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Delivery Room Interventions to Prevent Bronchopulmonary Dysplasia in Preterm Infants: A Protocol for a Systematic Review and Network Meta-Analysis

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Delivery Room Interventions to Prevent Bronchopulmonary Dysplasia in Preterm Infants: A Protocol for a Systematic Review and Network Meta-Analysis

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SM, GP, VC, have declared no conflict of interest. TD provides methodological advice for Cornerstone Research Group Inc. Cornerstone Research Group Inc. consults for various pharmaceutical and medical device companies. BD has provided device training and educational presentations to clinicians on behalf of Mallinckrodt Pharmaceuticals. GMS has registered the RETAIN neonatal resuscitation board (Tech ID 2017083) and RETAIN neonatal resuscitation video game (Tech ID 2017086) under Canadian copyright, and GMS is the owner of RETAIN Labs Inc. (<https://www.playretain.com>), which is distributing these games.

Keywords: INFANTS, NEWBORN, DELIVERY ROOM, BRONCHOPULMONARY DYSPLASIA

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Abbreviations:

| | |
|-----------|---|
| BPD | - Bronchopulmonary dysplasia |
| ELGAN | - Extremely low gestational age newborns |
| IQ | - Intelligence quotient |
| CPAP | - Continuous positive airway pressure |
| NMA | - Network meta-analysis |
| RE | - Random-effects model |
| RCT | - Randomized controlled trials |
| INSURE | - Intubate-Surfactant-Extubate technique |
| LISA/MIST | - Less-invasive surfactant administration/minimally invasive surfactant therapy |
| ROB | - Risk of bias |
| CrIs | - Credible intervals |
| RR | - Risk ratio |
| SUCRA | - Surface Under the Cumulative Ranking curve |
| FE | - Fixed-effect model |
| FOL | - First-order loops |
| SMAA | - Stochastic multicriteria acceptability analysis |

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3 **Abstract**

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5 **Introduction**

6 As gestational age decreases, incidence of bronchopulmonary dysplasia (BPD) and chronic lung

7 disease increases. There are many interventions used in the delivery room to prevent acute lung

8 injury and consequently BPD in these patients. The availability of different treatment options often

9 poses a practical challenge to the practicing neonatologist when it comes to making an evidence

10 based choice as the multitude of pairwise systematic reviews including Cochrane reviews that are

11 currently available only provide a narrow perspective through head-to-head comparisons.

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13 **Methods and Analysis**

14 To overcome this challenge, this review will use Bayesian network meta-analysis approach which

15 allows the comparison of the multiple delivery room interventions for prevention of BPD. This

16 systematic review will summarize the available evidence from randomized clinical trials using a

17 Bayesian network meta-analysis to determine the effectiveness and safety of delivery room

18 interventions for prevention of BPD.

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20 **Ethics and Dissemination**

21 The proposed protocol is a network meta-analysis, which has been registered on

22 PROSPERO International prospective register of systematic reviews (CRD42018078648). We

23 hope that this review will provide an evidence based guide to choosing the right sequence of early

24 postnatal interventions that will be associated with the least likelihood of inducing lung injury and

25 BPD in preterm infants.

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Strengths and limitations of this study

Strengths:

- Comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work
- Use the novel method for rating the confidence in the estimates recommended by the GRADE working group
- We will employ a novel Stochastic multicriteria acceptability analysis model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes

Limitations:

- We anticipate some degree of clinical heterogeneity while considering such a large number of competing and non-competing delivery room interventions
- Potential to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results

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Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory morbidity associated with premature birth. BPD is defined as either need of supplemental oxygen at i) 28 days postnatal age(1), or ii) 36 weeks' postmenstrual age with or without compatible clinical and radiographic findings(2). BPD affects 30-60% of prematurely born infants with the incidence being inversely proportional to gestational age(3). With increased survival of extremely low gestational age newborns (ELGAN), the incidence of BPD continues to increase despite improvement in neonatal care practices over the last two decades(3). BPD is known to be associated with long-term respiratory morbidity that persists into adolescence and adulthood(4,5). There is also increasing evidence that BPD and duration on supplemental oxygen have long-term adverse effects on cognitive and academic achievement with each percent increase in BPD rate being associated with a 0.01 standard deviation decrease in intelligence quotient (IQ) (0.15 IQ points) (p<0.001)(6,7).

Several antenatal, perinatal, and postnatal factors contribute to the development of BPD. It is postulated that early lung injury and inflammation play an important role in the pathogenesis of BPD (8,9). In the fetus, the gas exchange organ is the placenta and the function of gas exchange is transferred from the placenta to the lungs immediately after birth. Therefore, the newborn infant's lungs must open and be aerated to allow the transition from fetal to postnatal circulation and physiology. However, in ELGANs, several physiological factors prevent this transition. These include lack of surfactant leading to increased alveolar surface tension, non-compliant chest wall, and weak respiratory muscles(10-12). Therefore, most ELGANs require assisted ventilation and/or supplemental oxygen after birth to ensure optimal gas exchange. However, both therapies may also induce lung inflammation due to barotrauma and/or volutrauma and oxygen-free radical generation thereby initiating the pathogenesis of BPD. Therefore, any interventions targeted at limiting lung injury and oxidative stress during resuscitation in the delivery room immediately after the birth may help to prevent the development of BPD or reduce its severity.

A number of clinical trials have been conducted on a variety of delivery room interventions, including i) interventions prior to initiating breathing support (i.e., clamping vs. milking the umbilical cord); ii) interventions around initial breathing support (i.e., continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation, sustained lung inflation or endotracheal intubation); iii) interventions related to improving lung compliance (i.e., prophylactic

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3 surfactant therapy including the different variations in its administration modalities); iv)
4 interventions related to minimizing oxidative stress (i.e., higher vs. lower oxygen saturation
5 targets), v) use of cerebral oximetry, and vi) other potentially beneficial therapies such as caffeine
6 administration (Figure 1)(13,14).
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10 The availability of multiple potential interventions in a resuscitation scenario often poses
11 a practical challenge to health care professionals as to which sequence of interventions would
12 provide the greatest likelihood of minimizing BPD and which interventions are unnecessary and
13 unlikely to be of any benefit(13). There have been previous systematic reviews and pairwise meta-
14 analyses on the different competing interventions such as initial breathing support and oxygen
15 saturation targets(15-17). However, these meta-analyses, though well conducted, provide a narrow
16 perspective to the situation where a sequence of non-competing interventions occur within a short
17 time-frame whereas each intervention has potentially competing variations. Use of a network
18 meta-analysis (NMA) framework may help to provide a more feasible, comprehensive and
19 evidence-based solution to the dilemma that health care professionals face during resuscitation of
20 ELGANs with regards to multiple competing interventions aimed at mitigating lung injury. The
21 Cochrane handbook considers NMA as a highly valuable tool to evaluate and rank treatment
22 options according to their safety and effectiveness(18). Bayesian NMA have been proposed as an
23 effective method for evaluating the effectiveness of multiple competing interventions(18-20).
24 Delivery room interventions consist of a sequence of non-competing category of interventions and
25 within each category there are several potentially competing interventions (Figure 1). Given that
26 many of these competing delivery room interventions have not been compared in head-to-head
27 studies, we expect that some of the possible comparisons between the interventions will not have
28 direct evidence. Hence, we will perform a random effects network meta-analysis (NMA). Delivery
29 room interventions will be defined as all potential interventions in the immediate postnatal
30 period(21-23).
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48 OBJECTIVES

49 To determine the relative effectiveness of commonly practiced delivery room interventions
50 for preterm infants born <33 weeks of gestation in preventing BPD using a Bayesian network
51 meta-analysis.
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METHODS & DESIGN

This systematic review and NMA protocol has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). This protocol was developed following the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance(24). The final report will comply with the recommendations of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions(25).

Search Strategy

We will search from their inception to August 2018, the following databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). We will use combination of controlled terms (Medical Subject Heading, MeSH, and Emtree), and free-text terms with various synonyms for the different possible delivery room interventions and BPD. Search alerts will be set up for monthly notification and the search will be repeated before the final manuscript submission to identify any new relevant trials. Search strategies have been developed with liaison with an experienced librarian. No language, publication status or date limit will be used. The search strategies have been detailed in appendix A.

We will seek registered details of selected trials in the U.S. National Institutes of Health resource (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform Search Portal. We intend to obtain additional grey literature from personal communication from experts in the field, reviewing the reference lists of relevant articles, abstracts and conference proceedings (Society for Pediatric Research, European Society for Pediatric Research) and seeking results of unpublished trials. We intend to contact authors of unpublished work and authors of published trials in order to clarify information that is not clear in the articles.

Eligibility Criteria

We will include randomized controlled trials (RCTs) that evaluate the effectiveness of commonly practiced delivery room interventions. Studies will have to have the following characteristics regarding participants, intervention, control and type of study.

- a) Participants: Preterm infants (<33 weeks) requiring intervention(s) during neonatal transition within the golden hours after birth

- b) Interventions include the following: i) cord management (including immediate cord clamping, delayed cord clamping, cord milking, and/or resuscitation attached to the cord); ii) respiratory support (including positive pressure ventilation, CPAP, sustained lung inflation, and/or intubation, and mechanical ventilation); iii) surfactant delivery (type of surfactant delivered via endotracheal tube or laryngeal mask, INSURE (Intubate-Surfactant-Extubate) technique, LISA/MIST (less-invasive surfactant administration/minimally invasive surfactant therapy), and/or nebulized surfactant administration; iv) initial fractional concentration of inspired oxygen (FiO_2) (≤ 0.3 or ≥ 0.6); v) monitoring during resuscitation (respiratory function monitor, near-infrared spectroscopy); vi) medication (e.g., caffeine citrate, or diuretics); vii) use of heated, humidified gas
- c) Comparator: One or more of the above interventions compared to each other or no treatment. Since interventions possible in a delivery room are largely related to delivery room resources, we have *a priori* decided to only include interventions that the infants were subjected to in the immediate postnatal period irrespective of whether these interventions were physically carried out in the room where the infant was born. Studies that examined interventions that were carried out after the initial stabilization period will be excluded from the review.

Outcomes

Our primary outcome is bronchopulmonary dysplasia (defined as oxygen requirement at 36 weeks' postmenstrual age). Secondary outcomes include death at 36 weeks' postmenstrual age or before discharge; severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria)(26); any air leak syndromes (including pneumothorax or pulmonary interstitial emphysema); retinopathy of prematurity (any stage) and neurodevelopmental impairment at 18-24 months. All the outcomes, its definitions and measures are detailed in the table 1.

Patient and Public Involvement

Neither patients nor public were involved in the development of the research question or design of this study. This network meta-analysis does not recruit any patients. The study will be published and presented at conferences to healthcare professionals.

Study selection

The titles and abstracts retrieved will be screened by two independent reviewers in duplicate to assess its eligibility using the Covidence platform (27). As a second step, the full text articles of the potentially eligible studies will be screened to assess their eligibility. We will include the full text of all studies for which both reviewers agree about their inclusion. For both steps, any disagreements between the reviewers will be resolved by discussion and if no agreement can be reached, a third member of the team will decide whether the study shall be included or not. We will refer to inclusion and exclusion criteria during the screening process. Records of ineligible full text articles along with the reason for ineligibility will be saved for future reference. Eligible articles citations will be uploaded to Covidence. We will present the PRISMA flow diagram(28) demonstrating the search and screening process.

Data Abstraction

A pre-specified standardized data extraction form in a Microsoft Excel sheet will be used to extract the data from the eligible studies. The data extraction form will be pilot tested independently by all reviewers before its use, to standardize the process. Eight reviewers will carry out the extraction, working independently in pairs and in duplicate. In case of disagreement in assessing the methodological quality of the study we will try to resolve it by consensus. If consensus cannot be reached a third designated reviewer will be involved. We will contact authors of primary studies, during data extraction, to provide any missing information.

