ target); transcutaneous carbon dioxide levels; direct measures of cardiac output (LVO, as measured by echocardiography).• Outcomes measured after 10 minutes of stabilization at each PEEP level.	
Notes	Qualified for objective 1: comparison of different levels of PEEP in preterm infants requiring CMV for RDS <ul style="list-style-type: none">• Individual participant random sequence allocation and outcomes provided by corresponding author, allowing inclusion of data with restriction of outcomes to first cross-over period.• Participants randomized to initial PEEP 2 cmH₂O (n = 5) and PEEP 4 cmH₂O (n = 1) were considered 'low PEEP,' while participants randomized to initial PEEP 5 cmH₂O (n = 5) and PEEP 8 cmH₂O (n = 5) were considered 'high PEEP' as per dichotomy prespecified for this review.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not addressed
Allocation concealment (selection bias)	Unclear risk	Not addressed
Blinding (performance bias and detection bias) All outcomes	Low risk	Not addressed, but unlikely given nature of intervention and methods. However, unlikely to have influenced eligible outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome ascertainment complete
Selective reporting (reporting bias)	Unclear risk	Protocol registration not addressed in manuscript.

Other bias	High risk	Comparison of data prespecified for review and summary data collapsed across cross-over periods of original study suggested chance randomization imbalance in first cross-over period (see 'Discussion')
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Wu 2014

Methods	2-arm, parallel-group RCT Randomization via sequentially numbered, sealed, opaque envelopes. Blinding of intervention or outcome ascertainment not addressed, follow-up complete
Participants	24 infants from 1 center in Huaian, China with RDS diagnosed based on clinical and radiologic findings Inclusion criteria: GA 28-30 weeks, BW 1000-1500 g, ≥ 1 course of prenatal corticosteroids and requirement of endotracheal intubation and CMV within the first 6 hours of life Exclusion criteria: lethal congenital anomalies, IVH $>$ grade 2 and weak or absent spontaneous breathing All participants received surfactant immediately after endotracheal intubation. CMV provided with proportional assisted ventilation (Stephanie infant ventilator) with starting parameters of: Tv 4-6 mL/kg, PEEP 5 cmH ₂ O, backup ventilation after 10 seconds without spontaneous breathing suppressed with reinitiation of spontaneous breaths Randomization and intervention occurred within the "second 2 hours of life."
Interventions	Randomized to either receive LRM or no LRM. LRM consisted of a starting PEEP 5 cmH ₂ O, followed by repeated increments by 0.2 cmH ₂ O of PEEP every 5 minutes while evaluating for improvements in oxygenation by monitoring SpO ₂ levels (target 85-93%) and FiO ₂ requirements. PEEP progressively increased if oxygenation improved. If FiO ₂ reached 0.25, a slow stepwise PEEP reduction was started until oxygenation worsened. This was followed by a re-increase in PEEP until "stable oxygenation was achieved and the FiO ₂ level reached levels prior to the fall in oxygenation." The mean baseline PEEP level was 6.6 (SD 0.5) cmH ₂ O in the LRM group and 6.5 (SD 0.5) cmH ₂ O in the control group, reached a mean maximal level of 8.4 (SD 0.5) cmH ₂ O in the LRM group vs 6.7 (SD 0.6) cmH ₂ O in the control group and a mean final PEEP of 6.4 (SD 0.4) cmH ₂ O in the LRM group vs 6.6 (SD 0.4) cmH ₂ O in the control group.
Outcomes	<ul style="list-style-type: none"> Primary study outcome/objective: primary outcome not stated, objective was to investigate effects of LRM with PEEP on "oxygenation and outcomes." Outcomes eligible for this review: mortality by hospital discharge; incidence of BPD (defined as oxygen requirement at 36 weeks postmenstrual age, composite of death or BPD not provided); duration of invasive ventilatory support (unclear if this referred to total postnatal days or duration of initial ventilatory course); measures of oxygenation (lowest FiO₂ to maintain SpO₂ targets in the first 12 hours of life and arterial/alveolar oxygen ratio at conclusion of LRM).
Notes	Qualifies for objective 3: comparison of different methods for individualizing PEEP in preterm infants requiring CMV for RDS

