Guidelines on non-invasive respiratory support for neonates
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Annexes

1  Detailed GRADE profiles summarizing evidence

2  Summary of individual research studies which formed the basis of recommendations
### ABBREVIATIONS AND GLOSSARY

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AOP</td>
<td>Apnea of prematurity</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CLD</td>
<td>Chronic lung disease</td>
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<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<tr>
<td>ELBW</td>
<td>Extremely low birth weight</td>
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<tr>
<td>ES</td>
<td>Effect size</td>
</tr>
<tr>
<td>FiO₂</td>
<td>Fractional inspired oxygen concentration</td>
</tr>
<tr>
<td>GDG</td>
<td>Guideline development group</td>
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<tr>
<td>GRADE</td>
<td>System for grading the quality of evidence and the strength of recommendations</td>
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<tr>
<td>HFNC</td>
<td>Heated Humidified High-flow Nasal Cannula</td>
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<tr>
<td>NIPPV</td>
<td>Non-invasive positive pressure ventilation</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogram</td>
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<tr>
<td>l</td>
<td>Litre</td>
</tr>
<tr>
<td>LBW</td>
<td>Low birth weight</td>
</tr>
<tr>
<td>MAS</td>
<td>Meconium aspiration syndrome</td>
</tr>
<tr>
<td>MD</td>
<td>Mean difference</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PICO</td>
<td>Population, intervention, comparison, outcome</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>RDS</td>
<td>Respiratory distress syndrome</td>
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<td>ROP</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SGA</td>
<td>Small for gestational age</td>
</tr>
<tr>
<td>VLBW</td>
<td>Very low birth weight</td>
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<tr>
<td>WMD</td>
<td>Weighted mean difference</td>
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</table>
EXECUTIVE SUMMARY

Respiratory distress is a common symptom affecting up to 7% of all term infants and a greater percentage of preterm infants. It is also a common cause of neonatal intensive care admission among term and preterm infants (15-30%). Respiratory distress in a newborn infant is recognized by the presence of any two of the following signs; tachypnea, chest retractions, or grunting. Common respiratory diseases among term infants include transient tachypnea of newborn (TTN), neonatal pneumonia, meconium aspiration syndrome (MAS), and persistent pulmonary hypertension of the newborn (PPHN). Among preterm infants, respiratory distress syndrome (RDS) due to surfactant deficiency, apnea of prematurity, sepsis and bronchopulmonary dysplasia (BPD) are common. BPD results from lung injury due to mechanical ventilation, excessive oxygen exposure and inflammation in a developing lung of preterm infant. These injuries lead to an arrest in alveolarization and scarring from fibrosis. Up to one third of preterm infants and up to half of very low-birth-weight infants (VLBW) can develop BPD.

Various attempts have been made in recent times to prevent and decrease lung injury in neonates by avoidance of mechanical ventilation, judicious use of oxygen, use of non-invasive ventilatory strategies, prevention and treatment of sepsis and promotion of optimum growth. The various non-invasive ventilatory strategies include, nasal continuous positive airway pressure (nCPAP), nasal intermittent positive pressure ventilation (NIPPV), biphasic positive airway pressure (BiPAP), and high-flow nasal cannula (HFNC). Randomized controlled trials suggest that the use of non-invasive ventilatory strategies decrease the need for mechanical ventilation, use of surfactant and lung injury leading to BPD. Among various non-invasive strategies, the use of NIPPV and HFNC may be preferred over CPAP in certain conditions due to greater efficacy or due to greater ease of application and less nasal injury.

The objective of this guideline is to improve the quality of care and outcomes for preterm and term infants by providing recommendations on the use of non-invasive respiratory support in specific respiratory conditions like respiratory distress syndrome (RDS), apnea of prematurity, post-extubation setting and meconium aspiration syndrome in term and preterm infants. The guideline development group identified 15 research questions to be of the highest priority for development of recommendations. Most of the questions are relevant to newborn infants but some are specific to preterm infants and some others address specific disease conditions. For each question, the following four outcomes were considered to be critical: mortality, need for mechanical ventilation, need for surfactant therapy and BPD. Benefits and harms in critical outcomes formed the basis of the recommendations for each question.
A separate search strategy was used for each of the priority questions to identify studies for inclusion in this review. At least two or more databases were searched to identify eligible studies. Search was restricted to studies in English language.

A standardized form was used to extract relevant information from studies. Systematically extracted data included: study identifiers, setting, design, participants, sample size, intervention or exposure, control or comparison group, outcome measures and results. The following quality characteristics were recorded for all studies: allocation concealment, blinding of intervention, loss to follow up, and intention to treat analysis.

We used a GRADE approach for assessing the quality of evidence and the recommendations. The quality of the set of included studies reporting results for an outcome was graded as: high, moderate, low or very low.

The strength of a recommendation reflects the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. The decisions were made on the basis of evidence of benefits and harms; quality of evidence; values and preferences of policy-makers, health-care providers and parents; and whether costs are qualitatively justifiable relative to benefits in low- and middle-income countries.

Each recommendation was graded as **strong** when there was confidence that the benefits clearly outweigh the harms, or **weak** when the benefits probably outweigh the harms, but there was uncertainty about the trade-offs. A strong or weak recommendation was further classified as **situational** if the benefits outweigh the harms in some situations but not in others. For example, some recommendations were considered relevant only to settings in low- and middle-income countries where resources were very limited (e.g. Recommendations .................) while others were considered relevant only to settings where certain types of facilities were available (e.g. Recommendations ......................).
Recommendations on non-invasive respiratory support

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Type of recommendation</th>
<th>Quality of evidence (at least 1 critical outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Among preterm infants with RDS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INTRODUCTION

Respiratory distress is a common symptom affecting up to 7% of all term infants and a greater percentage of preterm infants. It is also a common cause of neonatal intensive care admission among term and preterm infants (15-30%). Respiratory distress in a newborn infant is recognized by the presence of any two of the following signs; tachypnea, chest retractions, or grunting. Common respiratory diseases among term infants include transient tachypnea of newborn (TTN), neonatal pneumonia, meconium aspiration syndrome (MAS), and persistent pulmonary hypertension of the newborn (PPHN). Among preterm infants, respiratory distress syndrome (RDS) due to surfactant deficiency, apnea of prematurity, sepsis and bronchopulmonary dysplasia (BPD) are common. BPD results from lung injury due to mechanical ventilation, excessive oxygen exposure and inflammation in a developing lung of preterm infant. These injuries lead to an arrest in alveolarization and scarring from fibrosis. Up to one third of preterm infants and up to half of very low-birth-weight infants (VLBW) can develop BPD.

Various attempts have been made in recent times to prevent and decrease lung injury in neonates by avoidance of mechanical ventilation, judicious use of oxygen, use of non-invasive ventilatory strategies, prevention and treatment of sepsis and promotion of optimum growth. The various non-invasive ventilatory strategies include, nasal continuous positive airway pressure (nCPAP), nasal intermittent positive pressure ventilation (NIPPV), biphasic positive airway pressure (BiPAP), and high-flow nasal cannula (HFNC). Randomized controlled trials suggest that the use of non-invasive ventilatory strategies decrease the need for mechanical ventilation, use of surfactant and lung injury leading to BPD. Among various non-invasive strategies, the use of NIPPV and HFNC may be preferred over CPAP in certain conditions due to greater efficacy or due to greater ease of application and less nasal injury.
Guideline Development Group

SCOPE OF THE GUIDELINES

Target audience
The primary audience for this guideline includes health-care professionals (pediatricians, nurses and other practitioners) who are responsible for delivering care for neonates in different levels of health care as well health programme managers and policymakers in all settings. The information in this guideline will be useful for developing job aids and tools for training of health professionals to enhance their delivery of neonatal care. These guidelines may also be used by health policymakers to set up facilities in special care newborn units for optimal care of infants.

Population of interest
The guidelines focus on the use of non-invasive respiratory support namely, CPAP, HFNC and NIPPV among term and preterm neonates admitted to healthcare settings with various respiratory conditions in low- and middle-income countries.

Critical outcomes
Four outcomes were considered to be critical by the guideline development group: mortality, severe morbidity, neurodevelopment and anthropometric status. Mortality and severe morbidity over the short term (e.g. during initial hospital stay after birth) or longer term (e.g. infant mortality) were
considered to be critical. However, neurodevelopment and anthropometric status were considered critical only if measured at age 6 months or more. Benefits and harms in critical outcomes formed the basis of the recommendations. When information on critical outcomes was not available, other non-critical outcomes were considered. Examples of these other outcomes include breastfeeding duration or exclusivity, short-term growth, duration of hospital stay, haemoglobin levels and bone mineralization.

Priority questions

These guidelines address the following questions that were identified to be of the highest priority, expressed in PICO (Population, Intervention, Comparison, Outcome) format:

A. **What should be the primary mode of non-invasive respiratory support among preterm infants with or at risk of RDS?**

1. Among preterm neonates with RDS (P), what is the effect of continuous positive airway pressure (CPAP) (I) when compared to oxygen therapy delivered by head box, facemask or nasal canula (C) on mortality and severe morbidities (O)?
2. Among preterm neonates with RDS (P), what is the effect of CPAP (I) when compared to high flow nasal cannula (HFNC) (C1) or nasal intermittent positive pressure ventilation (NIPPV) (C2) on mortality and severe morbidities?
3. Among preterm neonates with RDS (P), what is the effect of CPAP alone (I) when compared to CPAP therapy with early rescue surfactant (C) on mortality and severe morbidities (O)?
4. Among extreme preterm neonates with RDS (P), what is the effect of CPAP (I) when compared to routine intubation and ventilation (C) in the first few hours of life on mortality and severe morbidities (O)?
5. Among preterm neonates with RDS (P), what is the effect of early CPAP therapy (I) when compared to delayed CPAP therapy (C) on mortality and severe morbidities (O)?

B. **What should be the mode of non-invasive respiratory support among preterm infants with apnea of prematurity?**

6. Among neonates with apnea of prematurity (P), what is the effect of CPAP therapy (I) compared with no CPAP therapy (C) on the need for ventilation, mortality, and severe morbidities (O)?
7. Among neonates with apnea of prematurity (P), what is the effect of CPAP(I) therapy compared with HFNC (C1) or NIPPV (C2) on the need for ventilation, mortality and severe morbidities (O)?
C. **What should be the mode of non-invasive respiratory support among preterm infants who are extubated following a period of intubation and mechanical ventilation?**

8. Among preterm neonates being extubated following a period of intubation and mechanical ventilation (P), what is the effect of continuous positive airway pressure (CPAP) therapy (I) with no CPAP therapy (C) on the need for *additional ventilatory support, mortality, and severe morbidities* (O)?

9. Among preterm neonates being extubated following a period of intubation and mechanical ventilation (P), what is the effect of continuous positive airway pressure (CPAP) therapy (I) with high flow nasal cannula (HFNC) (C1) and nasal intermittent positive pressure ventilation (NIPPV) (C2) on the need for *additional ventilatory support, mortality, and severe morbidities (O)*?

D. **What should be the mode of non-invasive respiratory support among term infants with meconium aspiration syndrome?**

10. Among term neonates with meconium aspiration syndrome (MAS) (P), what is the effect of CPAP (I) when compared to oxygen therapy delivered by head box, facemask or nasal canula (C) on *mortality and severe morbidities (O)*?

11. Among term neonates with respiratory distress due to causes other than meconium aspiration syndrome (P), what is the effect of CPAP (I) when compared to oxygen therapy delivered by head box, facemask or nasal canula (C) on *mortality and severe morbidities (O)*?