Node Formation

Within each component of the stabilization pathway, we anticipate the identification numerous similar non-competing interventions (e.g. multiple synthetic and natural surfactants). In an iterative process, clinical experts (GS, SM, GP) blinded to the implications for effect estimates, will come to consensus on definitions of nodes and be presented with the implications of those decisions via network diagrams (e.g. lumping causing the loss of trials comparing lumped interventions, splitting causing disconnected networks). Experts will then be asked to identify whether groups of treatments should be defined as classes (e.g. natural vs synthetic surfactant) or lumped together. Class-based models have the advantage of offering an estimate of class effect as well as shrunken effects of individual treatments, while lumping can allow for more robust estimation of between-trial variability, and can reduce the probability of chance violations of NMA

assumptions. This process will be repeated until a consensus decision is reached on the node making algorithm that meets the criteria of satisfying clinical demands, preserving the assumption that interventions within nodes are sufficiently similar, and presenting data in the least aggregated form possible(29).

Assessment of Risk of Bias

The risk of bias (ROB) of eligible studies will be assessed according to a modified version of the Cochrane Collaboration's ROB tool(18). The six criteria to be assessed are sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow up, selective outcome reporting, and presence of other biases. Each domain will be assigned a score 'definitely low risk', or 'definitely high risk' or 'unclear risk'. Two independent reviewers will assess the ROB. We will try to reach consensus when disagreements between two reviewers when assessing the methodological quality of the studies. Nevertheless, if consensus cannot be reached, a third reviewer will resolve it.

Measures of Treatment Effect

Effect estimates along with 95% credible intervals (CrIs) will be estimated using risk ratios (RR) calculated using methods described by Dias, using the baseline risk parameter to convert odds ratios to risk ratios(29). When random effect models are used estimates will also be accompanied by their 95% predictive interval representing the interval within which we would expect the treatment effect of a future study to lie(30,31). Relative treatment rankings will be summarized using mean ranks with their 95% credible intervals and the Surface Under the Cumulative Ranking curve (SUCRA) values and cumulative probability rankograms(32). SUCRAs range from 0% to 100% with values of 100% representing a hypothetical treatment that is always best without uncertainty.

Assessment of reporting bias

We will construct a comparison adjusted funnel plot for the network to assess the potential publication bias and small-study effects(33), if we retrieve at least 10 studies. We will inspect plots visually for evidence of asymmetry and if publication bias is suspected we will conduct a sensitivity analysis using models described by Mavridis, Welton and Salanti(34).

Assessment of Transitivity Assumption

Clinical experts (GS, GP, SM) will assess trial characteristics using tables and visualizations to assess whether the transitivity assumption is likely to hold. The characteristics to be evaluated are those that are expected to be effect modifiers and will include gestational age, birth weight, baseline event risk, and ROB. These assessments will be made prior to any meta-analysis to limit to influence of presence or absence of statistical heterogeneity on the assessment of the transitivity assumption. The decision to pool data will be based on consensus. If it is determined that quantitative synthesis is inappropriate, we will summarize our findings narratively.

Direct treatment comparisons

Given that we expect clinical and methodological heterogeneity among the studies (see below in Rating the Confidence in Estimates section), which in turn will create statistical heterogeneity, we will pool evidence for each treatment comparison using a Bayesian random-effects (RE) model(35). In comparison to the fixed-effect model (FE), the RE model is conservative in the sense that it accounts for both within- and between-study variability. The RE model assumes that the observed treatment effect for a study is a combination of a treatment effect common to all studies plus a component specific to that study alone(36,37). Models will be based on standard code modified to include minimally informative priors on baselines, treatment effects, and between trial heterogeneity (38). These priors generally provide more stable estimates, particularly in cases where data are sparse, will be developed using the approach described by Gabry *et al* (39,40).

The Network Meta-Analysis

For each outcome, we will present the network diagram and a forest plot compared against the common comparator with the network estimates as well as league tables showing all pairwise comparisons. To capture the non-competing nature of interventions along the stabilization pathway and to directly fulfill the research objectives we will use component models as described by Welton *et al*(41). These models assume that interventions across domains of the stabilization pathway are additive on the linear predictor scale (e.g. additive on logit scale for dichotomous outcomes). In

the absence of direct evidence for a given comparison an indirect comparison will provide an estimate of the treatment effect. In the presence of direct evidence, the NMA will provide a combined estimate (i.e., direct and indirect evidence)(32). For instance, in a triangular network ABC composed by studies that directly compare A vs. B and A vs. C treatments, we can indirectly estimate the effect of B vs. C treatments. In case direct evidence of B vs. C treatment comparison is also available, then a combined estimate of direct and indirect evidence of B vs. C can be calculated using a NMA.

We will fit a Bayesian hierarchical model with weakly informative priors adjusting for correlation of multi-arm trials, and assuming a common-within network heterogeneity variance. We will assess heterogeneity by estimating the magnitude of the between-study variance (42). If the posterior estimate of between-study variance shows signs of prior dominance (e.g. extreme values and long tails), we will conduct sensitivity analysis using the empirically estimated informative prior distribution described by Turner *et al*(43). Markov chains will be run for a sufficient number of iterations to reach convergence, which we will assess on the basis of the Brooks-Gelman-Rubin diagnostic, with values less than 1.05 considered acceptable if consistent with visual inspection of convergence and time series plots(44). All analyses will be performed in JAGS or similar software via the statistical program R(45,46).

Assessment of Inconsistency

Inconsistency is the statistical manifestation of the violation of the transitivity assumption, which presents as a disagreement between direct and indirect estimates (loop inconsistency), and/or inconsistency between studies that inform the same treatment comparison, but include a different number of treatment arms (design inconsistency). To evaluate both design and loop inconsistency, we will apply the design-by-treatment interaction model with random inconsistency effects (47,48). These findings will be interpreted within the context of the estimate of between-trial variance as these concepts are closely related and difficult to separate. For example, large estimates of between-trial variance are indicative of heterogeneity within direct comparisons but may also be the result of inconsistency between direct and indirect evidence.

Exploration of heterogeneity and inconsistency

We will perform a network meta-regression using of potential effect modifiers to explore important heterogeneity and/or inconsistency. We propose, the following potential sources of heterogeneity, which could be possible effect modifiers: gestational age, birth weight and ROB. We hypothesize that lower gestational age, and low ROB will be related to less effectiveness of interventions. Overall risk of bias will be determined by taking the average of the three most important risk of bias items identified by expert consensus (sequence generation, allocation concealment, and blinding). Meta-regression models will assume a single shared coefficient for all non-baseline treatments(42). Interpretation of meta-regression models will be in keeping with suggestions from Dias et al., namely: (1) Inclusion of the coefficient leads to a decrease in the estimate of between-study variance; and (2) The 95% credible intervals of the estimated coefficient exclude the null (42).

Sensitivity Analyses

We plan to perform sensitivity analyses of different heterogeneity priors to assess the robustness of results(35,43,49). Further, findings from component models will be compared against a model without this assumption. In both cases, we will compare model fit using both absolute (residual deviance) and relative (DIC) measures as well as a qualitative assessment of whether the analysis leads to an important change in effect estimates.

Rating the confidence in estimates of the effect

We will assess the confidence in the estimates for each outcome using the GRADE approach (50). For this purpose, two authors will independently do the assessment. The confidence in the estimates will be based on four levels: high, moderate, low and very low. For the direct comparisons we will assess and rate each outcome based on the categories: ROB imprecision, inconsistency and publication bias(51-55). To assist with assessment of each domain, we will use threshold plots, which show the smallest change in study/contrast level estimates required to change the conclusions of the analysis.

We will assess and rate the confidence in all the indirect comparisons –if available- obtained from first order loops following the GRADE categories used for assessing the direct comparisons in addition to the transitivity assessment. Transitivity, also called similarity(56), is the assumption that an indirect comparison is a valid method to compare two treatments that have

not been compared in a head-to-head trial, because the studies are sufficiently similar in important clinical and methodological characteristics, or in other words, that they are similar in their distributions of effect modifiers(57,58). Then, we will rate the confidence in each NMA effect estimate using the higher rating when both direct and indirect evidence are present.

We will assess and rate the confidence in estimates of effect from the direct comparisons in our pairwise meta-analyses described previously. To rate the confidence in the indirect comparisons, we will focus our assessments on first-order loops (FOLs), i.e., loops connected to the interventions of interest through only one other intervention. For instance, if for A, B and C interventions, there are direct comparisons of A vs. B (AB) and B vs. C (BC), we will be able to indirectly estimate the effects of A vs. C (AC). The AC indirect estimation will be a FOL. We will choose the FOLs with the lowest variances for rating the confidence as they contribute the most to the estimates of effect.

Within FOLs, the indirect comparison confidence will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For example, if we find that AB has moderate confidence and BC has high confidence, we will judge the associated indirect comparison, AC, as moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption has been violated.

Our overall judgment of confidence in the NMA estimate for any pairwise comparison will be the higher of the confidence rating amongst the contributing direct and indirect comparisons. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates have inconsistency. For this purpose, the GRADE approach recommends to assess the incoherence (or inconsistency as described in the 'The Network Meta-Analysis' section) criteria, which is defined as the differences between direct and indirect estimates of effect(59).

Multi-criteria Acceptability Analysis

Network meta-analyses provide an estimate of effect estimates of competing interventions, but this alone is not sufficient to aid decision making. We will aim to supplement this review with a stochastic multi-criteria acceptability analysis using methods defined by Tervonen, and Van Valkenhoef(60). These methods use a partial value function to allow for a quantitative risk-benefit analysis across multiple outcomes, given an ordinal ranking of importance for decision making

(e.g. Mortality > BPD). Based on the best fitting NMA model, we will conduct stochastic multicriteria acceptability analyses (SMAA): One without preference criteria, and a second with preference criteria determined by expert consensus. Since SMAA is based on estimates constrained to the interval [0,1] we will calculate absolute risk of outcomes based on either a suitably designed observational trial or, if unavailable, a pooled control arm risk of included studies in the reference treatment(61). If treatments require the tradeoff of common (e.g. BPD) and very rare (e.g. mortality) events, we will use the 95% credible interval hull approach(62). The outputs of the SMAA will be a rankogram outlining the probability that a treatment is best, second best, etc., a vector of central weights, a confidence factor for the preference free model; and the rankogram for the ordered model. The vector of central weights provides a summary of the implied preferences required to hold an *a priori* preference for one treatment or another (i.e. the outcome preference implied by a clinician's current practice). The confidence factor is the probability that a treatment is best given these preferences, and is used as a measure of uncertainty.

Discussion

Interventions in the immediate postnatal period may have long-term clinical implications. This NMA will provide the relative effectiveness of commonly practiced delivery room interventions for preterm infants born <33 weeks of gestation in preventing BPD. To the best of our knowledge this will be the first review that will examine the relative effectiveness of each delivery room intervention individually and in combination with respect to important clinical outcomes using novel statistical techniques. Its results will be of interest for a broad range of audience: practice guideline developers, pediatricians, neonatologists, policy makers and researchers, as it could be used to provide clinical recommendations for the choice of sequence of delivery room interventions.

Our review will have several methodological strengths. First, we will implement a wide comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work. Second, we will use the novel method for rating the confidence in the estimates recommended by the GRADE working group. Third, we will employ a novel SMAA model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes(60). On the other hand, we anticipate some methodological challenges while undertaking such a review. We anticipate some degree of clinical

heterogeneity while considering such a large number of competing and non-competing delivery room interventions. Based on the number of interventions identified following the systematic review, we may have to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results.