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequentially numbered randomly selected envelopes
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not addressed, but unlikely given nature of intervention and methods and could have influenced some eligible outcomes, such as duration of ventilatory support
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome ascertainment complete
Selective reporting (reporting bias)	Unclear risk	Protocol registration not addressed in manuscript
Other bias	Low risk	

AaDO₂: alveolar to arterial oxygen tension difference; BPD: bronchopulmonary dysplasia; BW: birth weight; CMV: conventional mechanical ventilation; FiO₂: fraction of inspired oxygen; GA: gestational age; IVH: intraventricular hemorrhage; LRM: lung-recruitment maneuver; LVO: left ventricular output; n: sample size; NIH: National Institutes of Health; PaCO₂: arterial carbon dioxide pressure; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; RCT: randomized controlled trials; RDS: respiratory distress syndrome; SD: standard deviation; SpO₂: peripheral oxygen saturation; SVC: superior vena cava; Ti: inspiratory time; Tv: tidal volume.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Belenky 1976	Study did not meet criteria for inclusion. Abstract suggested possibility for a comparison of PEEP (intervention) vs ZEEP (control) in infants receiving CMV for RDS. Detailed review of methods revealed that the control group intervention did not include CMV unless the infant experienced clinical deterioration
Dimitriou 1999	Study met inclusion criteria but employed a cross-over study design. Outcome data were not presented to allow isolation of data obtained after the first cross-over period, as specified for inclusion. Contacted author who replied that the original data necessary for isolation of the relevant data were no longer available
Dinger 2001	Study met inclusion criteria but employed a cross-over study design. Outcome data were not presented to allow isolation of data obtained after the first cross-over period, as specified for inclusion. Attempts at contacting authors were unsuccessful

(Continued)

Durbin 1976	Abstract suggested possibility for a comparison of PEEP (intervention) vs ZEEP (control) in infants receiving CMV for RDS. Detailed review of methods revealed that infants randomized to the intervention group received either PEEP ("CPAP via an oroendotracheal tube") or continuous inflating pressure via a negative pressure tank, with only those infants deemed "seriously ill" receiving PEEP. This would have created a selection bias, with randomly selected controls compared against selected, "seriously ill," participants in the intervention group of interest
Finer 2004	Study did not meet criteria for inclusion. Initial uncertainty resulted from the use of the term PEEP to describe non-invasive continuous distending airway pressure in the context of delivery room resuscitation
Hausdorf 1987	Study did not meet criteria for inclusion. Abstract suggested possibility for a comparison of ZEEP vs low PEEP vs high PEEP in infants receiving CMV for RDS. Detailed review of methods revealed that the 3 different levels were applied in sequence to each participant. Randomization of participants to different PEEP levels did not occur
Herman 1973	Study methodology unclear. Potentially a 6-period cross-over design with randomization. Additional information and data would be required from study authors for consideration of inclusion. Efforts at correspondence with the study authors made without success
Jauncey-Cooke 2012	Published conference abstract. Details of patient population unclear; correspondence with author confirmed study performed in older children rather than preterm infants
Simbruner 1989	Report was available in abstract form only. The abstract suggested possibility for a comparison of low PEEP vs high PEEP in infants receiving CMV for RDS. Author was contacted for unpublished materials and replied that it was no longer available
Stewart 1981	Study did not meet criteria for inclusion. Abstract suggested possibility for a comparison of different PEEP levels in infants receiving CMV for RDS. Detailed review of methods revealed that infants were not randomized to specific PEEP levels, instead undergoing specified alterations in PEEP levels from different individual baselines

CMV: conventional mechanical ventilation; CPAP: continuous positive airway pressure; PEEP: positive end-expiratory pressure; RDS: respiratory distress syndrome; ZEEP: zero end-expiratory pressure.