E. **What should be the characteristics of optimal CPAP device for use as determined by comparison of the efficacy and safety of commonly used CPAP devices?**

12. Among neonates requiring CPAP therapy (P), what is the optimal CPAP device for use (as determined by comparison of the efficacy and safety of commonly used CPAP devices)?
   - Patient interfaces: nasal prongs (I) vs. masks (C1) vs. nasopharyngeal prongs (C2).
   - Pressure generators: Bubble (I) vs. ventilator (C1) vs. IFD (C2).
   - Initial pressure: 5 cm (I) vs. 7-8 cm (C) H2O
   - Weaning: cycling (I) vs. sudden cessation (C1) vs. others (C2)

F. **Among preterm neonates with RDS, which group of neonates are more likely to fail CPAP?**
The outcomes selected for each question and their definitions are presented in Annexe

The following table provides the list of critical outcomes and their definitions.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Definition</th>
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<tbody>
<tr>
<td>In-hospital mortality</td>
<td>All-cause death during the initial hospital stay</td>
</tr>
<tr>
<td>Air leaks</td>
<td>Any air leak syndromes such as pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, etc.</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (BPD)</td>
<td>Use of supplemental oxygen at 36 weeks postmenstrual age</td>
</tr>
<tr>
<td>Failure of extubation</td>
<td>Respiratory acidosis, increased oxygen requirement or apnoea that was frequent or severe leading to additional ventilatory support during the week post-extubation</td>
</tr>
<tr>
<td>Need for re-intubation</td>
<td>Need for intubation and mechanical ventilation for one or more of the reasons mentioned under ‘failure of extubation’ (see above)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Clinical features of sepsis with or without isolation of organisms from blood/CSF/urine and laboratory parameters suggestive of sepsis</td>
</tr>
<tr>
<td>Necrotising enterocolitis (NEC)</td>
<td>Stage 2 to 3 NEC, defined as per modified Bell’s criteria</td>
</tr>
<tr>
<td>Severe intraventricular haemorrhage (IVH)</td>
<td>Grade 3 to 4 IVH as per Papile’s or Volpe’s grading system</td>
</tr>
<tr>
<td>Duration of hospitalisation</td>
<td>Duration of hospital stay</td>
</tr>
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**METHODOLOGY**

**Evidence synthesis**

**Search strategy**

Using the assembled list of priority questions and critical outcomes from the scoping exercise, the guideline development group, along with reviewers identified systematic reviews that were either relevant or potentially relevant and assessed whether they needed to be updated. A systematic review was considered to be out of date if the last search date was two years or more prior to the date of assessment. If any relevant review was found to be out of date, it was updated. Cochrane systematic reviews were the primary source of evidence for the recommendations included in this guideline. In addition, key databases searched included the Cochrane database of systematic reviews
of RCTs, the Cochrane controlled trials register and MEDLINE (1966 to 2005). The reference lists of relevant articles and a number of key journals were hand searched. Details of search strategy is provided in appendix.

**Data abstraction and summary tables of individual studies**

A standardized form was used to extract information from relevant studies. Systematically extracted data included: study identifiers, setting, design, participants, sample size, intervention or exposure, control or comparison group, outcome measures and results. The following quality characteristics were recorded for RCTs: allocation concealment, blinding of intervention or observers, loss to follow up, intention to treat analysis, analysis adjusted for cluster randomization (the latter only for cluster RCTs). The quality characteristics recorded for observational studies were likelihood of reverse causality, selection bias and measurement bias, loss to follow-up and analysis adjusted for confounding. The studies were stratified according to the type of intervention or exposure, study design, birth weight and gestational age, where possible. Effects were expressed as relative risks (RR) or odds ratios (OR) for categorical data, and as mean differences (MD) or weighted mean differences (WMD) for continuous data where possible. All studies reporting on a critical outcome were summarized in a table of individual studies (see Annexes).

**Pooled effects**

Pooled effects for developing recommendations were considered, wherever feasible. Pooled effects from published systematic reviews were used if the meta-analysis was appropriately done, and the reviews were up to date. Where pooling of results was not possible, the range of effect sizes observed in the individual studies was used in the development of recommendations.

**Grading the quality of evidence**

Quality assessment of the body of evidence for each outcome was performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADE approach was used for all the critical outcomes identified in the PICOs, and a GRADE profile was prepared for each quantitative outcome within each PICO. Accordingly, the quality of evidence for each outcome was rated as “high”, “moderate”, “low”, or “very low” based on a set of criteria. As a baseline, RCTs provided “high-quality” evidence, while non-randomized trials and observational studies provided “low-quality” evidence. This baseline quality rating was then downgraded based on consideration of risk of bias, inconsistency, imprecision, indirectness and publication bias. For
observational studies, other considerations, such as magnitude of effect, could lead to upgrading of the rating if there were no limitations that indicated a need for downgrading.

The following briefly describes how these criteria were used:

**Study design**

We included only Randomized controlled studies. Observational studies, and non-randomized experimental studies were considered for narrative review.

GRADE profiler software was used to construct “Summary of Findings” tables for each priority question; these tables include the assessments and judgements relating to the elements described above. Relevant information and data were extracted in a consistent manner from the systematic reviews relating to each priority question by applying the following procedures. First, up-to-date review documents and/or data (e.g. RevMan file) were obtained from the Cochrane Library. Secondly, analyses relevant to the critical outcomes were identified and selected. The data were then imported from the RevMan file (for Cochrane reviews) or manually entered into the GRADE profilers (for non-Cochrane reviews). For each outcome, GRADE assessment criteria (as described above) were applied to evaluate the quality of the evidence. In the final step of the assessment process, GRADE evidence profiles were generated for each priority question.

**Limitations in methods**

Four criteria were used for assessing limitations in the methods of included studies.

1. **Risk of selection bias**: Appropriate allocation concealment and RCT design almost rule out this bias. Allocation is considered to be concealed if (i) central allocation is used including telephone, web-based and pharmacy-controlled randomization; (ii) sequentially numbered intervention packaging of identical appearance; (iii) study reported to be double-blind, placebo-controlled trial; or (iv) sequentially-numbered, opaque, sealed envelopes used. If a majority of evidence was from RCTs that reported adequate allocation concealment, the risk of bias was low. If allocation concealment was not done or was unclear in a majority of studies, it was considered high.

2. **Risk of measurement bias**: Measurement bias can be minimized by blinding the participants and researchers to the intervention. If that is not possible, the observers measuring outcome can be blinded. Lastly, measurement bias is less likely if the outcome
is "objective". If the majority of evidence was from studies where any of the above was done, the risk was low, otherwise it was considered high.

3. **Loss to follow-up:** A large loss to follow-up can lead to bias in results; 20% loss to follow-up was chosen arbitrarily as the cut-off point. If the majority of evidence was from studies where loss to follow-up was less than 20%, the risk was low.

4. **Appropriateness of analysis:** If the majority of evidence was from RCTs which had analysis by intention to treat, and additionally cluster adjustment was done when the design was cluster-RCT, the risk of bias was low, else it was high.

5. **Inconsistency of the results:** The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed from different studies. The quality of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas quality was downgraded when the results were in different directions and confidence limits showed minimal overlap. In case only one study was available, it was considered serious.

For example; if the 95% CI around the pooled effect **included no effect**, and the upper or lower confidence limits **do not** include an effect that, if real, would represent a meaningful benefit or an unacceptable harm, in-consistency was non-serious. Otherwise, it was considered serious.

If the 95% CI around the pooled effect **excluded no effect**, and **both** the upper or lower confidence limits include an effect that, if real, would represent a meaningful benefit or an unacceptable harm, in-consistency was non-serious. Otherwise, it was considered serious.

*Meaningful benefit or unacceptable harm:* For the purposes of these guidelines, a RR of 0.9 or lower, or a MD greater than 0.1 standard deviation (SD) was used as a guide for meaningful benefit. This translated to 10% or greater relative reduction in mortality, 10% or greater relative reduction in severe morbidity. Similarly, unacceptable harm involved a 10% or greater increase in mortality or morbidity.

6. **Indirectness:** Rating of the quality of evidence were downgraded where there were serious or very serious concerns regarding the directness of the evidence. If the
majority of evidence was from studies with both population and intervention the same as the population and intervention of interest, in-directness was non-serious. If the majority of evidence was from studies that had a population and intervention that were different from the population or intervention of interest for these guidelines, it was considered very serious; if either of them were different then, serious.

7. **Imprecision**: The degree of uncertainty around the estimate of effect was assessed. As this was often a function of sample size and number of events, studies with relatively few participants or events (and thus wide confidence intervals around effect estimates) were downgraded for imprecision.

8. **Publication bias**: Quality rating could also be affected by perceived or statistical evidence of bias that may have led to underestimation or overestimation of the effect of an intervention as a result of selective publication based on study results. Where publication bias was strongly suspected, evidence was downgraded by one level.

**Formulation of recommendations**

The GRADE system for grading recommendations was used. The strength of a recommendation reflects the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. The decisions were made on the basis of evidence of benefits and harms, quality of evidence, values and preferences of policy-makers, health-care providers and parents, and whether costs are qualitatively justifiable compared to the benefits in low- and middle-income countries. The recommendations were graded as one of three types:

A **strong recommendation** is one for which there is confidence that the benefits either clearly outweigh the harms or do not. The quality of evidence required to make such a recommendation is at least moderate, although the panel may make exceptions. Similarly, the benefits are likely to be valued highly, and costs appear to be justified by the benefits of making such a recommendation. A strong recommendation can be in favor of an intervention or against it.

A **weak recommendation** is one for which the benefits probably outweigh the harms, but there is high quality evidence; uncertainty in how policy-makers, health workers
and parents value the example, some recommendations were considered relevant only to settings in low- and middle- others were considered relevant only to settings where certain facilities were available (e.g. Recommendations 2 and 17).

RECOMMENDATIONS

What should be the primary mode of non-invasive respiratory support among preterm infants with or at risk of RDS?

QUESTION 1: Among preterm neonates with RDS (P), what is the effect of CPAP (I) when compared to oxygen therapy delivered by head box, facemask or nasal canula (C) on mortality and severe morbidities (O)?

Summary of evidence: Evidence for the use of CPAP as compared to standard treatment (oxygen hood, nasal prongs, oxygen by face-mask) is derived from a Cochrane review(1) that included 6 randomized/quasi-randomized trials(2-7). The entry criteria for participants were based on a clinical diagnosis of respiratory failure and spontaneous breathing in a FiO2 that ranged from 0.3 - 0.95. Antenatal steroids were administered to less than 20% and 35% of participants in the two trials that reported its usage.(7, 8) Only one trial reported the use of surfactant.(8) All the studies were conducted in high-income countries. Of these, one study was conducted in high level nursery (level-2b)(7) while the other five were conducted in level-3 neonatal intensive care units (NICU).