We hope that this review will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants.

Figure legend:

Figure 1: Physiological sequence of potential delivery room interventions

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Table 1. A priori defined outcome measures

| Outcome Measure | Definition |
|--|--|
| Bronchopulmonary dysplasia | No. of neonates who require oxygen at 36 weeks' postmenstrual age (PMA) |
| Mortality | Death before discharge |
| Severe intraventricular hemorrhage | No. of neonates with grades 3-4 based on the Papile criteria |
| Air leak syndromes | No. of neonates with pneumothorax or pulmonary interstitial emphysema confirmed by chest X ray |
| Retinopathy of prematurity (any stage) | No. of neonates with any stage of Retinopathy of prematurity as per the international classification of Retinopathy of prematurity |
| Neurodevelopmental impairment | No. of infants with any degree of neurodevelopmental impairment as assessed by a standardized and validated assessment tool, a child developmental specialist or both, at any age reported (outcome data grouped at 12, 18 and 24 months if available) |

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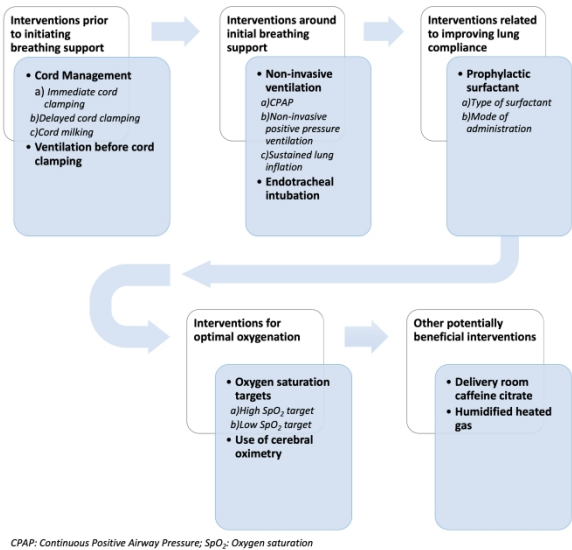


Figure 1: Physiological sequence of potential delivery room interventions

903x508mm (144 x 144 DPI)

Appendix 1: Search strategy for EMBASE, Medline, and PubMed

EMBASE

(newborn OR infant OR neonate OR preterm OR premature) AND [randomized controlled trial]/lim

AND

(continuous AND positive AND airway AND pressure OR cpap OR (nasal AND continuous AND positive AND airway AND pressure) OR ncpap OR (positive AND pressure AND ventilation) OR (intermittent AND positive AND pressure AND ventilation) OR (sustained AND lung AND inflation) OR (sustained AND inflation) OR si) AND [randomized controlled trial]/lim

OR

(supplemental AND oxygen OR (supplemental AND oxygen AND during AND resuscitation) OR oxygen OR surfactant OR (surfactant AND administration) OR (surfactant AND administration, AND early) OR (surfactant AND administration, AND late) OR (minimally AND invasive AND surfactant AND therapy) OR ('less invasive' AND surfactant AND administration)) AND [randomized controlled trial]/lim

OR

(lisa OR intubation OR (endotracheal AND intubation) OR (mechanical AND ventilation) OR caffeine OR (caffeine AND citrate) OR (respiratory AND function AND monitor) OR (delayed AND cord AND clamping) OR (cord AND milking)) AND [randomized controlled trial]/lim

AND

(randomized AND controlled AND trial OR 'randomized controlled trial':it OR (clinical AND trial)) AND [randomized controlled trial]/lim

AND

[randomized controlled trial]/lim AND [embase]/lim AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim)

Limited to embryo from Age Groups fetus from Age Groups newborn from Age Groups infant from Age Groups

Medline

| | |
|-----|--|
| Set | <div>Run Search</div> <div>MEDLINE</div> <div>Search History - " BPD"</div> |
| #5 | #3 AND #2 AND #1 Refined by: PUBLICATION TYPES: (RANDOMIZED CONTROLLED TRIAL) DocType=All document types; Language=All languages; |
| #4 | #3 AND #2 AND #1 DocType=All document types; Language=All languages; |
| #3 | (MH=randomized controlled trial OR TS=randomized controlled trial OR TS=clinical trial) AND DOCUMENT TYPES: (Randomized Controlled Trial) DocType=All document types; Language=All languages; |
| #2 | TS=continuous positive airway pressure OR TS=CPAP OR TS=nasal continuous positive airway pressure OR TS=nCPAP OR TS=positive pressure ventilation OR TS=intermittent positive pressure ventilation OR TS=sustained lung inflation OR TS=sustained inflation OR TS=SI OR TS=supplemental oxygen OR TS=supplemental oxygen during resuscitation OR TS=oxygen OR TS=surfactant OR TS=surfactant administration OR TS=surfactant administration, early OR TS=surfactant administration, late OR TS=minimally invasive surfactant therapy OR TS=less-invasive surfactant administration OR TS=LISA OR TS=intubation OR TS=endotracheal intubation OR TS=mechanical ventilation OR TS=caffeine OR TS=caffeine citrate OR TS=respiratory function monitor OR TS=delayed cord clamping OR TS=cord milking DocType=All document types; Language=All languages; |
| #1 | TS=newborn OR TS=premature OR TS=infant OR TS=neonate OR TS=preterm DocType=All document types; Language=All languages; |

PubMed

- #1 MeSH descriptor: [Infant] explode all trees
- #2 infant*:ti,ab
- #3 neonat*:ti,ab
- #4 newborn*:ti,ab
- #5 preterm:ti,ab
- #6 premature:ti,ab
- #7 #1 or #2 or #3 or #4 or #5 or #6
- #8 "continuous positive airway pressure":ti,ab
- #9 "positive pressure ventilation":ti,ab
- #10 (sustained near/2 inflation):ti,ab
- #11 (supplemental near/2 oxygen):ti,ab
- #12 oxygen:ti,ab
- #13 surfactant:ti,ab
- #14 intubation:ti,ab
- #15 (mechanical* near/1 ventilat*):ti,ab
- #16 caffeine:ti,ab
- #17 "respiratory function monitor":ti,ab
- #18 (cord near/2 ((clamping and delayed) or milking)):ti,ab
- #19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18

#20 #7 and #19

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BMJ Open

Delivery Room Interventions to Prevent Bronchopulmonary Dysplasia in Preterm Infants: A Protocol for a Systematic Review and Network Meta-Analysis

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| Secondary Subject Heading: | Research methods |
| Keywords: | Infants, Bronchopulmonary dysplasia, Delivery Room, Newborn |
| | |

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Manuscripts

**Delivery Room Interventions to Prevent Bronchopulmonary Dysplasia in Preterm
Infants: A Protocol for a Systematic Review and Network Meta-Analysis**

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Conflict of Interest:

SM, GP, VC, have declared no conflict of interest. TD provides methodological advice for Cornerstone Research Group Inc. Cornerstone Research Group Inc. consults for various pharmaceutical and medical device companies. BD has provided device training and educational presentations to clinicians on behalf of Mallinckrodt Pharmaceuticals. GMS has registered the RETAIN neonatal resuscitation board (Tech ID 2017083) and RETAIN neonatal resuscitation video game (Tech ID 2017086) under Canadian copyright, and GMS is the owner of RETAIN Labs Inc. (<https://www.playretain.com>), which is distributing these games.

Keywords: INFANTS, NEWBORN, DELIVERY ROOM, BRONCHOPULMONARY DYSPLASIA

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Figures: 1

Author’s contribution:

- Conception and design: GMS, SM
- Data analysis plan: GMS, SM, GP, TD, BDS, HM, VC, KJ
- Drafting of the article: GMS, SM, GP, TD, BDS, HM, VC, KJ
- Critical revision of the article for important intellectual content: GMS, SM, GP, TD, BDS, HM, VC, KJ
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Abbreviations:

| | |
|-----------|---|
| BPD | - Bronchopulmonary dysplasia |
| ELGAN | - Extremely low gestational age newborns |
| IQ | - Intelligence quotient |
| CPAP | - Continuous positive airway pressure |
| NMA | - Network meta-analysis |
| RE | - Random-effects model |
| RCT | - Randomized controlled trials |
| INSURE | - Intubate-Surfactant-Extubate technique |
| LISA/MIST | - Less-invasive surfactant administration/minimally invasive surfactant therapy |
| ROB | - Risk of bias |
| CrIs | - Credible intervals |
| RR | - Risk ratio |
| SUCRA | - Surface Under the Cumulative Ranking curve |
| FE | - Fixed-effect model |
| FOL | - First-order loops |
| SMAA | - Stochastic multicriteria acceptability analysis |

Abstract

Introduction

As gestational age decreases, incidence of bronchopulmonary dysplasia (BPD) and chronic lung disease increases. There are many interventions used in the delivery room to prevent acute lung injury and consequently BPD in these patients. The availability of different treatment options often poses a practical challenge to the practicing neonatologist when it comes to making an evidence based choice as the multitude of pairwise systematic reviews including Cochrane reviews that are currently available only provide a narrow perspective through head-to-head comparisons.

Methods and Analysis

We will conduct a systematic review of all randomized controlled trials evaluating delivery room interventions within the 1st golden hour after birth for prevention of BPD. The primary outcome BPD. Secondary outcomes include death at 36 weeks' postmenstrual age or before discharge; severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria); any air leak syndromes (including pneumothorax or pulmonary interstitial emphysema); retinopathy of prematurity (any stage) and neurodevelopmental impairment at 18-24 months. We will search Medline, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) as well as grey literature resources. Two reviewers will independently screen titles and abstracts, review full texts, extract information, and assess the risk of bias (ROB) and the confidence in the estimate (with Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach). This review will use Bayesian network meta-analysis approach which allows the comparison of the multiple delivery room interventions for prevention of BPD. We will perform a Bayesian network meta-analysis to combine the pooled direct and indirect treatment effect estimates for each outcome, effectiveness, and safety of delivery room interventions for prevention of BPD.

Ethics and Dissemination

The proposed protocol is a network meta-analysis, which has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). The results will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants. Furthermore, we will identify knowledge gaps and will encourage further research for other

therapeutic options. Therefore, its results will be disseminated through peer-reviewed publications and conference presentations. Due to the nature of the design, no ethics approval is necessary.

Strengths and limitations of this study

Strengths:

- Comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work
- Use the novel method for rating the confidence in the estimates recommended by the GRADE working group
- We will employ a novel Stochastic multicriteria acceptability analysis model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes

Limitations:

- We anticipate some degree of clinical heterogeneity while considering such a large number of competing and non-competing delivery room interventions
- Potential to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results

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Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory morbidity associated with premature birth. BPD is defined as either need of supplemental oxygen at i) 28 days postnatal age(1), or ii) 36 weeks' postmenstrual age with or without compatible clinical and radiographic findings(2). BPD affects 30-60% of prematurely born infants with the incidence being inversely proportional to gestational age(3). With increased survival of extremely low gestational age newborns (ELGAN), the incidence of BPD continues to increase despite improvement in neonatal care practices over the last two decades(3). BPD is known to be associated with long-term respiratory morbidity that persists into adolescence and adulthood(4,5). There is also increasing evidence that BPD and duration on supplemental oxygen have long-term adverse effects on cognitive and academic achievement with each percent increase in BPD rate being associated with a 0.01 standard deviation decrease in intelligence quotient (IQ) (0.15 IQ points) (p<0.001)(6,7).