DATA AND ANALYSES

Comparison 1. Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oxygenation measures: various, combined with standardized mean differences	2	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-1.12, 0.50]
2 Oxygenation measures: alveolar to arterial oxygen tension difference	1	12	Mean Difference (IV, Fixed, 95% CI)	-61.90 [-189.06, 65.26]
3 Oxygenation measures: fraction of inspired oxygen administered	1	16	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-11.87, 6.27]
4 Arterial or transcutaneous carbon dioxide pressure, combined with standardized mean differences	2	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.84, 0.76]
5 Arterial carbon dioxide pressure	1	12	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-16.56, 12.96]
6 Transcutaneous carbon dioxide pressure	1	16	Mean Difference (IV, Fixed, 95% CI)	0.70 [-13.62, 15.02]
7 Cardiac output: left ventricular output, as measured on echocardiogram	1	16	Mean Difference (IV, Fixed, 95% CI)	-126.0 [-201.58, -50.42]

Comparison 2. Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality by hospital discharge	2	44	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.17, 5.77]
2 Bronchopulmonary dysplasia	2	44	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.07]
3 Duration of invasive ventilatory support	2	44	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.85, -0.26]
4 Oxygenation measures: lowest fraction of inspired oxygen administered in the first 12 hours of life	2	44	Mean Difference (IV, Fixed, 95% CI)	-3.94 [-5.51, -2.36]
5 Oxygenation measures: arterial/alveolar oxygen ratio at end of LRM	2	44	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.06, 0.17]

Analysis 1.1. Comparison 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 1 Oxygenation measures: various, combined with standardized mean differences.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 1 Oxygenation measures: various, combined with standardized mean differences

Analysis 1.2. Comparison 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 2 Oxygenation measures: alveolar to arterial oxygen tension difference.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 2 Oxygenation measures: alveolar to arterial oxygen tension difference

Analysis 1.3. Comparison 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 3 Oxygenation measures: fraction of inspired oxygen administered.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 3 Oxygenation measures: fraction of inspired oxygen administered

Analysis 1.4. Comparison 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 4 Arterial or transcutaneous carbon dioxide pressure, combined with standardized mean differences.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 4 Arterial or transcutaneous carbon dioxide pressure, combined with standardized mean differences

Analysis 1.5. Comparison 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 5 Arterial carbon dioxide pressure.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 5 Arterial carbon dioxide pressure

Analysis 1.6. Comparison 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 6 Transcutaneous carbon dioxide pressure.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 6 Transcutaneous carbon dioxide pressure

Analysis 1.7. Comparison 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 7 Cardiac output: left ventricular output, as measured on echocardiogram.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 1 Low PEEP (less than 5 cmH₂O) versus high PEEP (5 cmH₂O or greater) in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 7 Cardiac output: left ventricular output, as measured on echocardiogram

Analysis 2.1. Comparison 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 1 Mortality by hospital discharge.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 1 Mortality by hospital discharge

Analysis 2.2. Comparison 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 2 Bronchopulmonary dysplasia.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 2 Bronchopulmonary dysplasia

Analysis 2.3. Comparison 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 3 Duration of invasive ventilatory support.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 3 Duration of invasive ventilatory support

Analysis 2.4. Comparison 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 4 Oxygenation measures: lowest fraction of inspired oxygen administered in the first 12 hours of life.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 4 Oxygenation measures: lowest fraction of inspired oxygen administered in the first 12 hours of life

Analysis 2.5. Comparison 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome, Outcome 5 Oxygenation measures: arterial/alveolar oxygen ratio at end of LRM.