Five studies used random allocation while one used alternate allocation(2). Only four studies ensured proper allocation concealment.(5-8) Blinding of treatment as well as outcome assessment was not done in any of the included studies. Post randomization exclusions were minimal in three studies.(5, 7, 8) The other three studies did not provide adequate information to estimate the numbers excluded after randomization.(2, 4, 6)

Two studies used negative-pressure chambers, two used face-mask CPAP and one used negative pressure for less severe illness and endotracheal CPAP for severe illness. Only the recent study done in 2007 in level-2 NICU used nasal CPAP using Hudson prong and bubble delivery circuit. Pooled analysis of these trials showed that CPAP reduced the rate of treatment failure (death or use of assisted ventilation) (5 studies, n= 314; RR 0.72; 95% CI, 0.56, 0.91) and mortality (6 studies; n= 355; RR 0.53; 95% CI, 0.32-0.87). However, more pneumothoraces occurred in the patients receiving CPAP (6 studies, n= 355; RR 2.64; 95% CI, 1.39, 5.04). These studies were conducted before the availability of surfactant, and are of limited relevance in the modern neonatal intensive care era.

Outcomes
**In-hospital mortality:** The quality of evidence was graded as *low*. Pooled analysis showed significant reduction in the risk of mortality during initial hospital stay in the CPAP group. CPAP therapy, as compared to administration of oxygen by hood/cannula/face mask, would result in 86 fewer deaths per 1000 neonates treated with CPAP (95% CI 23 fewer to 122 fewer).

**Bronchopulmonary dysplasia:** The quality of evidence was graded as *very low*. Pooled analysis showed no significant reduction in the risk of BPD.

**Respiratory failure warranting mechanical ventilation:** It was measured as failure of CPAP or oxygen therapy needing mechanical ventilation. The quality of evidence was graded as *low*. Pooled analysis showed significant reduction in the need for mechanical ventilation in the CPAP group (Tables 4 & 6). For every 1000 neonates treated with CPAP, 147 fewer neonates would require mechanical ventilation (95% CI 47 fewer to 231 fewer).

**Need for surfactant:** The quality of evidence was graded as *very low*. Pooled analysis showed no significant difference in the need for surfactant in the CPAP group compared to oxygen therapy group.

**Any air leaks:** The quality of evidence was graded as *low*. Pooled analysis showed significantly higher risk of air leaks in the CPAP group (Tables 4 & 6). CPAP therapy, as compared to oxygen by head box or cannula, would result in 87 more instances of air leaks for every 1000 neonates treated (95% CI 16 more to 224 more).

**Benefits and Harms:** There is low quality evidence that CPAP reduces the risk of mortality and need for mechanical ventilation but increases the risk of air leaks in preterm neonates with RDS. No other benefits or harms were observed following CPAP application. Majority of the included studies were done in 1970s to 1990s, when CPAP was just being introduced in neonatal units. The high risk of air leaks may be explained by lack of familiarity with the equipment, but the trial conducted in late 2000 also showed a clinically significant increase in the incidence of pneumothorax in the CPAP group.

**Values and preferences:** Notwithstanding the increased risk of air leaks, health care providers, policymakers, and parents in both high-income and low-and middle-income countries are likely to give a high value to the benefits observed in mortality following application of CPAP.

**Costs:** The cost of CPAP equipment and consumables is quite high. This can be minimized to great extent by using indigenous CPAP device and reusable circuits. Also, by reducing the need for mechanical ventilation and possibly surfactant therapy, CPAP could result in cost savings in any unit (the cost of ventilators is about 10 times that of CPAP devices).
RECOMMENDATION 1: Continuous positive airway pressure (CPAP) should be administered to all preterm neonates with RDS

(Strong recommendation, based on low quality evidence for benefit in mortality)

Table 1: Grade profile summary for question 1 (for continuous positive airway pressure vs. oxygen therapy)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>In-hospital mortality (assessed with: Mortality during initial hospital stay)</td>
<td>6</td>
<td>randomised trials</td>
<td>serious</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (assessed with: oxygen requirement at 28 days of age)</td>
<td>5</td>
<td>randomised trials</td>
<td>serious</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>Respiratory failure warranting mechanical ventilation</td>
<td>5</td>
<td>randomised trials</td>
<td>serious</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>Need for surfactant</td>
<td>1</td>
<td>randomised trials</td>
<td>serious</td>
<td>serious</td>
</tr>
<tr>
<td>Any air leak</td>
<td>6</td>
<td>randomised trials</td>
<td>serious</td>
<td>no serious inconsistency</td>
</tr>
</tbody>
</table>

1 Allocation concealment unclear in 2 studies with combined weight of >50%
2 All studies are from high-income countries (HIC)
3 Neither outcome assessors nor treatment team was blinded to group allocation
4 95% confidence interval around the pooled estimate includes both 1) no effect and 2) appreciable benefit or appreciable harm
5 Single study
6 Study from HIC

**QUESTION 2:**
Among preterm neonates, at risk of or with respiratory distress at birth, what is the effect of

a) continuous positive airway pressure (CPAP) therapy with High flow nasal canula (HFNC) as the first-line respiratory support after birth, on the need for mechanical ventilation, need for surfactant treatment, mortality, and severe morbidities?

b) CPAP therapy with nasal intermittent positive pressure ventilation (NIPPV) as the first-line respiratory support after birth on the need for mechanical ventilation, need for surfactant treatment, mortality, and severe morbidities?

**Summary of evidence for Question 2a:** We found one Cochrane systematic review that examined the effect of management with nasal CPAP therapy compared to HFNC among preterm neonates as primary mode of respiratory support. (9) It was last updated in January 2016. We found two non-Cochrane systematic reviews; by Hong et al (10) updated in 2018 and by Fleeman et al (11) last updated in March 2018. Since both the meta-analysis were published in 2019, we used the systematic review by Fleeman et al as the basis for this review as the authors used the same search strategy as the previous Cochrane review.

The ten studies (12-21) relevant to the analysis of primary respiratory support. There was one crossover trial (15) in which preterm infants were only treated for 24 hours before crossing over to the other treatment arm. Nine studies compared HFNC with NCPAP and one pilot study compared HFNC with NIPPV (14).

A total of 1,600 preterm infants were involved in the studies of HFNC versus NCPAP and the study sizes ranged from 20 to 564. The trial comparing HFNC with NIPPV included seventy-six infants. In most studies, where reported, the mean GA at baseline was approximately 32 to 33 weeks. In the crossover trial by Klingenberg et al (15), the mean GA was 29 weeks, and in Glackin et al (12), the mean GA was 27 weeks.

Only the study by Yoder et al (20), which also included preterm infants included participants who had received previous treatment with surfactant. Robert et al (18) explicitly excluded preterm infants who had previously received surfactant. Surfactant was permitted for preterm infants who met
prespecified criteria as part of their treatment in three other studies (13, 16, 21). It is unclear if participants received prior or concurrent surfactant in four studies (12, 14, 15, 17).

**Pooled effects of key outcomes**

The GRADE table 2 enlists the effect size for the available key outcomes for the comparison of CPAP vs. HFNC therapy as the first-line respiratory support after birth among preterm neonates as prophylaxis or for treatment of RDS

**Need for mechanical ventilation:** Six studies involving 1432 neonates reported this outcome. The quality of evidence was graded as moderate. There was no difference in the need for intubation and mechanical ventilation between the two groups (RR 1.15; 95% CI 0.87 to 1.52).

**Mortality:** Seven studies involving 1458 neonates reported this outcome. The quality of evidence was graded as low. There was no difference in the in-hospital mortality rate between the two groups (RR 1.03; 95% CI 0.75 to 1.75). There were few deaths in either arm: 5 (0.7 percent) of 717 preterm infants treated with HHHFNC, and 5 (0.7 percent) of 741 preterm infants treated NCPAP.

**Bronchopulmonary dysplasia:** Six studies involving 707 neonates reported this outcome. The quality of evidence was graded as low. There was no difference in the incidence of BPD between the two groups (RR 1.14; 95% CI 0.32 to 3.33).

**Air-leak:** Six studies involving 1429 neonates reported this outcome. The quality of evidence was graded as low. There was no difference in the incidence of air-leak between the two groups (RR 0.88; 95% CI 0.46 to 1.67). There were few occurrences of air leak in either arm: 15 (2.1 percent) of 702 preterm infants treated with HHHFNC and 18 (2.8 percent) of 727 preterm infants treated with NCPAP. There were no statistically significant differences for either air leak or nasal trauma for HHHFNC versus NIPPV.

**Nasal trauma:** Six studies involving 1179 neonates reported this outcome. The quality of evidence was graded as low. Neonates in the HFNC group had significantly lower risk of nasal trauma (RR 0.52; 95% CI 0.37-0.74)—for every 1000 neonates treated, 68 fewer neonates would have extubation failure (95% CI 37 to 85).

There is low quality evidence that HFNC does not reduce the risk of critical outcomes namely, need for mechanical ventilation within 7 days of trial entry, mortality and BPD when compared to CPAP as the primary mode of respiratory support among preterm infants with or at risk of RDS. There is low quality evidence that HFNC decreases the nasal trauma among these infants when compared to Nasal CPAP.
Table 2: Grade profile summary (for continuous positive airway pressure vs. HFNC as primary respiratory support)

<table>
<thead>
<tr>
<th>failures of primary respiratory support (follow up: mean 7 days; assessed with: need for mechanical ventilation or need for CPAP in HFNC group)</th>
<th>10 randomised trials</th>
<th>not serious</th>
<th>not serious</th>
<th>serious a</th>
<th>serious b</th>
<th>none</th>
<th>95/689 (13.8%)</th>
<th>93/705 (13.2%)</th>
<th>RR 1.03 (0.79 to 1.33)</th>
<th>4 more per 1,000 (from 28 fewer to 44 more)</th>
<th>⨁⨁◯ LOW IMPORT ANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for intubation and mechanical ventilation (follow up: mean 7 days)</td>
<td>6 randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious c</td>
<td>none</td>
<td>90/704 (12.8%)</td>
<td>61/728 (11.1%)</td>
<td>RR 1.15 (0.87 to 1.52)</td>
<td>17 more per 1,000 (from 14 fewer to 58 more)</td>
<td>⨁⨁◯ MODERATE CRITICA L</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>6 randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious c</td>
<td>none</td>
<td>27/348 (7.8%)</td>
<td>24/359 (6.7%)</td>
<td>RR 1.03 (0.32 to 3.33)</td>
<td>2 more per 1,000 (from 45 fewer to 156 more)</td>
<td>⨁⨁◯ MODERATE CRITICA L</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>7 randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious c</td>
<td>none</td>
<td>5/717 (0.7%)</td>
<td>5/741 (0.7%)</td>
<td>RR 1.03 (0.32 to 3.33)</td>
<td>0 fewer per 1,000 (from 5 fewer to 16 more)</td>
<td>⨁⨁◯ MODERATE CRITICA L</td>
</tr>
<tr>
<td>Air leak</td>
<td>6 randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious c</td>
<td>none</td>
<td>15/702 (2.1%)</td>
<td>18/727 (2.5%)</td>
<td>RR 0.88 (0.46 to 1.67)</td>
<td>3 fewer per 1,000 (from 13 fewer to 17 more)</td>
<td>⨁⨁◯ MODERATE IMPORT ANT</td>
</tr>
<tr>
<td>Nasal trauma</td>
<td>6 randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious c</td>
<td>none</td>
<td>15/702 (2.1%)</td>
<td>18/727 (2.5%)</td>
<td>RR 0.88 (0.46 to 1.67)</td>
<td>3 fewer per 1,000 (from 13 fewer to 17 more)</td>
<td>⨁⨁◯ MODERATE IMPORT ANT</td>
</tr>
</tbody>
</table>
CI: Confidence interval; RR: Risk ratio

Explanations
a. Many infants in trials are randomised after a trial of CPAP, the definition of CPAP failure was not uniform. In Hipster and Murki et it was need for higher respiratory support and in some it was need for ventilation
b. Total events only 188 in all the trails together
c. 95% CI for the outcome is crossing the clinical decision

Summary of evidence for Question 2b:
We found one Cochrane systematic review by Lemyre et al (22) in 2016 that compared early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants as primary mode of respiratory support. This systematic review included 10 RCTs (23-32). It was last updated in September 2015. The Cochrane review included ten trials, enrolling a total of 1061 infants.