Several antenatal, perinatal, and postnatal factors contribute to the development of BPD. It is postulated that early lung injury and inflammation play an important role in the pathogenesis of BPD (8,9). In the fetus, the gas exchange organ is the placenta and the function of gas exchange is transferred from the placenta to the lungs immediately after birth. Therefore, the newborn infant's lungs must open and be aerated to allow the transition from fetal to postnatal circulation and physiology. However, in ELGANs, several physiological factors prevent this transition. These include lack of surfactant leading to increased alveolar surface tension, non-compliant chest wall, and weak respiratory muscles(10-12). Therefore, most ELGANs require assisted ventilation and/or supplemental oxygen after birth to ensure optimal gas exchange. However, both therapies may also induce lung inflammation due to barotrauma and/or volutrauma and oxygen-free radical generation thereby initiating the pathogenesis of BPD. Therefore, any interventions targeted at limiting lung injury and oxidative stress during resuscitation in the delivery room immediately after the birth may help to prevent the development of BPD or reduce its severity.

A number of clinical trials have been conducted on a variety of delivery room interventions, including i) interventions prior to initiating breathing support (i.e., clamping vs. milking the umbilical cord); ii) interventions around initial breathing support (i.e., continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation, sustained lung inflation or endotracheal intubation); iii) interventions related to improving lung compliance (i.e., prophylactic

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3 surfactant therapy including the different variations in its administration modalities); iv)
4 interventions related to minimizing oxidative stress (i.e., higher vs. lower oxygen saturation
5 targets), v) use of cerebral oximetry, and vi) other potentially beneficial therapies such as caffeine
6 administration (Figure 1)(13,14).
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10 The availability of multiple potential interventions in a resuscitation scenario often poses
11 a practical challenge to health care professionals as to which sequence of interventions would
12 provide the greatest likelihood of minimizing BPD and which interventions are unnecessary and
13 unlikely to be of any benefit(13). There have been previous systematic reviews and pairwise meta-
14 analyses on the different competing interventions such as initial breathing support and oxygen
15 saturation targets(15-17). However, these meta-analyses, though well conducted, provide a narrow
16 perspective to the situation where a sequence of non-competing interventions occur within a short
17 time-frame whereas each intervention has potentially competing variations. Use of a network
18 meta-analysis (NMA) framework may help to provide a more feasible, comprehensive and
19 evidence-based solution to the dilemma that health care professionals face during resuscitation of
20 ELGANs with regards to multiple competing interventions aimed at mitigating lung injury. The
21 Cochrane handbook considers NMA as a highly valuable tool to evaluate and rank treatment
22 options according to their safety and effectiveness(18). Bayesian NMA have been proposed as an
23 effective method for evaluating the effectiveness of multiple competing interventions(18-20).
24 Delivery room interventions consist of a sequence of non-competing category of interventions and
25 within each category there are several potentially competing interventions (Figure 1). Given that
26 many of these competing delivery room interventions have not been compared in head-to-head
27 studies, we expect that some of the possible comparisons between the interventions will not have
28 direct evidence. Hence, we will perform a random effects network meta-analysis (NMA). Delivery
29 room interventions will be defined as all potential interventions in the immediate postnatal
30 period(21-23).
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48 OBJECTIVES

49 To determine the relative effectiveness of commonly practiced delivery room interventions
50 for preterm infants born <33 weeks of gestation in preventing BPD using a Bayesian network
51 meta-analysis.
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METHODS & DESIGN

This systematic review and NMA protocol has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). This protocol was developed following the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance(24). The final report will comply with the recommendations of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions(25).

Search Strategy

We will search from their inception to August 2018, the following databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). We will use combination of controlled terms (Medical Subject Heading, MeSH, and Emtree), and free-text terms with various synonyms for the different possible delivery room interventions and BPD. Search alerts will be set up for monthly notification and the search will be repeated before the final manuscript submission to identify any new relevant trials. Search strategies have been developed with liaison with an experienced librarian. No language, publication status or date limit will be used. The search strategies have been detailed in appendix A.

We will seek registered details of selected trials in the U.S. National Institutes of Health resource (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform Search Portal. We intend to obtain additional grey literature from personal communication from experts in the field, reviewing the reference lists of relevant articles, abstracts and conference proceedings (Society for Pediatric Research, European Society for Pediatric Research) and seeking results of unpublished trials. We intend to contact authors of unpublished work and authors of published trials in order to clarify information that is not clear in the articles.

Eligibility Criteria

We will include randomized controlled trials (RCTs) that evaluate the effectiveness of commonly practiced delivery room interventions. Studies will have to have the following characteristics regarding participants, intervention, control and type of study.

- a) Participants: Preterm infants (<33 weeks) requiring intervention(s) during neonatal transition within the 1st golden hour after birth

- b) Interventions include the following: i) cord management (including immediate cord clamping, delayed cord clamping, cord milking, and/or resuscitation attached to the cord); ii) respiratory support (including positive pressure ventilation, CPAP, sustained lung inflation, and/or intubation, and mechanical ventilation); iii) surfactant delivery (type of surfactant delivered via endotracheal tube or laryngeal mask, INSURE (Intubate-Surfactant-Extubate) technique, LISA/MIST (less-invasive surfactant administration/minimally invasive surfactant therapy), and/or nebulized surfactant administration; iv) initial fractional concentration of inspired oxygen (FiO_2) (≤ 0.3 or ≥ 0.6); v) monitoring during resuscitation (respiratory function monitor, near-infrared spectroscopy); vi) medication (e.g., caffeine citrate, or diuretics); vii) use of heated, humidified gas
- c) Comparator: One or more of the above interventions compared to each other or no treatment. Since interventions possible in a delivery room are largely related to delivery room resources, we have *a priori* decided to only include interventions that the infants were subjected to in the immediate postnatal period irrespective of whether these interventions were physically carried out in the room where the infant was born. Studies that examined interventions that were carried out after the initial stabilization period will be excluded from the review.

Outcomes

Our primary outcome is bronchopulmonary dysplasia (defined as oxygen requirement at 36 weeks' postmenstrual age). Secondary outcomes include death at 36 weeks' postmenstrual age or before discharge; severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria)(26); any air leak syndromes (including pneumothorax or pulmonary interstitial emphysema); retinopathy of prematurity (any stage) and neurodevelopmental impairment at 18-24 months. All the outcomes, its definitions and measures are detailed in the table 1. We aim to perform one subgroup analysis comparing infants <28 weeks versus 29-32 weeks.

Patient and Public Involvement

Neither patients nor public were involved in the development of the research question or design of this study. This network meta-analysis does not recruit any patients. The study will be published and presented at conferences to healthcare professionals.

Study selection

The titles and abstracts retrieved will be screened by two independent reviewers in duplicate to assess its eligibility using the Covidence platform (27). As a second step, the full text articles of the potentially eligible studies will be screened to assess their eligibility. We will include the full text of all studies for which both reviewers agree about their inclusion. For both steps, any disagreements between the reviewers will be resolved by discussion and if no agreement can be reached, a third member of the team will decide whether the study shall be included or not. We will refer to inclusion and exclusion criteria during the screening process. Records of ineligible full text articles along with the reason for ineligibility will be saved for future reference. Eligible articles citations will be uploaded to Covidence. We will present the PRISMA flow diagram(28) demonstrating the search and screening process.

Data Abstraction

A pre-specified standardized data extraction form in a Microsoft Excel sheet will be used to extract the data from the eligible studies. The data extraction form will be pilot tested independently by all reviewers before its use, to standardize the process. Eight reviewers will carry out the extraction, working independently in pairs and in duplicate. In case of disagreement in assessing the methodological quality of the study we will try to resolve it by consensus. If consensus cannot be reached a third designated reviewer will be involved. We will contact authors of primary studies, during data extraction, to provide any missing information.

Node Formation

Within each component of the stabilization pathway, we anticipate the identification numerous similar non-competing interventions (e.g. multiple synthetic and natural surfactants). In an iterative process, clinical experts (GS, SM, GP) blinded to the implications for effect estimates, will come to consensus on definitions of nodes and be presented with the implications of those decisions via network diagrams (e.g. lumping causing the loss of trials comparing lumped interventions, splitting causing disconnected networks). Experts will then be asked to identify whether groups of treatments should be defined as classes (e.g. natural vs synthetic surfactant) or lumped together. Class-based models have the advantage of offering an estimate of class effect as well as shrunken effects of individual treatments, while lumping can allow for more robust

estimation of between-trial variability, and can reduce the probability of chance violations of NMA assumptions. This process will be repeated until a consensus decision is reached on the node making algorithm that meets the criteria of satisfying clinical demands, preserving the assumption that interventions within nodes are sufficiently similar, and presenting data in the least aggregated form possible(29).

Assessment of Risk of Bias

The risk of bias (ROB) of eligible studies will be assessed according to a modified version of the Cochrane Collaboration's ROB tool(18). The six criteria to be assessed are sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow up, selective outcome reporting, and presence of other biases. Each domain will be assigned a score 'definitely low risk', or 'definitely high risk' or 'unclear risk'. Two independent reviewers will assess the ROB. We will try to reach consensus when disagreements between two reviewers when assessing the methodological quality of the studies. Nevertheless, if consensus cannot be reached, a third reviewer will resolve it.

Measures of Treatment Effect

Effect estimates along with 95% credible intervals (CrIs) will be estimated using risk ratios (RR) calculated using methods described by Dias, using the baseline risk parameter to convert odds ratios to risk ratios(29). When random effect models are used estimates will also be accompanied by their 95% predictive interval representing the interval within which we would expect the treatment effect of a future study to lie(30,31). Relative treatment rankings will be summarized using mean ranks with their 95% credible intervals and the Surface Under the Cumulative Ranking curve (SUCRA) values and cumulative probability rankograms(32). SUCRAs range from 0% to 100% with values of 100% representing a hypothetical treatment that is always best without uncertainty.

Assessment of reporting bias

We will construct a comparison adjusted funnel plot for the network to assess the potential publication bias and small-study effects(33), if we retrieve at least 10 studies. We will

inspect plots visually for evidence of asymmetry and if publication bias is suspected we will conduct a sensitivity analysis using models described by Mavridis, Welton and Salanti(34).

Assessment of Transitivity Assumption

Clinical experts (GS, GP, SM) will assess trial characteristics using tables and visualizations to assess whether the transitivity assumption is likely to hold. The characteristics to be evaluated are those that are expected to be effect modifiers and will include gestational age, birth weight, baseline event risk, and ROB. These assessments will be made prior to any meta-analysis to limit to influence of presence or absence of statistical heterogeneity on the assessment of the transitivity assumption. The decision to pool data will be based on consensus. If it is determined that quantitative synthesis is inappropriate, we will summarize our findings narratively.

Direct treatment comparisons

Given that we expect clinical and methodological heterogeneity among the studies (see below in Rating the Confidence in Estimates section), which in turn will create statistical heterogeneity, we will pool evidence for each treatment comparison using a Bayesian random-effects (RE) model(35). In comparison to the fixed-effect model (FE), the RE model is conservative in the sense that it accounts for both within- and between-study variability. The RE model assumes that the observed treatment effect for a study is a combination of a treatment effect common to all studies plus a component specific to that study alone(36,37). Models will be based on standard code modified to include minimally informative priors on baselines, treatment effects, and between trial heterogeneity (38). These priors generally provide more stable estimates, particularly in cases where data are sparse, will be developed using the approach described by Gabry *et al* (39,40).

The Network Meta-Analysis

For each outcome, we will present the network diagram and a forest plot compared against the common comparator with the network estimates as well as league tables showing all pairwise comparisons. To capture the non-competing nature of interventions along the stabilization pathway and to directly fulfill the research objectives we will use component models as described by Welton

et al(41). These models assume that interventions across domains of the stabilization pathway are additive on additive on logit scale for dichotomous outcomes (e.g. mortality). In the absence of direct evidence for a given comparison an indirect comparison will provide an estimate of the treatment effect. In the presence of direct evidence, the NMA will provide a combined estimate (i.e., direct and indirect evidence)(32). For instance, in a triangular network ABC composed by studies that directly compare A vs. B and A vs. C treatments, we can indirectly estimate the effect of B vs. C treatments. In case direct evidence of B vs. C treatment comparison is also available, then a combined estimate of direct and indirect evidence of B vs. C can be calculated using a NMA.