Review: Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia

Comparison: 2 Oxygen-guided lung-recruitment maneuver (LRM) versus routine care for individualizing PEEP to an optimal level in preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome

Outcome: 5 Oxygenation measures: arterial/alveolar oxygen ratio at end of LRM

ADDITIONAL TABLES

Table 1. Table of comparisons

A. PEEP vs ZEEP in preterm infants requiring CMV for RDS (objective 1)

Planned subgroups: gestational age (< 28 weeks, 28-31 weeks, ≥ 32 weeks) and presurfactant vs postsurfactant therapy

Outcomes

- Mortality by hospital discharge
- Neurodevelopmental impairment at approximately 2 years' corrected age
- Incidence of BPD
- Incidence of air leak syndromes
- Duration of invasive ventilatory support
- Oxygenation measures
- PaCO₂ or transcutaneous CO₂ levels
- Cardiac output
- Blood pressure measurements and requirement for fluid boluses/inotropic support
- Brain injury
- Functional residual capacity

Table 1. Table of comparisons (Continued)

<p>B. Low PEEP vs high PEEP in preterm infants requiring CMV for RDS (objective 1)</p> <p>Planned subgroups: gestational age (< 28 weeks, 28-31 weeks, ≥ 32 weeks) and presurfactant vs postsurfactant therapy</p> <p>Outcomes</p> <ul style="list-style-type: none"> • Mortality by hospital discharge • Neurodevelopmental impairment at approximately 2 years' corrected age • Incidence of BPD • Incidence of air leak syndromes • Duration of invasive ventilatory support • Oxygenation measures • PaCO₂ or transcutaneous CO₂ levels • Cardiac output • Blood pressure measurements and requirement for fluid boluses/inotropic support • Brain injury • Functional residual capacity
<p>C. PEEP vs ZEEP in preterm infants requiring CMV for BPD (objective 2)</p> <p>Outcomes</p> <ul style="list-style-type: none"> • Mortality by 2 years of age • Neurodevelopmental impairment at approximately 2 years' corrected age • Incidence of air leak syndromes • Duration of invasive ventilatory support • Oxygenation measures • PaCO₂ or transcutaneous CO₂ levels • Cardiac output • Blood pressure measurements and requirement for fluid boluses/inotropic support • Brain injury • Functional residual capacity
<p>D. Low PEEP vs high PEEP in preterm infants requiring CMV for BPD (objective 2)</p> <p>Outcomes</p> <ul style="list-style-type: none"> • Mortality by 2 years of age • Neurodevelopmental impairment at approximately 2 years' corrected age • Incidence of air leak syndromes • Duration of invasive ventilatory support • Oxygenation measures • PaCO₂ or transcutaneous CO₂ levels • Cardiac output • Blood pressure measurements and requirement for fluid boluses/inotropic support • Brain injury • Functional residual capacity
<p>E. Strategy X vs Strategy Y vs Strategy Z (...) for individualizing PEEP to an optimal level in preterm infants requiring CMV for RDS (objective 3)</p> <p>Outcomes</p> <ul style="list-style-type: none"> • Mortality by hospital discharge • Neurodevelopmental impairment at approximately 2 years' corrected age • Incidence of BPD • Incidence of air leak syndromes • Duration of invasive ventilatory support

Table 1. Table of comparisons (Continued)

- Oxygenation measures PaCO₂ or transcutaneous CO₂ levels
- Cardiac output
- Blood pressure measurements and requirement for fluid boluses/inotropic support
- Brain injury
- Functional residual capacity

For detailed description and definitions of outcome measures, refer to [Types of outcome measures](#) within [Methods](#) section.

BPD: bronchopulmonary dysplasia; CMV: conventional mechanical ventilation; CO₂: carbon dioxide; PaCO₂: arterial carbon dioxide pressure; PEEP: positive end-expiratory pressure; RDS: respiratory distress syndrome; ZEEP: zero end-expiratory pressure.

APPENDICES

Appendix 1. Standard search methodology

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase: ((exp infant) OR (infan* OR newborn or neonat* OR premature or very low birth weight or low birth weight or VLBW or LBW).mp AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp

CINAHL: (infan* OR newborn OR neonat* OR premature OR low birth weight OR VLBW OR LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Previous search methodology

Search methodology for review published in 2011:

1. Ovid MEDLINE

Notes:

Controlled vocabulary (MeSH) terms were searched as both keywords and subject headings, this is indicated by the “Term X”.mp. or exp Term X/” format seen below. Text words were searched as keywords, as indicated by the “Term X”.mp format seen below.

The search was limited by application of a filter for randomized clinical trials, as seen in item #24.