We used the same search strategy to update the search in MEDLINE via PubMed (September 29, 2015 to August 31, 2019) using the following search terms: (nasal continuous positive airway pressure OR NCPAP OR nasal intermittent positive pressure ventilation OR NIPPV OR nasal intermittent mandatory ventilation OR NIMV OR nasal distending pressure OR nasal positive pressure OR nasal ventilation OR non-invasive positive pressure ventilation OR synchronized intermittent mandatory ventilation OR SIMV OR nasopharyngeal synchronized intermittent mandatory ventilation OR bilevel CPAP OR BiCPAP OR BiPAP OR BiPAP OR SiPAP), plus database-specific limiters for RCTs and neonates.

In the updated search, we identified 241 new citations and 6 new eligible studies (33-37).

Pooled effects of key outcomes
The GRADE table 3 enlists the effect size for the available key outcomes for the comparison of CPAP vs. NIPPV for critical outcomes

Results: NIPPV vs CPAP for primary respiratory support

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of studies</th>
<th>No of participants</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for intubation</td>
<td>15</td>
<td>1745</td>
<td>0.73 [0.62, 0.87]</td>
</tr>
<tr>
<td>Mortality during study period</td>
<td>14</td>
<td>1715</td>
<td>0.65 [0.46, 0.91]</td>
</tr>
</tbody>
</table>
Chronic lung disease | 12 | 1403 | 0.84 [0.64, 1.10]
--- | --- | --- | ---
Pneumothorax | 15 | 1776 | 0.83 [0.50, 1.37]
1.6 Intraventricular hemorrhage (all grades) | 10 | 1085 | 0.98 [0.71, 1.34]
1.8 Necrotizing enterocolitis (≥ Bell’s stage 2) | 10 | 1222 | 0.53 [0.30, 0.91]
1.9 Sepsis | 3 | 220 | 0.96 [0.51, 1.84]
1.10 Retinopathy of prematurity (≥ stage 3) | 4 | 529 | 1.14 [0.58, 2.26]

1. **Need for endotracheal tube ventilation**: Fifteen trials reported on this outcome (n = 1745), which could not be ascertained in one trial (Ramanathan 2012)(29). Meta-analysis showed statistically significant benefit for infants initially treated with NIPPV (typical RR 0.73, 95% CI 0.62 to 0.87).

2. **Mortality during study period**: Fourteen trials (n= 1715) reported this outcome. Overall, small reduction in mortality during neonatal intensive care unit (NICU) admission is noted (typical RR 0.65, 95% CI 0.46 to 0.91).

3. **Chronic lung disease**: Twelve trials (n=1403) reported oxygen need at 36 weeks’ corrected gestational age (CLD). One study defined BPD as oxygen need as day 28 of life(36) (Gharehbaghi 2018) and another did not define BPD (Esmaeilnia 2016)(34) and both were excluded from analyses. Only one trial(29) (Ramanathan 2012), in which infants received surfactant before randomization, reported a decrease in CLD. Meta-analysis did not show a reduction in CLD (typical RR 0.84, 95% CI 0.64, 1.10).

4. **Pneumothorax**: Fifteen trials (n= 1776) reported this outcome. Regardless of the population (surfactant or not before randomization), results showed no difference in the incidence of pneumothorax between infants randomized to NIPPV and those randomized to NCPAP (typical RR 0.83, 95%CI 0.50 to 1.37).

5. **Intraventricular hemorrhage, all grades (Outcome 1.6)** Ten trials (n= 1085) reported on this outcome. Sai Sunil Kishore 2009 (30)reported a combined outcome of IVH and periventricular leukomalacia. No trial showed a difference in IVH between treatment groups (typical RR 0.98, 95% CI 0.71 to 1.34)

6. **Necrotizing enterocolitis (Bell’s stage 2 or more)** Ten trials (n=1222) reported on this outcome. No trial showed a reduction in necrotizing enterocolitis stage 2 or greater in one treatment group compared with the other. The meta-analysis showed a slight reduction (typical RR 0.53, 95%CI 0.30 to 0.91).

7. **Sepsis**: Only three studies (n = 220) reported on this outcome. Results of meta-analysis showed no difference between groups (typical RR 0.96, 95%CI 0.51 to 1.84)
8. Retinopathy of prematurity (≥ stage 3) Only four studies (n = 529) reported on this outcome. Meta-analysis showed no difference between groups (typical RR 1.14, 95% CI 0.58 to 2.26)

NIPPV versus NCPAP (by device)

Eleven trials used NIPPV delivered via ventilator (Bisceglia 2007; Sai Sunil Kishore 2009; Kugelman 2007; Meneses 2011; Armanian 2014; Salama 2015, Oncel 2015, Silveria 2015, Gharehbaghi 2018, Esmaeilnia 2016 and Dursan 2018), three used bilevel devices(27, 32, 33) (Lista 2009; Wood 2013, and Aguiar 2014), and two used both ventilator-driven and bilevel devices (25, 29) (Kirpalani 2013; Ramanathan 2012).

1. Need for intubation: Meta-analysis of 11 trials using ventilator derived NIPPV showed a reduction in need for intubation NIPPV group (RR 0.66; 95% CI 0.54- 0.81; Risk difference -0.11; 95% CI -0.15, -0.06). Results showed no evidence of benefit in the two trials using bilevel devices.

2. Mortality and CLD by device delivering NIPPV, we observed that ventilator derived NIPPV was associated with lesser mortality (RR 0.66; 95% CI 0.48, 0.93) and CLD (RR 0.60; 95% CI 0.42, 0.86). We noted no difference in the rate of pneumothoraces and severe IVH within subgroups

NIPPV vs NCPAP (by device)

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Risk Difference (M-H, Fixed, 95% CI)</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for intubation</td>
<td>16</td>
<td>Subtotals only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ventilator-generated NIPPV</td>
<td>11</td>
<td>1181</td>
<td>-0.11 [-0.15, -0.06]</td>
<td></td>
</tr>
<tr>
<td>• Bilevel NIPPV</td>
<td>3</td>
<td>380</td>
<td>-0.02 [-0.09, 0.05]</td>
<td></td>
</tr>
<tr>
<td>• Mixed devices</td>
<td>2</td>
<td>294</td>
<td>-0.11 [-0.20, -0.02]</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>14</td>
<td>1691</td>
<td>0.66 [0.48, 0.91]</td>
<td></td>
</tr>
<tr>
<td>• Ventilator-generated NIPPV</td>
<td>9</td>
<td>1016</td>
<td>0.66 [0.48, 0.93]</td>
<td></td>
</tr>
<tr>
<td>• Bilevel NIPPV</td>
<td>3</td>
<td>380</td>
<td>0.42 [0.06, 2.85]</td>
<td></td>
</tr>
<tr>
<td>• Mixed devices</td>
<td>2</td>
<td>295</td>
<td>0.78 [0.21, 2.83]</td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>14</td>
<td>Subtotals only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ventilator-generated NIPPV</td>
<td>9</td>
<td>952</td>
<td>0.55 [0.39, 0.77]</td>
<td></td>
</tr>
<tr>
<td>• Bilevel NIPPV</td>
<td>3</td>
<td>380</td>
<td>1.07 [0.50, 2.28]</td>
<td></td>
</tr>
</tbody>
</table>
• Mixed devices  2  282  0.85 [0.54, 1.32]
Pneumothorax  15  Subtotals only
  • Ventilator-generated NIPPV  10  1101  0.71 [0.38, 1.32]
  • Bilevel NIPPV  3  380  0.99 [0.35, 2.78]
  • Mixed devices  2  295  1.42 [0.28, 7.29]
Severe intraventricular hemorrhage (grade III/IV)  8  1061  1.29 [0.75, 2.25]
  • Ventilator-generated NIPPV  6  731  1.06 [0.58, 1.92]
  • Mixed devices  2  330  4.39 [0.76, 25.54]

NIPPV versus NCPAP (by synchronization)

Non-synchronized studies showed benefit (typical RR 0.65, 95% CI 0.54 to 0.79), and synchronized studies showed a trend toward benefit (typical RR 0.67, 95% CI 0.42 to 1.06). Non-synchronized studies also showed benefit in mortality; RR 0.66; 95% CI 0.48, 0.91 and CLD; RR 0.66; 95% CI 0.49, 0.90. We observed no difference in the rate of pneumothoraces between groups. No study using synchronized NIPPV reported on severe IVH.

NIPPV vs NCPAP (by synchronization)

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for intubation</td>
<td>16</td>
<td>1855</td>
<td>0.66 [0.57, 0.78]</td>
</tr>
<tr>
<td>Nonsynchronized NIPPV</td>
<td>11</td>
<td>1367</td>
<td>0.65 [0.54, 0.79]</td>
</tr>
<tr>
<td>Synchronized NIPPV</td>
<td>4</td>
<td>304</td>
<td>0.67 [0.42, 1.06]</td>
</tr>
<tr>
<td>Mixed methods</td>
<td>1</td>
<td>184</td>
<td>0.74 [0.44, 1.22]</td>
</tr>
<tr>
<td>Mortality</td>
<td>14</td>
<td>1692</td>
<td>0.66 [0.48, 0.91]</td>
</tr>
<tr>
<td>Synchronized NIPPV</td>
<td>3</td>
<td>220</td>
<td>0.25 [0.03, 2.19]</td>
</tr>
<tr>
<td>Nonsynchronized NIPPV</td>
<td>10</td>
<td>1287</td>
<td>0.68 [0.49, 0.95]</td>
</tr>
<tr>
<td>Mixed methods</td>
<td>1</td>
<td>185</td>
<td>0.71 [0.16, 3.09]</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>14</td>
<td>1614</td>
<td>0.71 [0.55, 0.92]</td>
</tr>
<tr>
<td>Nonsynchronized NIPPV</td>
<td>9</td>
<td>1138</td>
<td>0.66 [0.49, 0.90]</td>
</tr>
<tr>
<td>Synchronized NIPPV</td>
<td>4</td>
<td>304</td>
<td>0.43 [0.18, 1.01]</td>
</tr>
<tr>
<td>Mixed methods</td>
<td>1</td>
<td>172</td>
<td>1.38 [0.70, 2.72]</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>15</td>
<td>1776</td>
<td>0.83 [0.50, 1.37]</td>
</tr>
<tr>
<td>Nonsynchronized NIPPV</td>
<td>10</td>
<td>1287</td>
<td>0.73 [0.40, 1.34]</td>
</tr>
<tr>
<td>Synchronized NIPPV</td>
<td>4</td>
<td>304</td>
<td>0.86 [0.30, 2.43]</td>
</tr>
</tbody>
</table>
Mixed methods | 1 | 185 | 4.74 [0.23, 97.39]  
Severe intraventricular hemorrhage (grade III/IV) | 8 | 1061 | 1.30 [0.75, 2.25]  
Synchronized NIPPV | 0 | 0 | Not estimable  
Nonsynchronized NIPPV | 8 | 1061 | 1.30 [0.75, 2.25]

**NIPPV vs. CPAP therapy as primary mode of respiratory support: summary**

There is moderate quality evidence that NIPPV does reduce the risk of critical outcomes namely, need for mechanical ventilation within 7 days of trial entry and mortality and BPD when compared to CPAP as the primary mode of respiratory support among preterm infants with or at risk of RDS. There is low quality evidence that NIPPV does not decrease CLD, pneumothorax, ROP and IVH (all grades) when compared to Nasal CPAP.