We will fit a Bayesian hierarchical model with weakly informative priors (i.e. normal with mean zero and standard deviation 5 for outcomes on the logit scale) adjusting for correlation of multi-arm trials, and assuming a common-within network heterogeneity variance (uniform on 0-2). We will assess heterogeneity by estimating the magnitude of the between-study variance (42). If the posterior estimate of between-study variance shows signs of prior dominance (e.g. extreme values and long tails, odds ratios approaching infinity), we will assess whether using the empirically estimated informative prior distribution described by Turner *et al*(43) provides more sensible estimates. If the network structure is such that estimates of credible intervals are sufficiently different from original trial estimates and lack clinical validity, we will also present results from a fixed effect model. In this case, we will caution against overinterpretation of credible intervals. Markov chains will be run for a sufficient number of iterations to reach convergence, which we will assess on the basis of the Brooks-Gelman-Rubin diagnostic, with values less than 1.05 considered acceptable if consistent with visual inspection of convergence and time series plots(44). All analyses will be performed in JAGS or similar software via the statistical program R(45,46).

Assessment of Inconsistency

Inconsistency is the statistical manifestation of the violation of the transitivity assumption, which presents as a disagreement between direct and indirect estimates (loop inconsistency), and/or inconsistency between studies that inform the same treatment comparison, but include a different number of treatment arms (design inconsistency). To evaluate both design and loop inconsistency, we will apply the design-by-treatment interaction model with random inconsistency

effects (47,48). These findings will be interpreted within the context of the estimate of between-trial variance as these concepts are closely related and difficult to separate. For example, large estimates of between-trial variance are indicative of heterogeneity within direct comparisons but may also be the result of inconsistency between direct and indirect evidence.

Exploration of heterogeneity and inconsistency

We will perform a network meta-regression using of potential effect modifiers to explore important heterogeneity and/or inconsistency. We propose, the following potential sources of heterogeneity, which could be possible effect modifiers: gestational age, birth weight and ROB. We hypothesize that lower gestational age, and low ROB will be related to less effectiveness of interventions. Overall risk of bias will be determined by taking the average of the three most important risk of bias items identified by expert consensus (sequence generation, allocation concealment, and blinding). Meta-regression models will assume a single shared coefficient for all non-baseline treatments(42). Interpretation of meta-regression models will be in keeping with suggestions from Dias et al., namely: (1) Inclusion of the coefficient leads to a decrease in the estimate of between-study variance; and (2) The 95% credible intervals of the estimated coefficient exclude the null (42).

Sensitivity Analyses

We plan to perform sensitivity analyses of different heterogeneity priors to assess the robustness of results(35,43,49). Further, findings from component models will be compared against a model without this assumption. In both cases, we will compare model fit using both absolute (residual deviance) and relative (DIC) measures as well as a qualitative assessment of whether the analysis leads to an important change in effect estimates.

Rating the confidence in estimates of the effect

We will assess the confidence in the estimates for each outcome using the GRADE approach (50). For this purpose, two authors will independently do the assessment. The confidence in the estimates will be based on four levels: high, moderate, low and very low. For the direct comparisons we will assess and rate each outcome based on the categories: ROB imprecision, inconsistency and publication bias(51-55). To assist with assessment of each

domain, we will use threshold plots, which show the smallest change in study/contrast level estimates required to change the conclusions of the analysis.

We will assess and rate the confidence in all the indirect comparisons –if available– obtained from first order loops following the GRADE categories used for assessing the direct comparisons in addition to the transitivity assessment. Transitivity, also called similarity⁽⁵⁶⁾, is the assumption that an indirect comparison is a valid method to compare two treatments that have not been compared in a head-to-head trial, because the studies are sufficiently similar in important clinical and methodological characteristics, or in other words, that they are similar in their distributions of effect modifiers^(57,58). Then, we will rate the confidence in each NMA effect estimate using the higher rating when both direct and indirect evidence are present.

We will assess and rate the confidence in estimates of effect from the direct comparisons in our pairwise meta-analyses described previously. To rate the confidence in the indirect comparisons, we will focus our assessments on first-order loops (FOLs), i.e., loops connected to the interventions of interest through only one other intervention. For instance, if for A, B and C interventions, there are direct comparisons of A vs. B (AB) and B vs. C (BC), we will be able to indirectly estimate the effects of A vs. C (AC). The AC indirect estimation will be a FOL. We will choose the FOLs with the lowest variances for rating the confidence as they contribute the most to the estimates of effect.

Within FOLs, the indirect comparison confidence will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For example, if we find that AB has moderate confidence and BC has high confidence, we will judge the associated indirect comparison, AC, as moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption has been violated.

Our overall judgment of confidence in the NMA estimate for any pairwise comparison will be the higher of the confidence rating amongst the contributing direct and indirect comparisons. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates have inconsistency. For this purpose, the GRADE approach recommends to assess the incoherence (or inconsistency as described in the ‘The Network Meta-Analysis’ section) criteria, which is defined as the differences between direct and indirect estimates of effect⁽⁵⁹⁾.

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3 **Multi-criteria Acceptability Analysis**
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5 Network meta-analyses provide an estimate of effect estimates of competing interventions,
6 but this alone is not sufficient to aid decision making. We will aim to supplement this review with
7 a stochastic multi-criteria acceptability analysis using methods defined by Tervonen, and Van
8 Valkenhoef(60). These methods use a partial value function to allow for a quantitative risk-benefit
9 analysis across multiple outcomes, given an ordinal ranking of importance for decision making
10 (e.g. Mortality > BPD). Based on the best fitting NMA model, we will conduct stochastic
11 multicriteria acceptability analyses (SMAA): One without preference criteria, and a second with
12 preference criteria determined by expert consensus. Since SMAA is based on estimates constrained
13 to the interval [0,1] we will calculate absolute risk of outcomes based on either a suitably designed
14 observational trial or, if unavailable, a pooled control arm risk of included studies in the reference
15 treatment(61). If treatments require the tradeoff of common (e.g. BPD) and very rare (e.g.
16 mortality) events, we will use the 95% credible interval hull approach(62). The outputs of the
17 SMAA will be a rankogram outlining the probability that a treatment is best, second best, etc., a
18 vector of central weights, a confidence factor for the preference free model; and the rankogram for
19 the ordered model. The vector of central weights provides a summary of the implied preferences
20 required to hold an *a priori* preference for one treatment or another (i.e. the outcome preference
21 implied by a clinician’s current practice). The confidence factor is the probability that a treatment
22 is best given these preferences, and is used as a measure of uncertainty.
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38 **Discussion**
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40 Interventions in the immediate postnatal period may have long-term clinical implications.
41 This NMA will provide the relative effectiveness of commonly practiced delivery room
42 interventions for preterm infants born <33 weeks of gestation in preventing BPD. To the best of
43 our knowledge this will be the first review that will examine the relative effectiveness of each
44 delivery room intervention individually and in combination with respect to important clinical
45 outcomes using novel statistical techniques. Its results will be of interest for a broad range of
46 audience: practice guideline developers, pediatricians, neonatologists, policy makers and
47 researchers, as it could be used to provide clinical recommendations for the choice of sequence of
48 delivery room interventions.
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Our review will have several methodological strengths. First, we will implement a wide comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work. Second, we will use the novel method for rating the confidence in the estimates recommended by the GRADE working group. Third, we will employ a novel SMAA model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes(60). On the other hand, we anticipate some methodological challenges while undertaking such a review. We anticipate some degree of clinical heterogeneity while considering such a large number of competing and non-competing delivery room interventions. Based on the number of interventions identified following the systematic review, we may have to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results.

We hope that this review will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants.

Figure legend:

Figure 1: Physiological sequence of potential delivery room interventions

For peer review only

Table 1. A priori defined outcome measures

| Outcome Measure | Definition |
|--|--|
| Bronchopulmonary dysplasia | No. of neonates who require oxygen at 36 weeks' postmenstrual age (PMA) |
| Mortality | Death before discharge |
| Severe intraventricular hemorrhage | No. of neonates with grades 3-4 based on the Papile criteria |
| Air leak syndromes | No. of neonates with pneumothorax or pulmonary interstitial emphysema confirmed by chest X ray |
| Retinopathy of prematurity (any stage) | No. of neonates with any stage of Retinopathy of prematurity as per the international classification of Retinopathy of prematurity |
| Neurodevelopmental impairment | No. of infants with any degree of neurodevelopmental impairment as assessed by a standardized and validated assessment tool, a child developmental specialist or both, at any age reported (outcome data grouped at 12, 18 and 24 months if available) |

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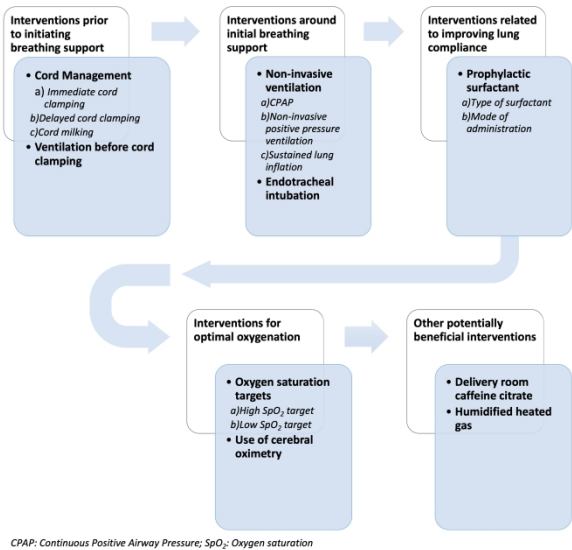


Figure 1: Physiological sequence of potential delivery room interventions

903x508mm (144 x 144 DPI)

Appendix 1: Search strategy for EMBASE, Medline, and PubMed

EMBASE

(newborn OR infant OR neonate OR preterm OR premature) AND [randomized controlled trial]/lim

AND

(continuous AND positive AND airway AND pressure OR cpap OR (nasal AND continuous AND positive AND airway AND pressure) OR ncpap OR (positive AND pressure AND ventilation) OR (intermittent AND positive AND pressure AND ventilation) OR (sustained AND lung AND inflation) OR (sustained AND inflation) OR si) AND [randomized controlled trial]/lim

OR

(supplemental AND oxygen OR (supplemental AND oxygen AND during AND resuscitation) OR oxygen OR surfactant OR (surfactant AND administration) OR (surfactant AND administration, AND early) OR (surfactant AND administration, AND late) OR (minimally AND invasive AND surfactant AND therapy) OR ('less invasive' AND surfactant AND administration)) AND [randomized controlled trial]/lim

OR

(lisa OR intubation OR (endotracheal AND intubation) OR (mechanical AND ventilation) OR caffeine OR (caffeine AND citrate) OR (respiratory AND function AND monitor) OR (delayed AND cord AND clamping) OR (cord AND milking)) AND [randomized controlled trial]/lim

AND

(randomized AND controlled AND trial OR 'randomized controlled trial':it OR (clinical AND trial)) AND [randomized controlled trial]/lim

AND

[randomized controlled trial]/lim AND [embase]/lim AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim)

Limited to embryo from Age Groups fetus from Age Groups newborn from Age Groups infant from Age Groups