The search was applied to both the standard database as well as to “In-Process & Other Non-Indexed Citations.” The search included studies in these databases through November 2010.

1. Infant, Premature.mp. or exp Infant, Premature/
2. Preterm Birth.mp
3. Preterm Infant.mp
4. Preterm Neonate.mp
5. Premature Birth.mp or exp Premature Birth/

6. Premature Infant.mp
7. Premature Neonate.mp
8. Infant, Newborn.mp or exp Infant, Newborn
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

10. Respiratory Distress Syndrome, Newborn.mp or exp Respiratory Distress Syndrome, Newborn/
11. Hyaline Membrane Disease.mp or exp Hyaline Membrane Disease/
12. Bronchopulmonary Dysplasia.mp or exp Bronchopulmonary Dysplasia/
13. Chronic Lung Disease.mp
14. Respiratory Distress Syndrome.mp
15. RDS.mp
16. BPD.mp
17. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16

18. Positive Pressure Respiration.mp or exp Positive Pressure Respiration/
19. Positive Pressure Ventilation
20. PEEP.mp
21. Positive End Expiratory Pressure.mp
22. #18 OR #19 OR #20 OR #21

23. #9 AND #17 AND #22
24. limit #23 to "therapy (sensitivity)"

II. CENTRAL

Notes:

Studies found within Ovid MEDLINE and Embase were excluded from this search to avoid redundancy. The steps necessary to execute this are seen in steps #22 through #25.

1. Preterm Birth
2. Preterm Infant
3. Preterm Neonate
4. Premature Birth
5. Premature Infant
6. Premature Neonate
7. Newborn Infant
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

9. Respiratory Distress Syndrome
10. Hyaline Membrane Disease
11. Bronchopulmonary Dysplasia
12. Chronic Lung Disease
13. RDS
14. BPD
15. #9 OR #10 OR #11 OR #12 OR #13 OR #14

16. Positive Pressure Respiration
17. Positive Pressure Ventilation
18. Positive End Expiratory Pressure
19. PEEP
20. #16 OR #17 OR #18 OR #19

21. #8 AND #15 AND #20

22. "accession number" near pubmed

23. "accession number" near2 embase

24. #22 OR #23

25. #21 NOT #24

III. Ovid Embase

Notes:

Controlled vocabulary was examined and used by mapping terms to EMTREE terminology. Additionally, each term was searched as both "map to preferred terminology" and "search also for synonyms, explosion on preferred terminology." This was found to be the most sensitive search strategy.

It was noted that including multiple-word term with or without quotation resulted in a different number of search results. Furthermore, it was noted that neither including or excluding quotation marks consistently resulted in a more sensitive search result, with some terms having a greater return of results with quotations while others had a greater return of results without quotations. As such, each term was searched both with and without quotations. Ultimately these results were combined. This technique is reflected throughout the search strategy below. Terms searched without quotations were displayed with an "AND" between words.

The search was limited by application of a filter for randomized clinical trials, as seen in item #24.

1. newborn/syn

2. prematurity/syn

3. 'preterm birth'/syn

4. preterm AND birth/syn

5. 'preterm infant'/syn

6. preterm AND infant/syn

7. 'preterm neonate'/syn

8. preterm AND neonate/syn

9. 'premature birth'/syn

10. premature AND birth/syn

11. 'premature infant'/syn

12. premature AND infant/syn

13. 'premature neonate'/syn

14. premature AND neonate/syn

15. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

16. 'neonatal respiratory distress syndrome'/syn

17. neonatal AND respiratory AND distress AND syndrome/syn AND

18. 'hyaline membrane disease'/syn

19. hyaline AND membrane AND disease/syn

20. 'lung dysplasia'/syn

21. lung AND dysplasia/syn

22. 'bronchopulmonary dysplasia'/syn

23. bronchopulmonary AND dysplasia/syn

24. 'chronic lung disease'/syn

25. chronic AND lung AND disease/syn

26. 'respiratory distress syndrome'/syn

27. respiratory AND distress AND syndrome/syn

28. RDS/syn

29. BPD/syn
 30. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
 31. 'positive pressure ventilation'/syn
 32. positive AND pressure AND ventilation/syn
 33. 'positive pressure respiration'/syn
 34. positive AND pressure AND respiration/syn
 35. 'positive end expiratory pressure'/syn
 36. positive AND end AND expiratory AND pressure/syn
 37. PEEP/syn
 38. #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38
 39. #15 AND #30 AND #38
 40. #15 AND #30 AND #38 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)