**Table 3: Grade profile summary (for continuous positive airway pressure vs. NIMV as primary respiratory support)**

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainy</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Need for intubation and mechanical ventilation (follow up: mean 7 days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 randomised trials</td>
<td>Serious a</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td><strong>Mortality during study period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 randomised trials</td>
<td>Serious a</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td><strong>Chronic lung disease (assessed with: Oxygen need at 36 weeks PMA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 randomised trials</td>
<td>Serious a</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious b</td>
</tr>
<tr>
<td><strong>Pneumothorax</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 randomised trials</td>
<td>Serious a</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious b</td>
</tr>
</tbody>
</table>
## Intraventricular hemorrhage (assessed with: All grades)

<table>
<thead>
<tr>
<th></th>
<th>randomised trials</th>
<th>serio us a</th>
<th>not serious</th>
<th>not serious</th>
<th>serious b</th>
<th>none</th>
<th>59/539 (10.9 %)</th>
<th>64/546 (11.7 %)</th>
<th>RR 0.98 (0.71 to 1.34)</th>
<th>2 fewer per 1,000 (from 34 fewer to 40 more)</th>
<th></th>
</tr>
</thead>
</table>

### Necrotizing enterocolitis (assessed with: Bells’ stage 2 or more)

<table>
<thead>
<tr>
<th></th>
<th>randomised trials</th>
<th>serio us a</th>
<th>serious b</th>
<th>not serious</th>
<th>none</th>
<th>18/608 (3.0 %)</th>
<th>35/614 (5.7 %)</th>
<th>RR 0.53 (0.30 to 0.91)</th>
<th>27 fewer per 1,000 (from 40 fewer to 5 fewer)</th>
<th></th>
</tr>
</thead>
</table>

### Retinopathy of Prematurity (assessed with: Stage 3 or more)

<table>
<thead>
<tr>
<th></th>
<th>randomised trials</th>
<th>serio us a</th>
<th>not serious</th>
<th>not serious</th>
<th>serious b</th>
<th>none</th>
<th>15/259 (5.8 %)</th>
<th>14/270 (5.2 %)</th>
<th>RR 1.14 (0.58 to 2.26)</th>
<th>7 more per 1,000 (from 22 fewer to 65 more)</th>
<th></th>
</tr>
</thead>
</table>

CI: Confidence interval; RR: Risk ratio

**Explanations**
- a. Unblinded studies
- b. wide confidence intervals
- c. Individual studies did not show any benefit and have wide confidence intervals

### Evidence to recommendation: Role of HFNC and NIPPV as compared to CPAP as primary mode of support for preterm neonates at risk of RDS

### Balance of benefits and harms

1. When compared to CPAP, high flow nasal cannula (HFNC) does not reduce the risk of need for mechanical ventilation within 7 days of trial entry, mortality and BPD when used as the primary mode of respiratory support among preterm infants with or at risk of RDS (moderate quality evidence). There is moderate quality evidence that HFNC decreases the nasal trauma among these infants when compared to Nasal CPAP.

2. When compared to CPAP, there is moderate quality evidence that NIPPV decreases the risk of need for mechanical ventilation within 7 days of trial entry and mortality (moderate quality evidence) but does not reduce the risk BPD, pneumothorax, ROP or IVH.

3. No major harms were observed with any of the three non-invasive strategies – CPAP, HFNC or NIPPV in preterm neonates as primary respiratory support

### Values and preferences
1. Given the possible beneficial effects observed with NIPPV, health care providers are likely to value the intervention high as the primary therapy for treating preterm neonates who are at risk of RDS. However, they are still likely to prefer using CPAP in these neonates because of its ease of use and possibly lesser need for sophisticated equipment and skilled expertise for setting up and monitoring with NIPPV.

2. Health care providers are unlikely to give high value to the beneficial effects of HFNC on nasal injury as compared to CPAP due to lack of benefits on critical outcomes (need for intubation, BPD and mortality), uncertainty regarding the pressures delivered at different flow rates, and issues in wide spread availability in most settings in India.

Costs

1. The scenario of HFNC vs. CPAP is likely to be different in India, where the indigenous and bubble CPAP machines are available at a much lower cost than the standard HFNC equipment. Also, being a low maintenance equipment, CPAP is likely to be used for more than 6.8 years in most units.

2. No cost-effectiveness or cost-minimisation studies are available for the comparison of NIPPV and CPAP. Unlike CPAP, NIPPV requires the use of a ventilator that is much costlier than typical CPAP devices. Also, the availability of ventilators and trained personnel who can use them optimally is a major issue in most neonatal units, particularly in level-2 units, across the country.

Draft recommendations

1. Preterm very low birth weight neonates at risk of RDS should be initiated on one of the two non-invasive ventilation modes – continuous positive airway pressure (CPAP) or nasal intermittent positive pressure ventilation (NIPPV)

   **Strong recommendation**, based on moderate quality of evidence for benefits in two critical outcomes with NIPPV and consensus among experts for beneficial effects with CPAP

2. Nasal intermittent positive pressure ventilation (NIPPV) delivered by a ventilator using synchronised or non-synchronised methods may preferably be used in preterm very low birth weight neonates as the primary mode of respiratory support where equipment and its expertise are available

   **Weak, situational recommendation** applicable to settings with optimal availability of ventilators and trained manpower, based on low to moderate quality of evidence for benefits in two critical outcomes

**QUESTION 3:** Among preterm neonates with RDS (P), what is the effect of CPAP alone (I) when compared to CPAP therapy with early rescue surfactant (C) on mortality and severe morbidities (O)?

**QUESTION 4:** Among extreme preterm neonates with RDS (P), what is the effect of CPAP (I) when compared to routine intubation and ventilation (C) in the first few hours of life on mortality and severe morbidities (O)?
QUESTION 5: Among preterm neonates with RDS (P), what is the effect of early CPAP therapy (I) when compared to delayed CPAP therapy (C) on mortality and severe morbidities (O)?

What should be the mode of non-invasive respiratory support among preterm infants with apnea of prematurity?

QUESTION 6: Among neonates with apnea of prematurity (P), what is the effect of CPAP therapy (I) compared with no CPAP therapy (C) on the need for ventilation, mortality, and severe morbidities (O)?

Summary of evidence
We did not find any systematic review that compared the effect of CPAP with oxygen therapy by head box or cannula in preterm neonates with apnea. We found one Cochrane systematic review(38) that examined the effect of CPAP therapy compared to theophylline for apnea among preterm infants. It was last updated in March 2005. On updating the search, no new studies eligible for inclusion were identified.

The existing Cochrane review included only a single RCT that compared face mask CPAP therapy with theophylline for management of apnea(39). Of all the outcomes of interest, the data was available only on the requirement of mechanical ventilation and in-hospital mortality.

In-hospital mortality: The quality of evidence was graded as very low. There was no significant difference in the risk of mortality between the CPAP and theophylline groups.

Need for mechanical ventilation: The quality of evidence was graded as low. As compared to neonates in the theophylline group, those in the CPAP group had a significantly higher risk of requiring mechanical ventilation – for every 1000 neonates treated with CPAP, 581 more neonates would require mechanical ventilation (95% CI 117 to 1000).

Other outcomes in the study: The use of mask CPAP was associated with a higher treatment failure rate as measured by less than a 50% reduction in apnea or use of an alternative treatment (RR 2.89, 95% CI 1.12 to 7.47). For every 2.4 infants (95% CI 1.4, 9.5) treated with mask CPAP rather than theophylline, one treatment failure occurred. In the mask CPAP group there was more use of IPPV (RR 3.09, 95% CI 1.42 to 6.70). For every 1.7 infants (95% CI 1.2, 3.3) treated with mask CPAP rather than theophylline, one infant required intubation and mechanical ventilation. In the mask CPAP group, there was a trend towards more deaths in the first year and in death or major disability in survivors at follow up. There were no differences in rates of necrotizing enterocolitis or major disability in survivors at follow up.
Summary
There is low quality evidence that CPAP administered by face mask increases the need for mechanical ventilation, when compared to theophylline, in neonates with apnea of prematurity. There is very low-quality evidence that face mask CPAP does not affect the risk of mortality in these infants. No studies were identified that had compared the effects of CPAP with oxygen therapy by head box or cannula in preterm neonates with apnea.

Evidence to recommendation

Balance of benefits and harms: There is low quality evidence from a single study that CPAP administered by face mask increases the need for mechanical ventilation in preterm neonates with apnea. No other benefits or harms were observed following face mask CPAP application. Given that CPAP is no longer administered by face mask, these results have limited significance for current clinical practice. Moreover, the study was done in early 1980s, when CPAP was just being introduced in neonatal units.

Values and preferences: Given the lack of evidence for benefits or harms with currently used CPAP methods, health care providers are likely to continue with the current practice of administering CPAP by nasal prongs or nasopharyngeal prongs in preterm neonates with Apnea of prematurity.

Costs: The cost of CPAP equipment and consumables is high; but this can be minimized to great extent by using indigenous CPAP device and reusable circuits. The alternative treatment strategies – caffeine and mechanical ventilation – are possibly as or more expensive than CPAP.

Draft recommendation
Table 5: Grade profile summary (for continuous positive airway pressure vs. theophylline for apnea)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trials</td>
<td>no serious risk of bias</td>
<td>serious</td>
<td>serious</td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trials</td>
<td>no serious risk of bias</td>
<td>serious</td>
<td>serious</td>
</tr>
</tbody>
</table>

1 Study from high-income country
2 95% confidence interval around the pooled estimate includes both 1) no effect and 2) appreciable benefit or appreciable harm
3 Single study
Evidence summary

As a first step, we searched for existing systematic reviews – and identified one Cochrane review that compared Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity (40). We updated using the same search strategy used in the review. The Cochrane review included 2 studies Lin 1998 (41) and Ryan 1989 (42). In the updated search, we identified 2 more studies, Gizzi 2014 (43) and Pantalitschka 2009 (44).

Only 2 studies Ryan 1989 and Lin 1998 were included in the meta-analysis. These two trials identified examined the short term (4 - 6 hours) effects of NCPAP and NIPPV in treating apnea of prematurity. No attempt was made to assess longer-term effects such as endotracheal intubation beyond the trial period, in-hospital mortality, air leaks or gastrointestinal complications.

Two other studies, Gizzi 2014 and Pantalitschka 2009 were crossover RCTs. Gizzi compared Flow-SNIPPV, NIPPV and NCPAP all delivered via ventilator and Pantalitschka 2009 compared 4 different modes; NIPPV via a conventional ventilator, NIPPV and NCPAP via a variable flow device, and NCPAP delivered via a constant flow underwater bubble system. Both examined short term outcomes (rates of apnea and desaturation) and had small sample size. The outcomes were reported in median and IQR and the distribution was skewed. Hence, they were not combined in meta-analysis.