Medline

| | |
|-----|---|
| Set | <div>Run Search</div> <div>MEDLINE</div> <div>Search History - " BPD"</div> |
| #5 | #3 AND #2 AND #1 Refined by: PUBLICATION TYPES: (RANDOMIZED CONTROLLED TRIAL) <i>DocType=All document types; Language=All languages;</i> |
| #4 | #3 AND #2 AND #1 <i>DocType=All document types; Language=All languages;</i> |
| #3 | (MH=randomized controlled trial OR TS=randomized controlled trial OR TS=clinical trial) AND DOCUMENT TYPES: (Randomized Controlled Trial) <i>DocType=All document types; Language=All languages;</i> |
| #2 | TS=continuous positive airway pressure OR TS=CPAP OR TS=nasal continuous positive airway pressure OR TS=nCPAP OR TS=positive pressure ventilation OR TS=intermittent positive pressure ventilation OR TS=sustained lung inflation OR TS=sustained inflation OR TS=SI OR TS=supplemental oxygen OR TS=supplemental oxygen during resuscitation OR TS=oxygen OR TS=surfactant OR TS=surfactant administration OR TS=surfactant administration, early OR TS=surfactant administration, late OR TS=minimally invasive surfactant therapy OR TS=less-invasive surfactant administration OR TS=LISA OR TS=intubation OR TS=endotracheal intubation OR TS=mechanical ventilation OR TS=caffeine OR TS=caffeine citrate OR TS=respiratory function monitor OR TS=delayed cord clamping OR TS=cord milking <i>DocType=All document types; Language=All languages;</i> |
| #1 | TS=newborn OR TS=premature OR TS=infant OR TS=neonate OR TS=preterm <i>DocType=All document types; Language=All languages;</i> |

PubMed

- #1 MeSH descriptor: [Infant] explode all trees
- #2 infant*:ti,ab
- #3 neonat*:ti,ab
- #4 newborn*:ti,ab
- #5 preterm:ti,ab
- #6 premature:ti,ab
- #7 #1 or #2 or #3 or #4 or #5 or #6
- #8 "continuous positive airway pressure":ti,ab
- #9 "positive pressure ventilation":ti,ab
- #10 (sustained near/2 inflation):ti,ab
- #11 (supplemental near/2 oxygen):ti,ab
- #12 oxygen:ti,ab
- #13 surfactant:ti,ab
- #14 intubation:ti,ab
- #15 (mechanical* near/1 ventilat*):ti,ab
- #16 caffeine:ti,ab
- #17 "respiratory function monitor":ti,ab
- #18 (cord near/2 ((clamping and delayed) or milking)):ti,ab
- #19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18

#20 #7 and #19

For peer review only

BMJ Open

Delivery Room Interventions to Prevent Bronchopulmonary Dysplasia in Preterm Infants: A Protocol for a Systematic Review and Network Meta-Analysis

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Manuscripts

Delivery Room Interventions to Prevent Bronchopulmonary Dysplasia in Preterm Infants: A Protocol for a Systematic Review and Network Meta-Analysis

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Conflict of Interest:

SM, GP, VC, have declared no conflict of interest. TD provides methodological advice for Cornerstone Research Group Inc. Cornerstone Research Group Inc. consults for various pharmaceutical and medical device companies. BD has provided device training and educational presentations to clinicians on behalf of Mallinckrodt Pharmaceuticals. GMS has registered the RETAIN neonatal resuscitation board (Tech ID 2017083) and RETAIN neonatal resuscitation video game (Tech ID 2017086) under Canadian copyright, and GMS is the owner of RETAIN Labs Inc. (<https://www.playretain.com>), which is distributing these games.

Keywords: INFANTS, NEWBORN, DELIVERY ROOM, BRONCHOPULMONARY DYSPLASIA

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Abbreviations:

| | |
|-----------|---|
| BPD | - Bronchopulmonary dysplasia |
| ELGAN | - Extremely low gestational age newborns |
| IQ | - Intelligence quotient |
| CPAP | - Continuous positive airway pressure |
| NMA | - Network meta-analysis |
| RE | - Random-effects model |
| RCT | - Randomized controlled trials |
| INSURE | - Intubate-Surfactant-Extubate technique |
| LISA/MIST | - Less-invasive surfactant administration/minimally invasive surfactant therapy |
| ROB | - Risk of bias |
| CrIs | - Credible intervals |
| RR | - Risk ratio |
| SUCRA | - Surface Under the Cumulative Ranking curve |
| FE | - Fixed-effect model |
| FOL | - First-order loops |
| SMAA | - Stochastic multicriteria acceptability analysis |

Abstract

Introduction

As gestational age decreases, incidence of bronchopulmonary dysplasia (BPD) and chronic lung disease increases. There are many interventions used in the delivery room to prevent acute lung injury and consequently BPD in these patients. The availability of different treatment options often poses a practical challenge to the practicing neonatologist when it comes to making an evidence based choice as the multitude of pairwise systematic reviews including Cochrane reviews that are currently available only provide a narrow perspective through head-to-head comparisons.

Methods and Analysis

We will conduct a systematic review of all randomized controlled trials evaluating delivery room interventions within the 1st golden hour after birth for prevention of BPD. The primary outcome BPD. Secondary outcomes include death at 36 weeks' postmenstrual age or before discharge; severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria); any air leak syndromes (including pneumothorax or pulmonary interstitial emphysema); retinopathy of prematurity (any stage) and neurodevelopmental impairment at 18-24 months. We will search from their inception to August 2018, the following databases: Medline, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) as well as grey literature resources. Two reviewers will independently screen titles and abstracts, review full texts, extract information, and assess the risk of bias (ROB) and the confidence in the estimate (with Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach). This review will use Bayesian network meta-analysis approach which allows the comparison of the multiple delivery room interventions for prevention of BPD. We will perform a Bayesian network meta-analysis to combine the pooled direct and indirect treatment effect estimates for each outcome, effectiveness, and safety of delivery room interventions for prevention of BPD.

Ethics and Dissemination

The proposed protocol is a network meta-analysis, which has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). The results will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants. Furthermore, we will identify knowledge gaps and will encourage further research for other

therapeutic options. Therefore, its results will be disseminated through peer-reviewed publications and conference presentations. Due to the nature of the design, no ethics approval is necessary.

Strengths and limitations of this study

Strengths:

- Comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work
- Use the novel method for rating the confidence in the estimates recommended by the GRADE working group
- We will employ a novel Stochastic multicriteria acceptability analysis model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes

Limitations:

- We anticipate some degree of clinical heterogeneity while considering such a large number of competing and non-competing delivery room interventions
- Potential to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results

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Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory morbidity associated with premature birth. BPD is defined as either need of supplemental oxygen at i) 28 days postnatal age(1), or ii) 36 weeks' postmenstrual age with or without compatible clinical and radiographic findings(2). BPD affects 30-60% of prematurely born infants with the incidence being inversely proportional to gestational age(3). With increased survival of extremely low gestational age newborns (ELGAN), the incidence of BPD continues to increase despite improvement in neonatal care practices over the last two decades(3). BPD is known to be associated with long-term respiratory morbidity that persists into adolescence and adulthood(4,5). There is also increasing evidence that BPD and duration on supplemental oxygen have long-term adverse effects on cognitive and academic achievement with each percent increase in BPD rate being associated with a 0.01 standard deviation decrease in intelligence quotient (IQ) (0.15 IQ points) (p<0.001)(6,7).

Several antenatal, perinatal, and postnatal factors contribute to the development of BPD. It is postulated that early lung injury and inflammation play an important role in the pathogenesis of BPD (8,9). In the fetus, the gas exchange organ is the placenta and the function of gas exchange is transferred from the placenta to the lungs immediately after birth. Therefore, the newborn infant's lungs must open and be aerated to allow the transition from fetal to postnatal circulation and physiology. However, in ELGANs, several physiological factors prevent this transition. These include lack of surfactant leading to increased alveolar surface tension, non-compliant chest wall, and weak respiratory muscles(10-12). Therefore, most ELGANs require assisted ventilation and/or supplemental oxygen after birth to ensure optimal gas exchange. However, both therapies may also induce lung inflammation due to barotrauma and/or volutrauma and oxygen-free radical generation thereby initiating the pathogenesis of BPD. Therefore, any interventions targeted at limiting lung injury and oxidative stress during resuscitation in the delivery room immediately after the birth may help to prevent the development of BPD or reduce its severity.

A number of clinical trials have been conducted on a variety of delivery room interventions, including i) interventions prior to initiating breathing support (i.e., clamping vs. milking the umbilical cord); ii) interventions around initial breathing support (i.e., continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation, sustained lung inflation or endotracheal intubation); iii) interventions related to improving lung compliance (i.e., prophylactic

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3 surfactant therapy including the different variations in its administration modalities); iv)
4 interventions related to minimizing oxidative stress (i.e., higher vs. lower oxygen saturation
5 targets), v) use of cerebral oximetry, and vi) other potentially beneficial therapies such as caffeine
6 administration (Figure 1)(13,14).
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10 The availability of multiple potential interventions in a resuscitation scenario often poses
11 a practical challenge to health care professionals as to which sequence of interventions would
12 provide the greatest likelihood of minimizing BPD and which interventions are unnecessary and
13 unlikely to be of any benefit(13). There have been previous systematic reviews and pairwise meta-
14 analyses on the different competing interventions such as initial breathing support and oxygen
15 saturation targets(15-17). However, these meta-analyses, though well conducted, provide a narrow
16 perspective to the situation where a sequence of non-competing interventions occur within a short
17 time-frame whereas each intervention has potentially competing variations. Use of a network
18 meta-analysis (NMA) framework may help to provide a more feasible, comprehensive and
19 evidence-based solution to the dilemma that health care professionals face during resuscitation of
20 ELGANs with regards to multiple competing interventions aimed at mitigating lung injury. The
21 Cochrane handbook considers NMA as a highly valuable tool to evaluate and rank treatment
22 options according to their safety and effectiveness(18). Bayesian NMA have been proposed as an
23 effective method for evaluating the effectiveness of multiple competing interventions(18-20).
24 Delivery room interventions consist of a sequence of non-competing category of interventions and
25 within each category there are several potentially competing interventions (Figure 1). Given that
26 many of these competing delivery room interventions have not been compared in head-to-head
27 studies, we expect that some of the possible comparisons between the interventions will not have
28 direct evidence. Hence, we will perform a random effects network meta-analysis (NMA). Delivery
29 room interventions will be defined as all potential interventions in the immediate postnatal
30 period(21-23).
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48 OBJECTIVES

49 To determine the relative effectiveness of commonly practiced delivery room interventions
50 for preterm infants born <33 weeks of gestation in preventing BPD using a Bayesian network
51 meta-analysis.
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METHODS & DESIGN

This systematic review and NMA protocol has been registered on PROSPERO International prospective register of systematic reviews (CRD42018078648). This protocol was developed following the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance(24). The final report will comply with the recommendations of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions(25).

Search Strategy

We will search from their inception to August 2018, the following databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). We will use combination of controlled terms (Medical Subject Heading, MeSH, and Emtree), and free-text terms with various synonyms for the different possible delivery room interventions and BPD. Search alerts will be set up for monthly notification and the search will be repeated before the final manuscript submission to identify any new relevant trials. Search strategies have been developed with liaison with an experienced librarian. No language, publication status or date limit will be used. The search strategies have been detailed in appendix A.

We will seek registered details of selected trials in the U.S. National Institutes of Health resource (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform Search Portal. We intend to obtain additional grey literature from personal communication from experts in the field, reviewing the reference lists of relevant articles, abstracts and conference proceedings (Society for Pediatric Research, European Society for Pediatric Research) and seeking results of unpublished trials. We intend to contact authors of unpublished work and authors of published trials in order to clarify information that is not clear in the articles.