Appendix 3. 'Risk of bias' tool

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorized the method used to generate the allocation sequence as:

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorized the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorized the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorized the methods as:

- low risk, high risk, or unclear risk for participants; and
- low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorized the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorized the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we reincluded missing data in the analyses. We categorized the methods as:

- low risk (less than 20% missing data);
- high risk (20% missing data or greater); or

- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. We assessed the methods as:

- low risk (where it was clear that all the study's prespecified outcomes and all expected outcomes of interest to the review were reported);
- high risk (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified outcomes of interest and were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported); or
- unclear risk (if the study protocols was not registered or published).

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk; or
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
5 September 2018	New citation required and conclusions have changed	Conclusions changed, new implications for research
5 September 2018	New search has been performed	Review updated; three new studies added.

CONTRIBUTIONS OF AUTHORS

NB was responsible for designing the original search strategies, designing the data extraction form, undertaking the original searches, screening search results, organizing retrieval of studies, screening retrieved studies against eligibility criteria, extracting data from studies, appraising risk of bias from included studies, assessing the quality of evidence, data management for the review, entering review data into Review Manager 5 ([Review Manager 2014](#)), analysis of data, interpretation of data, corresponding with study authors, and editing and primary writing of the review.

JF was responsible for screening search results, organizing retrieval of studies, screening retrieved studies against eligibility criteria, extracting data from studies, appraising risk of bias from included studies, assessing the quality of evidence, and editing the review.

YW was responsible for screening search results, screening retrieved papers against eligibility criteria, and editing the review.

DM was responsible for conceiving the review; designing the initial review; writing the protocol; entering protocol data into Review Manager 5 ([Review Manager 2014](#)); providing additional data about papers; and writing, editing, and providing general advice on the review.

HK was responsible for conceiving the review, designing the review, co-ordinating the review, resolving differences and uncertainties related to the review, corresponding with study authors, securing funding of the original review, and editing and writing the review.

DECLARATIONS OF INTEREST

NB: none.

JF: none.

YW: none.

DM: none.

HK: none.

SOURCES OF SUPPORT

Internal sources

- 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

Differences between protocol and initial review ([Bamat 2012](#)): the background of the review was slightly modified from the protocol for improved clarity and organization; the search strategy was modified to be in accordance with the then current guidelines and standard search protocol of Cochrane Neonatal Review Group (CNRG) and to increase the sensitivity of the search results.

For the current review update, we modified the background to be in accordance with current CNRG formatting; modified the methods to: reflect changes in the standard CNRG search strategy and technologic resources (e.g. Covidence) available for managing the review process; include the use a PRISMA diagram to illustrate study selection; align participants and outcomes with those typically included and reported in contemporary neonatal trials; clarify and expand upon the approach for measures of treatment effect, assessment of heterogeneity, and data synthesis as per CNRG recommendations; include an approach for unit of analysis issues, dealing with missing data and sensitivity analyses, simplify [Table 1](#) by listing subgroups within the primary comparisons rather than as separate comparisons; include a 'Summary of findings' table, expand and clarify the domains used to assess risk of bias and incorporate GRADE recommendations.

INDEX TERMS

Medical Subject Headings (MeSH)

Bronchopulmonary Dysplasia [*therapy]; Infant, Premature; Positive-Pressure Respiration [adverse effects; *methods; standards]; Pulmonary Gas Exchange; Randomized Controlled Trials as Topic; Respiration, Artificial [adverse effects]; Respiratory Distress Syndrome, Newborn [mortality; *therapy]

MeSH check words

Humans; Infant, Newborn