Pooled effect size

**Need for mechanical ventilation:** The quality of evidence was graded as very low. There was no difference in the need for mechanical ventilation between NIPPV and CPAP groups

**Rates of apnea:** The quality of evidence was graded as very low. When compared to CPAP, neonates treated with NIPPV, there was a decrease in the incidence of apneic events- for 1000 infants treated with NIPPV, there was 1.19 apneic events lesser as compared to CPAP (95% CI 2.31- 0.07)
Gizzi 2014: The median event rate (desaturations/ bradycardia) per hour during flow SNIPPV, NIPPV and NCPAP was 2.9, 6.1 and 5.9, respectively (p<0.001 and 0.009, compared with flow-SNIPPV). Central apneas per hour were 2.4, 6.3 and 5.4, respectively (p=0.001, for both compared with flow-SNIPPV), while no differences in any other parameter studied were recorded. The authors concluded that flow-SNIPPV seems more effective than NIPPV and NCPAP in reducing the incidence of desaturations, bradycardias and central apnoea episodes in preterm infants.

Pantalitschka 2009: The median event rate (desaturations and bradycardia) was 6.7 per hour with the conventional ventilator in NIPPV mode, and 2.8 and 4.4 per hour with the variable flow device in NCPAP and NIPPV mode, respectively (p value,0.03 for both compared to NIPPV/conventional ventilator). There was no significant difference between the NIPPV/conventional ventilator and the underwater bubble system. The authors concluded that a variable flow NCPAP device may be more effective in treating AOP in preterm infants than a conventional ventilator in NIPPV mode. It remains unclear whether synchronised NIPPV would be even more effective.

Summary

There is very low-quality evidence that non-synchronised NIPPV decreases the apneic events as compared to nasal CPAP in neonates with apnea of prematurity. There is no difference in the need for mechanical ventilation. The effects of synchronized NIPPV and NCPAP delivered through variable flow devices in preterm infants with apnea of prematurity needs further study.

Evidence to recommendation

Balance of benefits and harms: There is very low quality evidence from two studies that non-synchronised NIPPV decreases apneic events in preterm neonates with apnea. No other benefits or harms were observed following NIPPV application.

Values and preferences: Given the benefit of reduction in apneic events health care providers are likely to use NIPPV in treating neonates with apnea that is frequent or severe.

Costs: The cost of administering NIPPV using a ventilator is higher than the use of CPAP device.

Recommendation:
**What should be the mode of non-invasive respiratory support among preterm infants who are extubated following a period of intubation and mechanical ventilation?**

**QUESTION 9:** Among preterm neonates being extubated following a period of intubation and mechanical ventilation (P) *continuous positive airway pressure (CPAP)* therapy with no CPAP therapy on the need for additional ventilatory support, mortality, and severe morbidities?

**Summary of evidence**

We found one Cochrane systematic review that examined the effect of management with nasal CPAP therapy compared to extubation directly to head box oxygen in preterm neonates following a period of mechanical ventilation. (9) It was last updated in December 2007.

We updated the search by searching PubMed using the same search strategy. A total of 415 citations were identified, of which no studies were found to be eligible for inclusion in the review. Consequently, the results of the Cochrane review were used to estimate the pooled effect sizes for different outcomes.

Of the nine trials included in the review (45-54), eight used random allocation for group assignment while seven trials specified the use of sealed envelopes. Because of the nature of the interventions, masking of group assignment was not undertaken in all the studies. Blinding of outcome assessors was not done in most studies. Completeness of outcome assessment was achieved for all patients in six studies.

**Pooled effects of key outcomes**

The GRADE table (see below) enlists the effect size for the available key outcomes for the comparison of CPAP vs. no CPAP therapy following extubation in preterm neonates.

**Need for mechanical ventilation:** Nine studies involving 726 neonates reported this outcome. The quality of evidence was graded as low. There was no difference in the need for reintubation and mechanical ventilation between the two groups (RR 0.87; 95% CI 0.69 to 1.08).

**Failure of extubation:** Nine studies involving 726 neonates reported this outcome. The quality of evidence was graded as low. Neonates in the CPAP group had significantly lower risk of extubation failure— for every 1000 neonates treated, 166 fewer neonates would have extubation failure (95% CI 105 to 215).

**Bronchopulmonary dysplasia:** Five studies involving 433 neonates reported this outcome. The quality of evidence was graded as low. There was no difference in the incidence of BPD between the two groups.

**CPAP vs. no CPAP therapy: summary**

There is low quality evidence that CPAP decreases the incidence of treatment failure, when compared to no CPAP in neonates who were extubated from mechanical ventilation. But there is low quality evidence that
CPAP does not reduce the risk of the need for reintubation and ventilation or BPD in these infants. No information was available for other critical outcomes including mortality and air leaks.
| Question: Should Continuous positive airway pressure therapy (CPAP) vs No CPAP be used in preterm neonates following extubation from mechanical ventilation? |

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Need for mechanical ventilation (assessed with: In the post extubation period)</td>
<td>9 randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Failure of treatment (assessed with: Apneic episodes, respiratory acidosis and increasing oxygen requirement needing the use of additional ventilatory support)</td>
<td>9 randomised trials</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (assessed with: Oxygen requirement at 28 days of life)</td>
<td>5 randomised trials</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

* Neither intervention nor was outcome assessment blinded in all studies.

b 95% CI around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm.

© P for heterogeneity <0.05.
QUESTION 10: Among preterm neonates being extubated following a period of intubation and mechanical ventilation (P), what is the effect of CPAP therapy with high flow nasal cannula (HFNC) on the need for additional ventilatory support, mortality, and severe morbidities?

Summary of evidence: We found one systematic review that examined the efficacy and safety of respiratory support by HFNC with nasal CPAP therapy in preterm neonates following a period of mechanical ventilation(11). The review was published in 2019 (search done till March 2018). Given that the review was published less than 6 months ago, we did not update the search. The results of the review were used as such to estimate the pooled effect sizes of different outcomes.

A total of 10 studies involving 1,201 preterm neonates were included in the review(20, 55-63). Two of the studies included both preterm and term neonates but the review authors used only the data relating to preterm neonates from these two studies. In four studies the mean or median GA was 27 to 28 weeks; in one study 29 weeks; and in three other studies, it was 32 weeks. The sample size of the studies ranged from 49 to 303. Participants in nine studies received surfactant before trial entry (it was unclear in one study).

Eight studies used proper random sequence generation while six studies employed adequate allocation concealment. Blinding of intervention was not possible in all the studies. Blinding of outcome assessors was done in only two studies. Two studies had 20% or more loss to follow-up.

Pooled effects of key outcomes
The GRADE table (see below) enlists the effect size for the available key outcomes for the comparison of CPAP vs. no CPAP therapy following extubation in preterm neonates.

**In-hospital mortality:** A total of seven studies involving 1020 neonates reported this outcome. The quality of evidence was graded as moderate. There was no significant difference in the risk of mortality between the HFNC and CPAP groups (RR 0.71; 95% CI 0.31 to 1.60).

**Air leaks:** Seven studies involving 1037 neonates reported this outcome. The quality of evidence was graded as very low. There was a significant reduction in the incidence of pulmonary air leaks in neonates who received HFNC (RR 0.29; 95% CI 0.11 to 0.76) - for every 1000 neonates managed with HFNC, 21 fewer neonates would develop air leaks (95% CI 7 to 26).

**Bronchopulmonary dysplasia (BPD):** Seven studies involving 1130 neonates reported this outcome. The quality of evidence was graded as low. No significant difference was observed in the risk of BPD between HFNC and CPAP groups (RR 0.86; 95% CI 0.70 to 1.06).
**Respiratory failure requiring re-intubation:** Five studies involving 478 neonates reported this outcome. The quality of evidence was graded as very low. There was no significant difference in the incidence of extubation failure requiring re-intubation and mechanical ventilation between the two groups (RR 1.24; 95% CI 0.81 to 1.89).

**Nasal trauma:** Seven studies involving 860 neonates reported this outcome. The quality of evidence was graded as moderate. There was a significant reduction in the incidence of nasal trauma in neonates who received HFNC (RR 0.35; 95% CI 0.27 to 0.46) - for every 1000 neonates managed with HFNC, 232 fewer neonates would develop air leaks (95% CI 193 to 260).

**CPAP vs. HFNC: summary**

There is very low-quality evidence that high flow nasal cannula (HFNC) reduces the incidence of air leaks, when compared to CPAP in neonates being extubated from mechanical ventilation. But there is low to moderate quality evidence that HFNC does not reduce the risk of mortality or BPD, the other two critical outcomes. There is moderate quality evidence that it reduces the incidence of nasal trauma in these neonates.
### Question: HFNC compared to CPAP for preterm neonates after extubation

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIPPV</td>
<td>NCPAP</td>
<td>Relative</td>
<td>Absolute</td>
</tr>
<tr>
<td></td>
<td>(synchronised)</td>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td></td>
<td></td>
<td>RR</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>9/508 (1.8%)</td>
<td>13/512 (2.5%)</td>
<td>0.71 (0.31 to 1.60)</td>
<td>7 fewer per 1,000 (from 15 more to 18 fewer)</td>
</tr>
<tr>
<td>Pulmonary air leak</td>
<td></td>
<td></td>
<td>RR</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3/518 (0.6%)</td>
<td>15/519 (2.9%)</td>
<td>0.29 (0.11 to 0.76)</td>
<td>21 fewer per 1,000 (from 7 fewer to 26 fewer)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (oxygen supplementation at 36 weeks)</td>
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<tr>
<td>8</td>
<td>113/560 (20.2%)</td>
<td>133/570 (23.3%)</td>
<td>0.86 (0.70 to 1.06)</td>
<td>33 fewer per 1,000 (from 14 more to 70 fewer)</td>
</tr>
<tr>
<td>Respiratory failure requiring re-intubation (within 3 days)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>40/234 (17.1%)</td>
<td>33/244 (13.5%)</td>
<td>1.24 (0.81 to 1.89)</td>
<td>32 more per 1,000 (from 26 fewer to 120 more)</td>
</tr>
<tr>
<td>Nasal trauma</td>
<td></td>
<td></td>
<td>RR</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>54/428 (12.6%)</td>
<td>124/432 (28.6%)</td>
<td>0.35 (0.27 to 0.46)</td>
<td>232 fewer per 1,000 (from 193 fewer to 260 fewer)</td>
</tr>
</tbody>
</table>

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

### Explanations

a. Blinding of outcome assessment not done in most studies, but outcome is objective.
b. 95% CI crosses the clinical decision threshold between recommending and not recommending treatment.
c. Blinding of outcome assessment not done in most studies.
d. Allocation concealment details not provided in studies with >50% weightage in pooled analysis.
e. 95% CI does not cross the clinical decision threshold, but the optimal information size is not met (too few events).
QUESTION 11: Among preterm neonates being extubated following a period of intubation and mechanical ventilation (P), what is the effect of CPAP therapy with nasal intermittent positive pressure ventilation (NIPPV) on the need for additional ventilatory support, mortality, and severe morbidities?

Summary of evidence:

We identified one Cochrane review on NIPPV versus CPAP therapy following extubation in preterm neonates (Lemyre 2017) (22). The review had identified 10 trials enrolling a total of 1431 neonates and comparing extubation of infants to NIPPV or NCPAP(25, 64-72). The authors of the review had searched the relevant databases till September 28, 2015.

We updated the search using the same search strategy used in the review. A total of 226 citations were identified, of which two studies were found to be eligible for inclusion in the review.(73, 74)

Of the 12 trials included, 8 enrolled very low birth weight (VLBW) neonates; 1 trial enrolled only extremely low birth weight neonates (ELBW); while three trials enrolled premature infants at less than 35 or 36 weeks’ gestation. Neonates were extubated from generally low levels of ventilator support (ventilator rates less than 25 breaths per minute and oxygen concentrations less than 40%). Most trials extubated infants at a median age of less than one week. Only five trials synchronised NIPPV delivery – three trials used the Infant Star ventilator with Star Synch abdominal capsule while two used more recent ventilators.