Eligibility Criteria

We will include randomized controlled trials (RCTs) that evaluate the effectiveness of commonly practiced delivery room interventions. Studies will have to have the following characteristics regarding participants, intervention, control and type of study.

- a) Participants: Preterm infants (<33 weeks) requiring intervention(s) during neonatal transition within the 1st golden hour after birth

- b) Interventions include the following: i) cord management (including immediate cord clamping, delayed cord clamping, cord milking, and/or resuscitation attached to the cord); ii) respiratory support (including positive pressure ventilation, CPAP, sustained lung inflation, and/or intubation, and mechanical ventilation); iii) surfactant delivery (type of surfactant delivered via endotracheal tube or laryngeal mask, INSURE (Intubate-Surfactant-Extubate) technique, LISA/MIST (less-invasive surfactant administration/minimally invasive surfactant therapy), and/or nebulized surfactant administration; iv) initial fractional concentration of inspired oxygen (FiO_2) (≤ 0.3 or ≥ 0.6); v) monitoring during resuscitation (respiratory function monitor, near-infrared spectroscopy); vi) medication (e.g., caffeine citrate, or diuretics); vii) use of heated, humidified gas
- c) Comparator: One or more of the above interventions compared to each other or no treatment. Since interventions possible in a delivery room are largely related to delivery room resources, we have *a priori* decided to only include interventions that the infants were subjected to in the immediate postnatal period irrespective of whether these interventions were physically carried out in the room where the infant was born. Studies that examined interventions that were carried out after the initial stabilization period (no randomization within the first hour after birth e.g., feeding, indomethacin, antibiotics) will be excluded from the review. Furthermore, studies must have randomized within the first hour after birth to be eligible. This approach potentially will include studies with randomization within the first hour after birth but study intervention administration within the first two hours after birth (e.g. surfactant or caffeine administration).

Outcomes

Our primary outcome is bronchopulmonary dysplasia (defined as oxygen requirement at 36 weeks' postmenstrual age). Secondary outcomes include death at 36 weeks' postmenstrual age or before discharge; severe intraventricular hemorrhage (grade 3 or 4 based on the Papile criteria)(26); any air leak syndromes (including pneumothorax or pulmonary interstitial emphysema); retinopathy of prematurity (any stage) and neurodevelopmental impairment at 18-24 months. All the outcomes, its definitions and measures are detailed in the table 1. We aim to perform one subgroup analysis comparing infants <28 weeks versus 29-32 weeks.

Patient and Public Involvement

Neither patients nor public were involved in the development of the research question or design of this study. This network meta-analysis does not recruit any patients. The study will be published and presented at conferences to healthcare professionals.

Study selection

The titles and abstracts retrieved will be screened by two independent reviewers in duplicate to assess its eligibility using the Covidence platform (27). As a second step, the full text articles of the potentially eligible studies will be screened to assess their eligibility. We will include the full text of all studies for which both reviewers agree about their inclusion. For both steps, any disagreements between the reviewers will be resolved by discussion and if no agreement can be reached, a third member of the team will decide whether the study shall be included or not. We will refer to inclusion and exclusion criteria during the screening process. Records of ineligible full text articles along with the reason for ineligibility will be saved for future reference. Eligible articles citations will be uploaded to Covidence. We will present the PRISMA flow diagram(28) demonstrating the search and screening process.

Data Abstraction

A pre-specified standardized data extraction form in a Microsoft Excel sheet will be used to extract the data from the eligible studies. The data extraction form will be pilot tested independently by all reviewers before its use, to standardize the process. Eight reviewers will carry out the extraction, working independently in pairs and in duplicate. In case of disagreement in assessing the methodological quality of the study we will try to resolve it by consensus. If consensus cannot be reached a third designated reviewer will be involved. We will contact authors of primary studies, during data extraction, to provide any missing information.

Node Formation

Within each component of the stabilization pathway, we anticipate the identification numerous similar non-competing interventions (e.g. multiple synthetic and natural surfactants). In an iterative process, clinical experts (GS, SM, GP) blinded to the implications for effect estimates, will come to consensus on definitions of nodes and be presented with the implications of those decisions via network diagrams (e.g. lumping causing the loss of trials comparing lumped

interventions, splitting causing disconnected networks). Experts will then be asked to identify whether groups of treatments should be defined as classes (e.g. natural vs synthetic surfactant) or lumped together. Class-based models have the advantage of offering an estimate of class effect as well as shrunken effects of individual treatments, while lumping can allow for more robust estimation of between-trial variability, and can reduce the probability of chance violations of NMA assumptions. This process will be repeated until a consensus decision is reached on the node making algorithm that meets the criteria of satisfying clinical demands, preserving the assumption that interventions within nodes are sufficiently similar, and presenting data in the least aggregated form possible(29).

Assessment of Risk of Bias

The risk of bias (ROB) of eligible studies will be assessed according to a modified version of the Cochrane Collaboration's ROB tool(18). The six criteria to be assessed are sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow up, selective outcome reporting, and presence of other biases. Each domain will be assigned a score 'definitely low risk', or 'definitely high risk' or 'unclear risk'. Two independent reviewers will assess the ROB. We will try to reach consensus when disagreements between two reviewers when assessing the methodological quality of the studies. Nevertheless, if consensus cannot be reached, a third reviewer will resolve it.

Measures of Treatment Effect

Effect estimates along with 95% credible intervals (CrIs) will be estimated using risk ratios (RR) calculated using methods described by Dias, using the baseline risk parameter to convert odds ratios to risk ratios(29). When random effect models are used estimates will also be accompanied by their 95% predictive interval representing the interval within which we would expect the treatment effect of a future study to lie(30,31). Relative treatment rankings will be summarized using mean ranks with their 95% credible intervals and the Surface Under the Cumulative Ranking curve (SUCRA) values and cumulative probability rankograms(32). SUCRAs range from 0% to 100% with values of 100% representing a hypothetical treatment that is always best without uncertainty.

Assessment of reporting bias

We will construct a comparison adjusted funnel plot for the network to assess the potential publication bias and small-study effects(33), if we retrieve at least 10 studies. We will inspect plots visually for evidence of asymmetry and if publication bias is suspected we will conduct a sensitivity analysis using models described by Mavridis, Welton and Salanti(34).

Assessment of Transitivity Assumption

Clinical experts (GS, GP, SM) will assess trial characteristics using tables and visualizations to assess whether the transitivity assumption is likely to hold. The characteristics to be evaluated are those that are expected to be effect modifiers and will include gestational age, birth weight, baseline event risk, and ROB. These assessments will be made prior to any meta-analysis to limit to influence of presence or absence of statistical heterogeneity on the assessment of the transitivity assumption. The decision to pool data will be based on consensus. If it is determined that quantitative synthesis is inappropriate, we will summarize our findings narratively.

Direct treatment comparisons

Given that we expect clinical and methodological heterogeneity among the studies (see below in Rating the Confidence in Estimates section), which in turn will create statistical heterogeneity, we will pool evidence for each treatment comparison using a Bayesian random-effects (RE) model(35). In comparison to the fixed-effect model (FE), the RE model is conservative in the sense that it accounts for both within- and between-study variability. The RE model assumes that the observed treatment effect for a study is a combination of a treatment effect common to all studies plus a component specific to that study alone(36,37). Models will be based on standard code modified to include minimally informative priors on baselines, treatment effects, and between trial heterogeneity (38). These priors generally provide more stable estimates, particularly in cases where data are sparse, will be developed using the approach described by Gabry *et al* (39,40).

The Network Meta-Analysis

For each outcome, we will present the network diagram and a forest plot compared against the common comparator with the network estimates as well as league tables showing all pairwise comparisons. To capture the non-competing nature of interventions along the stabilization pathway and to directly fulfill the research objectives we will use component models as described by Welton *et al*(41). These models assume that interventions across domains of the stabilization pathway are additive on additive on logit scale for dichotomous outcomes (e.g. mortality). In the absence of direct evidence for a given comparison an indirect comparison will provide an estimate of the treatment effect. In the presence of direct evidence, the NMA will provide a combined estimate (i.e., direct and indirect evidence)(32). For instance, in a triangular network ABC composed by studies that directly compare A vs. B and A vs. C treatments, we can indirectly estimate the effect of B vs. C treatments. In case direct evidence of B vs. C treatment comparison is also available, then a combined estimate of direct and indirect evidence of B vs. C can be calculated using a NMA.

We will fit a Bayesian hierarchical model with weakly informative priors (i.e. normal with mean zero and standard deviation 5 for outcomes on the logit scale) adjusting for correlation of multi-arm trials, and assuming a common-within network heterogeneity variance (uniform on 0-2). We will assess heterogeneity by estimating the magnitude of the between-study variance (42). If the posterior estimate of between-study variance shows signs of prior dominance (e.g. extreme values and long tails, odds ratios approaching infinity), we will assess whether using the empirically estimated informative prior distribution described by Turner *et al*(43) provides more sensible estimates. If the network structure is such that estimates of credible intervals are sufficiently different from original trial estimates and lack clinical validity, we will also present results from a fixed effect model. In this case, we will caution against overinterpretation of credible intervals. Markov chains will be run for a sufficient number of iterations to reach convergence, which we will assess on the basis of the Brooks-Gelman-Rubin diagnostic, with values less than 1.05 considered acceptable if consistent with visual inspection of convergence and time series plots(44). All analyses will be performed in JAGS or similar software via the statistical program R(45,46).

Assessment of Inconsistency

Inconsistency is the statistical manifestation of the violation of the transitivity assumption, which presents as a disagreement between direct and indirect estimates (loop inconsistency), and/or inconsistency between studies that inform the same treatment comparison, but include a different number of treatment arms (design inconsistency). To evaluate both design and loop inconsistency, we will apply the design-by-treatment interaction model with random inconsistency effects (47,48). These findings will be interpreted within the context of the estimate of between-trial variance as these concepts are closely related and difficult to separate. For example, large estimates of between-trial variance are indicative of heterogeneity within direct comparisons but may also be the result of inconsistency between direct and indirect evidence.

Exploration of heterogeneity and inconsistency

We will perform a network meta-regression using of potential effect modifiers to explore important heterogeneity and/or inconsistency. We propose, the following potential sources of heterogeneity, which could be possible effect modifiers: gestational age, birth weight and ROB. We hypothesize that lower gestational age, and low ROB will be related to less effectiveness of interventions. Overall risk of bias will be determined by taking the average of the three most important risk of bias items identified by expert consensus (sequence generation, allocation concealment, and blinding). Meta-regression models will assume a single shared coefficient for all non-baseline treatments(42). Interpretation of meta-regression models will be in keeping with suggestions from Dias et al., namely: (1) Inclusion of the coefficient leads to a decrease in the estimate of between-study variance; and (2) The 95% credible intervals of the estimated coefficient exclude the null (42).

Sensitivity Analyses

We plan to perform sensitivity analyses of different heterogeneity priors to assess the robustness of results(35,43,49). Further, findings from component models will be compared against a model without this assumption. In both cases, we will compare model fit using both absolute (residual deviance) and relative (DIC) measures as well as a qualitative assessment of whether the analysis leads to an important change in effect estimates.

Rating the confidence in estimates of the effect

We will assess the confidence in the estimates for each outcome using the GRADE approach (50). For this purpose, two authors will independently do the assessment. The confidence in the estimates will be based on four levels: high, moderate, low and very low. For the direct comparisons we will assess and rate each outcome based on the categories: ROB imprecision, inconsistency and publication bias(51-55). To assist with assessment of each domain, we will use threshold plots, which show the smallest change in study/contrast level estimates required to change the conclusions of the analysis.

We will assess and rate the confidence in all the indirect comparisons –if available– obtained from first order loops following the GRADE categories used for assessing the direct comparisons in addition to the transitivity assessment. Transitivity, also called similarity(56), is the assumption that an indirect comparison is a valid method to compare two treatments that have not been compared in a head-to-head trial, because the studies are sufficiently similar in important clinical and methodological characteristics, or in other words, that they are similar in their distributions of effect modifiers(57,58). Then, we will rate the confidence in each NMA effect estimate using the higher rating when both direct and indirect evidence are present.

We will assess and rate the confidence in estimates of effect from the direct comparisons in our pairwise meta-analyses described previously. To rate the confidence in the indirect comparisons, we will focus our assessments on first-order loops (FOLs), i.e., loops connected to the interventions of interest through only one other intervention. For instance, if for A, B and C interventions, there are direct comparisons of A vs. B (AB) and B vs. C (BC), we will be able to indirectly estimate the effects of A vs. C (AC). The AC indirect estimation will be a FOL. We will choose the FOLs with the lowest variances for rating the confidence as they contribute the most to the estimates of effect.

Within FOLs, the indirect comparison confidence will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For example, if we find that AB has moderate confidence and BC has high confidence, we will judge the associated indirect comparison, AC, as moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption has been violated.

Our overall judgment of confidence in the NMA estimate for any pairwise comparison will be the higher of the confidence rating amongst the contributing direct and indirect comparisons.

However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates have inconsistency. For this purpose, the GRADE approach recommends to assess the incoherence (or inconsistency as described in the ‘The Network Meta-Analysis’ section) criteria, which is defined as the differences between direct and indirect estimates of effect(59).

Multi-criteria Acceptability Analysis

Network meta-analyses provide an estimate of effect estimates of competing interventions, but this alone is not sufficient to aid decision making. We will aim to supplement this review with a stochastic multi-criteria acceptability analysis using methods defined by Tervonen, and Van Valkenhoef(60). These methods use a partial value function to allow for a quantitative risk-benefit analysis across multiple outcomes, given an ordinal ranking of importance for decision making (e.g. Mortality > BPD). Based on the best fitting NMA model, we will conduct stochastic multicriteria acceptability analyses (SMAA): One without preference criteria, and a second with preference criteria determined by expert consensus. Since SMAA is based on estimates constrained to the interval [0,1] we will calculate absolute risk of outcomes based on either a suitably designed observational trial or, if unavailable, a pooled control arm risk of included studies in the reference treatment(61). If treatments require the tradeoff of common (e.g. BPD) and very rare (e.g. mortality) events, we will use the 95% credible interval hull approach(62). The outputs of the SMAA will be a rankogram outlining the probability that a treatment is best, second best, etc., a vector of central weights, a confidence factor for the preference free model; and the rankogram for the ordered model. The vector of central weights provides a summary of the implied preferences required to hold an *a priori* preference for one treatment or another (i.e. the outcome preference implied by a clinician’s current practice). The confidence factor is the probability that a treatment is best given these preferences, and is used as a measure of uncertainty.

Discussion

Interventions in the immediate postnatal period may have long-term clinical implications. This NMA will provide the relative effectiveness of commonly practiced delivery room interventions for preterm infants born <33 weeks of gestation in preventing BPD. To the best of our knowledge this will be the first review that will examine the relative effectiveness of each delivery room intervention individually and in combination with respect to important clinical

outcomes using novel statistical techniques. Its results will be of interest for a broad range of audience: practice guideline developers, pediatricians, neonatologists, policy makers and researchers, as it could be used to provide clinical recommendations for the choice of sequence of delivery room interventions.

Our review will have several methodological strengths. First, we will implement a wide comprehensive search to include published randomized clinical trials in the most important databases, as well as unpublished work. Second, we will use the novel method for rating the confidence in the estimates recommended by the GRADE working group. Third, we will employ a novel SMAA model to determine the most effective sequence of delivery room interventions with respect to the most important clinical outcomes(60). On the other hand, we anticipate some methodological challenges while undertaking such a review. We anticipate some degree of clinical heterogeneity while considering such a large number of competing and non-competing delivery room interventions. Based on the number of interventions identified following the systematic review, we may have to lump interventions into single nodes or split a node into multiple nodes to generate clinically meaningful results.

We hope that this review will provide an evidence based guide to choosing the right sequence of early postnatal interventions that will be associated with the least likelihood of inducing lung injury and BPD in preterm infants.

Figure legend:

Figure 1: Physiological sequence of potential delivery room interventions

For peer review only

Table 1. A priori defined outcome measures

| Outcome Measure | Definition |
|--|--|
| Bronchopulmonary dysplasia | No. of neonates who require oxygen at 36 weeks' postmenstrual age (PMA) |
| Mortality | Death before discharge |
| Severe intraventricular hemorrhage | No. of neonates with grades 3-4 based on the Papile criteria |
| Air leak syndromes | No. of neonates with pneumothorax or pulmonary interstitial emphysema confirmed by chest X ray |
| Retinopathy of prematurity (any stage) | No. of neonates with any stage of Retinopathy of prematurity as per the international classification of Retinopathy of prematurity |
| Neurodevelopmental impairment | No. of infants with any degree of neurodevelopmental impairment as assessed by a standardized and validated assessment tool, a child developmental specialist or both, at any age reported (outcome data grouped at 12, 18 and 24 months if available) |

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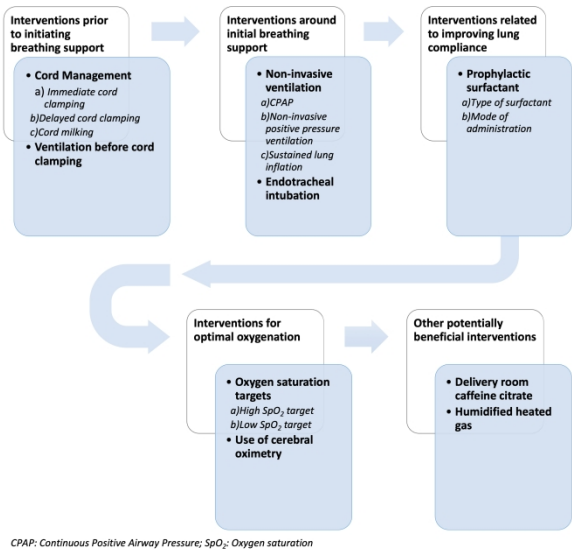


Figure 1: Physiological sequence of potential delivery room interventions

903x508mm (144 x 144 DPI)

Appendix 1: Search strategy for EMBASE, Medline, and PubMed

EMBASE

(newborn OR infant OR neonate OR preterm OR premature) AND [randomized controlled trial]/lim

AND

(continuous AND positive AND airway AND pressure OR cpap OR (nasal AND continuous AND positive AND airway AND pressure) OR ncpap OR (positive AND pressure AND ventilation) OR (intermittent AND positive AND pressure AND ventilation) OR (sustained AND lung AND inflation) OR (sustained AND inflation) OR si) AND [randomized controlled trial]/lim

OR

(supplemental AND oxygen OR (supplemental AND oxygen AND during AND resuscitation) OR oxygen OR surfactant OR (surfactant AND administration) OR (surfactant AND administration, AND early) OR (surfactant AND administration, AND late) OR (minimally AND invasive AND surfactant AND therapy) OR ('less invasive' AND surfactant AND administration)) AND [randomized controlled trial]/lim

OR

(lisa OR intubation OR (endotracheal AND intubation) OR (mechanical AND ventilation) OR caffeine OR (caffeine AND citrate) OR (respiratory AND function AND monitor) OR (delayed AND cord AND clamping) OR (cord AND milking)) AND [randomized controlled trial]/lim

AND

(randomized AND controlled AND trial OR 'randomized controlled trial':it OR (clinical AND trial)) AND [randomized controlled trial]/lim

AND

[randomized controlled trial]/lim AND [embase]/lim AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim)

Limited to embryo from Age Groups fetus from Age Groups newborn from Age Groups infant from Age Groups

Medline

| | |
|-----|---|
| Set | <div>Run Search</div> <div>MEDLINE</div> <div>Search History - " BPD"</div> |
| #5 | #3 AND #2 AND #1 Refined by: PUBLICATION TYPES: (RANDOMIZED CONTROLLED TRIAL) <i>DocType=All document types; Language=All languages;</i> |
| #4 | #3 AND #2 AND #1 <i>DocType=All document types; Language=All languages;</i> |
| #3 | (MH=randomized controlled trial OR TS=randomized controlled trial OR TS=clinical trial) AND DOCUMENT TYPES: (Randomized Controlled Trial) <i>DocType=All document types; Language=All languages;</i> |
| #2 | TS=continuous positive airway pressure OR TS=CPAP OR TS=nasal continuous positive airway pressure OR TS=nCPAP OR TS=positive pressure ventilation OR TS=intermittent positive pressure ventilation OR TS=sustained lung inflation OR TS=sustained inflation OR TS=SI OR TS=supplemental oxygen OR TS=supplemental oxygen during resuscitation OR TS=oxygen OR TS=surfactant OR TS=surfactant administration OR TS=surfactant administration, early OR TS=surfactant administration, late OR TS=minimally invasive surfactant therapy OR TS=less-invasive surfactant administration OR TS=LISA OR TS=intubation OR TS=endotracheal intubation OR TS=mechanical ventilation OR TS=caffeine OR TS=caffeine citrate OR TS=respiratory function monitor OR TS=delayed cord clamping OR TS=cord milking <i>DocType=All document types; Language=All languages;</i> |
| #1 | TS=newborn OR TS=premature OR TS=infant OR TS=neonate OR TS=preterm <i>DocType=All document types; Language=All languages;</i> |

PubMed

- #1 MeSH descriptor: [Infant] explode all trees
- #2 infant*:ti,ab
- #3 neonat*:ti,ab
- #4 newborn*:ti,ab
- #5 preterm:ti,ab
- #6 premature:ti,ab
- #7 #1 or #2 or #3 or #4 or #5 or #6
- #8 "continuous positive airway pressure":ti,ab
- #9 "positive pressure ventilation":ti,ab
- #10 (sustained near/2 inflation):ti,ab
- #11 (supplemental near/2 oxygen):ti,ab
- #12 oxygen:ti,ab
- #13 surfactant:ti,ab
- #14 intubation:ti,ab
- #15 (mechanical* near/1 ventilat*):ti,ab
- #16 caffeine:ti,ab
- #17 "respiratory function monitor":ti,ab
- #18 (cord near/2 ((clamping and delayed) or milking)):ti,ab
- #19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18

#20 #7 and #19

For peer review only

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 1 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|----------------------------|----|---|-------------------------------------|--------------------------|----------------|
| | | | Yes | No | |
| ADMINISTRATIVE INFORMATION | | | | | |
| Title | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | <input type="checkbox"/> | <input type="checkbox"/> | N/A |
| Registration | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 113-114 |
| Abstract | | | | | |
| Authors | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 15 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 3 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | <input type="checkbox"/> | <input type="checkbox"/> | N/A |
| Support | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 36-42 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 36-42 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 36-42 |
| INTRODUCTION | | | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 135-190 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 192-195 |
| METHODS | | | | | |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|-----|---|-------------------------------------|--------------------------|----------------|
| | | | Yes | No | |
| Eligibility criteria | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 222-247 |
| Information sources | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 205-220 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including limits, such that it could be repeated | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 205-220 |
| STUDY RECORDS | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 275-282 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 263-273 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 275-282 |
| Data items | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 249-256 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 249-256 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 300-308 |
| DATA | | | | | |
| Synthesis | 15a | Describe criteria under which study data will be quantitatively synthesized | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 310-446 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 310-446 |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 310-446 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 310-446 |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 448-466 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 411-446 |