Random sequence generation was done in most trials but allocation concealment was not described in four studies. None of the included studies blinded the intervention or the outcome assessment. Loss to follow-up was minimal to nil in almost all the studies.

Pooled effects of key outcomes

The GRADE table (see below) enlists the effect size for the available key outcomes following therapy with NIPPV versus CPAP following extubation in preterm neonates.

In-hospital mortality: A total of seven studies involving 1338 neonates reported this outcome. The quality of evidence was graded as moderate. There was a significant reduction in the risk of mortality in neonates who received NIPPV (RR 0.70; 95% CI 0.49 to 0.99).

Air leaks: Seven studies involving 1323 neonates reported this outcome. The quality of evidence was graded as low. There was a significant reduction in the risk of pulmonary air leaks in neonates who received NIPPV (RR 0.65; 95% CI 0.42 to 0.98).
**Bronchopulmonary dysplasia (BPD):** Seven studies involving 1209 neonates reported this outcome. The quality of evidence was graded as *low*. No significant difference was observed in the risk of BPD between NIPPV and CPAP groups (RR 0.93; 95% CI 0.80 to 1.09).

**Respiratory failure requiring re-intubation:** Twelve studies involving 1604 neonates reported this outcome. The quality of evidence was graded as *moderate*. There was a significant reduction in the incidence of extubation failure requiring re-intubation and mechanical ventilation in the NIPPV group (RR 0.69; 95% CI 0.60 to 0.79).

**Necrotizing enterocolitis (NEC):** Seven studies involving 1315 neonates reported this outcome. The quality of evidence was graded as *low*. No significant difference was observed in the risk of NEC between NIPPV and CPAP groups (RR 0.87; 95% CI 0.64 to 1.19).

**Duration of hospitalization:** Four studies involving 244 neonates reported this outcome. The quality of evidence was graded as *low*. No significant difference was observed in the duration of hospital stay between NIPPV and CPAP groups (mean difference: 2.7 days; 95% CI -0.01 to 5.44).

**Subgroup analysis**

**Synchronised NIPPV vs. CPAP**

On subgroup analysis comparing NIPPV delivered by synchronised methods with CPAP, no significant difference was observed in the risk of in-hospital mortality (RR 0.97; 95% CI 0.21 to 4.44) or NEC (0.88; 0.64 to 1.2) between the two groups. However, there was a significant reduction in the incidence of air leaks (RR 0.35; 95% CI 0.14 to 0.9), BPD (0.64; 0.44 to 0.95), and extubation failure requiring re-intubation (0.25; 0.15 to 0.41) in neonates who received synchronised NIPPV.

**Non-synchronised NIPPV vs. CPAP**

Subgroup analysis comparing non-synchronised NIPPV with CPAP revealed no significant difference between the groups in the risk of air leaks (RR 0.96; 95% CI 0.52 to 1.79), BPD (0.77; 0.52 to 1.16), or NEC (0.72; 0.11 to 4.79). However, there was a significant reduction in the risk of in-hospital mortality (RR 0.38; 95% CI 0.19 to 0.79) and extubation failure requiring re-intubation (0.63; 0.46 to 0.86) in neonates who received non-synchronised NIPPV.

**HFNC vs. CPAP therapy: summary**

There is low to moderate quality evidence that NIPPV reduces the risk of two critical outcomes namely, in-hospital mortality and air leaks but does not reduce the risk of the other critical outcome – bronchopulmonary dysplasia – in preterm neonates extubated after a period of mechanical
ventilation. There is moderate quality evidence that NIPPV reduces the incidence of extubation failure requiring re-intubation in the first week following extubation.

Evidence to recommendation: **Role of CPAP and other non-invasive ventilation strategies in post-extubation**

**Balance of benefits and harms**

1. When compared to no CPAP therapy, CPAP does reduce the incidence of treatment failure in the week after extubation in preterm neonates. It doesn't reduce the incidence of BPD but its effects on the other two critical outcomes are not known.

2. When compared to CPAP, high flow nasal cannula (HFNC) reduces the incidence of air leaks (very low-quality evidence) and nasal trauma (moderate quality) but does not reduce the risk of mortality, BPD or extubation failure.

3. When compared to CPAP, NIPPV reduces the risk of in-hospital mortality (moderate quality evidence) and air leaks (low quality evidence) but does not reduce the risk of BPD. It also reduces the incidence of extubation failure requiring re-intubation in the week following extubation.

4. No major harms were observed with any of the three non-invasive strategies – CPAP, HFNC or NIPPV in preterm neonates being extubated after mechanical ventilation.

**Values and preferences**

3. Even in the absence of high quality evidence for or against CPAP therapy vis-à-vis no CPAP therapy, health care providers are likely to value CPAP intervention high for treating preterm neonates being extubated after a brief period of ventilation. Indeed, CPAP has long been accepted as the ‘standard of care’ in these preterm neonates – no studies that compared the effect of CPAP and no CPAP have been published since 2005; almost all the studies included in the review were conducted in 1980s and 1990s.

4. Health care providers are unlikely to give high value to the beneficial effects of HFNC on air leaks because of the very low quality evidence supporting it, no evidence for benefits on other critical outcomes (BPD and mortality), uncertainty regarding the pressures delivered at different flow rates, and issues in wide spread availability in most settings in India.

5. Given the possible beneficial effects observed with NIPPV, health care providers are likely to value the intervention high for treating preterm neonates post-extubation. However, they are still likely to prefer using CPAP in these neonates because of its ease of use and possibly lesser need for intensive monitoring.

**Costs**

3. Cost-minimisation analysis by Fleeman et al for NHS, UK estimated the total cost of all consumables to be £67 per week for HFNC and £55 per week for NCPAP (major difference was in the equipment cost – CPAP being roughly £3000 costlier than HFNC.(75) The threshold analysis showed that if the lifespan of the machines reaches 6.8 years, then CPAP becomes the less costly option.
4. The scenario of HFNC vs. CPAP is likely to be different in India, where the indigenous and bubble CPAP machines are available at a much lower cost than the standard HFNC equipment. Also, being a low maintenance equipment, CPAP is likely to be used for more than 6.8 years in most units.

5. No cost-effectiveness or cost-minimisation studies are available for the comparison of NIPPV and CPAP. Unlike CPAP, NIPPV requires the use of a ventilator that is much costlier than typical CPAP devices. Also, the availability of ventilators and trained personnel who can use them optimally is a major issue in most neonatal units, particularly in level-2 units, across the country.

Draft recommendations

1. Preterm very low birth weight neonates being extubated after a brief period of ventilation should be weaned off to one of the two non-invasive ventilation modes – continuous positive airway pressure (CPAP) or nasal intermittent positive pressure ventilation (NIPPV)

   **Strong recommendation**, based on low to moderate quality of evidence for benefits in two critical outcomes with NIPPV and consensus among experts for beneficial effects with CPAP

2. Nasal intermittent positive pressure ventilation (NIPPV) delivered by a ventilator using synchronised or non-synchronised methods may preferably be used in preterm very low birth weight neonates being extubated after a brief period of ventilation

   **Weak, situational recommendation** applicable to settings with optimal availability of ventilators and trained manpower, based on low to moderate quality of evidence for benefits in two critical outcomes
Question: NIPPV compared to NCPAP for preterm neonates after extubation

<table>
<thead>
<tr>
<th>Event</th>
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<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td></td>
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</tr>
<tr>
<td>Pulmonary air leak</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure post extubation</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Necrotising enterocolitis</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hospitalisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### In-hospital mortality

<table>
<thead>
<tr>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>NIPP V</th>
<th>NCPAP (synchronised)</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
<td>47/659 (7.1%)</td>
<td>66/679 (9.7%)</td>
<td>RR 0.70 (0.49 to 0.99)</td>
<td>29 fewer per 1,000 (from 50 fewer to 1 fewer)</td>
<td>⨁⨁⨁</td>
<td>CRITICALLY</td>
</tr>
</tbody>
</table>

### Pulmonary air leak

<table>
<thead>
<tr>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>NIPP V</th>
<th>NCPAP (synchronised)</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 randomised trials</td>
<td>serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
<td>33/651 (5.1%)</td>
<td>46/672 (6.8%)</td>
<td>RR 0.65 (0.42 to 0.98)</td>
<td>24 fewer per 1,000 (from 40 fewer to 1 fewer)</td>
<td>⨁◯</td>
<td>LOW</td>
</tr>
</tbody>
</table>

### Bronchopulmonary dysplasia (oxygen supplementation at 36 weeks)

<table>
<thead>
<tr>
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<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>NIPP V</th>
<th>NCPAP (synchronised)</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 randomised trials</td>
<td>serious d</td>
<td>not serious</td>
<td>not serious</td>
<td>serious d</td>
<td>none</td>
<td>194/600 (32.3%)</td>
<td>206/609 (33.8%)</td>
<td>RR 0.93 (0.80 to 1.09)</td>
<td>24 fewer per 1,000 (from 68 fewer to 30 more)</td>
<td>⨁◯</td>
<td>LOW</td>
</tr>
</tbody>
</table>

### Respiratory failure post extubation

<table>
<thead>
<tr>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>NIPP V</th>
<th>NCPAP (synchronised)</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
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</thead>
<tbody>
<tr>
<td>12 randomised trials</td>
<td>serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>217/796 (27.3%)</td>
<td>318/808 (39.4%)</td>
<td>RR 0.69 (0.60 to 0.79)</td>
<td>122 fewer per 1,000 (from 157 fewer to 83 fewer)</td>
<td>⨁◯</td>
<td>MODERATE</td>
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### Necrotising enterocolitis

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<thead>
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<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>NIPP V</th>
<th>NCPAP (synchronised)</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 randomised trials</td>
<td>serious d</td>
<td>not serious</td>
<td>not serious</td>
<td>serious d</td>
<td>none</td>
<td>67/650 (10.3%)</td>
<td>76/665 (11.4%)</td>
<td>RR 0.87 (0.64 to 1.19)</td>
<td>15 fewer per 1,000 (from 41 fewer to 22 more)</td>
<td>⨁◯</td>
<td>LOW</td>
</tr>
</tbody>
</table>

### Duration of hospitalisation (days)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>NIPP V</th>
<th>NCPAP (synchronised)</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 randomised trials</td>
<td>serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>serious d</td>
<td>none</td>
<td>124</td>
<td>120</td>
<td>-</td>
<td>MD 2.72 higher (0.01 lower to)</td>
<td>⨁◯</td>
<td>LOW</td>
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</table>
What should be the mode of non-invasive respiratory support among term infants with meconium aspiration syndrome?

**QUESTION 13:** Among term neonates with meconium aspiration syndrome (MAS) (P), what is the effect of CPAP (I) when compared to oxygen therapy delivered by head box, facemask or nasal canula (C) on mortality and severe morbidities (O)?

**Summary of evidence**

We searched MEDLINE (1966 to August 31, 2019) using the following strategy: (non-invasive ventilation OR non-invasive respiratory support OR continuous positive airway pressure OR CPAP) AND (Meconium Aspiration Syndrome/ or Meconium/). A total of 64 citations were identified, of which one RCT by Pandita et al was found to be eligible for inclusion in the review (76).

The study by Pandita et al (76) was a multicenter open label RCT. Participants were > 35 weeks’ gestation and birth weight > 2000 g born through meconium staining of amniotic fluid and admitted to the neonatal intensive care unit in the first 24 hours of birth due to respiratory distress (defined as Downe’ score >4 and peripheral capillary oxygen saturation [SpO2] <90% on room air), and chest radiograph suggestive of MAS. Infants requiring intubation at admission, severe asphyxia (5-minute Apgar score < 3 and cord pH < 7), air leak before randomization and major malformations were excluded.

The intervention group was started on a bubble nasal continuous positive airway pressure generator (Fisher and Paykel) using short binausal prongs. The starting pressure was 5 cm H₂O. Both the pressure and the fraction of inspired oxygen were adjusted to maintain target oxygen saturation between 90% and 95%. The neonate was weaned from nasal continuous positive airway pressure when oxygen saturation was consistently > 90%, the fraction of inspired oxygen < 25% and there was no respiratory distress (respiratory rate < 60 breaths/minute, and no grunting). After weaning, oxygen was administered, if needed, via a hood or binausal oxygen prongs. The control group was started on hood oxygen, administered at 5 to 10 l/min. Infants whose hood oxygen failed (ie, oxygen saturation < 90%
for > 15 minutes on fraction of inspired oxygen of 100%) were rescued either with nasal continuous positive airway pressure or mechanical ventilation

Randomization was done using computer generated blocks of 2 or 4, stratified by center and allocation was concealed using opaque sealed envelope. The study was unblinded to clinicians but blinded to the statistician analyzing the outcomes. Infants were followed until discharge from the hospital. The primary outcome was the need for MV in the first 7 days of life. The secondary outcomes were death, pneumothorax, need for surfactant, pulmonary hypertension, culture-positive sepsis (onset of sepsis >72 hours of birth), duration of oxygen, and duration of hospital stay.

Pooled effects of key outcomes

**Need for mechanical ventilation**: One RCT involving 135 neonates reported this outcome. The quality of evidence was graded as low. Infants randomized to the bubble NCPAP group needed mechanical ventilation less frequently in the first 7 days of life compared with oxygen therapy alone (2 [3.0%] vs 17 [25.0%]); odds ratio, 0.09; 95% CI, 0.02-0.43; P = .002).

**Air leak**: One RCT involving 135 neonates reported this outcome. The quality of evidence was graded as low. Only one infant in the CPAP group and none in oxygen therapy group developed pneumothorax.

**In-hospital mortality**: One RCT involving 135 neonates reported this outcome. The quality of evidence was graded as low. Only one infant in oxygen therapy group died. The cause of death was reported as massive pulmonary hemorrhage, secondary to severe sepsis and disseminated intravascular coagulopathy.

**Need for surfactant**: The need for surfactant was less in the CPAP group compared to oxygen therapy (3 [4.5%] vs 11 [16.2%]; odds ratio, 0.24; 95% CI, 0.05-0.87)

**Duration of oxygen therapy**: There was an increased duration of oxygen therapy (median [interquartile range], 45.5 [28.0-78.3] vs 26 [20.0-48.0] hours; P = .001) in the oxygen therapy group compared to CPAP group.

**Incidence of Persistent Pulmonary hypertension (PPHN)**: In the NCPAP group vs standard care group, incidence of persistent pulmonary hypertension treated with inotropes, respiratory support and or sildenafil, was similar (9 [13%] vs 19 [28%]; odds ratio, 0.42; 95% CI, 0.17-1.01)

**Duration of hospital stay**: The duration of hospital stay (median [interquartile range], 5.0 [4.0-8.8] vs 4.0 [4.0-6.0] days; P = .14) was similar

**CPAP vs. no CPAP therapy: summary**

There is low quality evidence that CPAP decreases the need for mechanical ventilation in the first 7 days of life compared with no CPAP or oxygen therapy alone. There is low quality evidence that CPAP therapy is associated with less need for surfactant. There was no difference in mortality between the two groups.
Table: Grade profile summary (for continuous positive airway pressure vs. no CPAP for among late preterm and term infants with meconium aspiration syndrome

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Murki S, Sivanandan S</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>CPAP Oxygen therapy (head box or nasal prong) etc</th>
<th>Number of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 randomised trials</td>
<td>not serious</td>
<td>67</td>
<td>0/67</td>
<td>0.33 (0.01 to 8.30)</td>
<td>OR: 0.33 (0.01 to 8.30)</td>
</tr>
<tr>
<td></td>
<td>not serious</td>
<td>68</td>
<td>1/68</td>
<td>1.5%</td>
<td>OR: 1.5%</td>
</tr>
</tbody>
</table>

| Need for mechanical ventilation |                                              |                   |        |           |            |
| 1 randomised trials | not serious                                   | 67                | 2/67   | 3.0%      | OR: 3.0%   | 221 fewer per 1,000 (from 243 fewer to 125 fewer) | CRITICAL |
|                      | not serious                                   | 68                | 17/68  | 25.0%     | OR: 25.0%  | LOW       |

| Air leak             |                                              |                   |        |           |            |
| 1 randomised trials  | not serious                                   | 67                | 1/67   | 1.5%      | OR: 1.5%   | 0 fewer per 1,000 (from 0 fewer to 0 fewer) | IMPORTANT |
|                      | not serious                                   | 68                | 0/68   | 0.0%      | OR: 0.0%   | LOW       |

| Need for surfactant therapy |                                              |                   |        |           |            |
| 1 randomised trials     | not serious                                   | 67                | 3/67   | 4.5%      | OR: 4.5%   | 117 fewer per 1,000 (from 152 fewer to 18 fewer) | IMPORTANT |
|                        | not serious                                   | 68                | 11/68  | 16.2%     | OR: 16.2%  | LOW       |

Explanations

a. Single RCT
b. Low event rate and the CI for the Odds ratio is very wide
c. Single study and the event rate is low and the CI for the Odds ratio is very wide
Evidence to recommendation: **Role of CPAP in late preterm and term infants with meconium aspiration syndrome**

**Balance of benefits and harms**

When compared to no CPAP therapy, CPAP does reduce the need for mechanical ventilation among infants with MAS. It also decreases the need for surfactant therapy but no effect on mortality. CPAP therapy theoretically can increase the risk of air-leak syndromes especially in larger infants with meconium aspiration syndrome where the lung pathology includes a combination of hyperinflation and atelectasis. While, no significant difference in air-leak was observed, the event rate was very low and only one RCT was included.

**Values and preferences**

One third to half of neonates with MAS have severe disease that requires mechanical ventilation. Health care providers are likely to value CPAP intervention high for treating infants with MAS because of the benefits of decreased need for mechanical ventilation and surfactant therapy. CPAP therapy is easy to administer and can be provided by nurses also.

**Costs**

No cost-effectiveness studies are available for the comparison CPAP versus no CPAP therapy in MAS. However, CPAP therapy may reduce costs to the healthcare system, especially in lower resourced settings by decreasing the need for mechanical ventilation and surfactant therapy. It is also less invasive for the neonates. This is important for resource limited settings where the availability of ventilators and trained personnel who can use them optimally is a major issue.

**Recommendations**

Late preterm and term infants with meconium aspiration syndrome should preferably be started on continuous positive airway pressure (CPAP)

**Strong recommendation, based on low quality of evidence for benefit in one critical outcome (need for mechanical ventilation) and one important outcome (need for surfactant therapy) with CPAP and consensus among experts for beneficial effects with CPAP**

13. Among term neonates with respiratory distress due to causes other than meconium aspiration syndrome (P), what is the effect of CPAP (I) when compared to oxygen therapy delivered by head box, facemask or nasal canula (C) on mortality and severe morbidities (O)?

What should be the characteristics of optimal CPAP device for use as determined by comparison of the efficacy and safety of commonly used CPAP devices?

14. Among neonates requiring CPAP therapy (P), what is the optimal CPAP device for use (as determined by comparison of the efficacy and safety of commonly used CPAP devices)?
   - Patient interfaces: nasal prongs (I) vs. masks (C1) vs. nasopharyngeal prongs (C2).
• Pressure generators: Bubble (I) vs. ventilator (C1) vs. IFD (C2).
• Initial pressure: 5 cm (I) vs. 7-8 cm (C) H2O
• Weaning: cycling (I) vs. sudden cessation (C1) vs. others (C2)

**CPAP DEVICES**

We chose to evaluate the efficacy and safety of the 3 pressure generating devices in the following comparisons

1. Ventilator versus Bubble CPAP
2. Infant flow driver versus ventilator CPAP
3. Infant flow driver versus bubble CPAP

All randomised control trials comparing either of the 3 nasal CPAP pressure generating devices, irrespective of the type of nasal interface (short binasal prongs / nasal masks) were included. In order to avoid the potential confounding effect of interfaces on the outcomes, we excluded studies which used different types of interfaces in the comparison groups. For eg., a trial comparing ventilator versus bubble CPAP was excluded if the trial used single nasal prongs in one group and binasal prongs in the other group. We only included trials which compared two CPAP devices keeping the nasal interface constant in the comparison groups.

We excluded studies which reported only physiological parameters such as heart rate, oxygen saturations, cerebral oxygenation as assessed by Near infra-red spectroscopy etc as outcome parameters without describing any of the clinical outcome parameters listed below.

**Summary of evidence**

We identified one Cochrane systematic review by DePaoli, et al, published in 2008 comparing the effects of different CPAP devices – pressure generators or patient interfaces – on mortality, severe morbidities like air leaks, sepsis, and bronchopulmonary dysplasia, and incidence of treatment failure and complications. It was last updated in August 2007 (1).

Two eligible studies (Stefanescu 2003 and Sun 1999) included in the Cochrane compared different NCPAP devices (ventilator CPAP versus infant flow driver CPAP) in the post extubation setting. Both the studies enrolled intubated preterm very low birth weight infants at the time of extubation (2,3).

We updated the search until July 2019 using terms: (infant, newborn) AND (continuous positive airway pressure or continuous distending pressure) in Pubmed with no filters. A total of 1248 citations were identified, of which 31 were found eligible on screening titles and abstracts. After screening the full text articles of these 31 citations, 7 were found to be eligible for inclusion in the review.
We identified the following studies under the 3 comparison groups for the purpose of analysis:

**Comparison of CPAP generator (keeping the interface common in both groups)**
- Ventilator versus Bubble CPAP (3 studies; Yadav 2012, Tagare 2010, Colaizy 2004 [data NA])
- Infant flow driver versus ventilator CPAP (4 studies; Stefanesco 2003, Sun 1999, Bober 2012; Buettiker 2004 [data NA])

The Grade profile of evidence on ventilator CPAP versus bubble CPAP.

**Ventilator versus bubble CPAP**
1. Need for ventilation (‘CPAP failure’): The quality of evidence was graded as very low. Pooled analysis showed no significant difference in the need for intubation in preterm neonates managed with ventilator CPAP versus bubble CPAP.
2. Bronchopulmonary dysplasia: The quality of evidence was graded as very low. Pooled analysis showed no significant difference in the risk of BPD.
3. Air leaks: The quality of evidence was graded as low. Pooled analysis showed no significant difference in the incidence of air leaks between the two groups.
4. IVH: The quality of evidence was graded as very low. Pooled analysis showed no significant difference in the risk of IVH between the two groups.
5. Nasal septal injury: The quality of evidence was graded as very low. Pooled analysis showed no significant difference in the risk of nasal septal injury between the two groups.
6. Duration of CPAP: The quality of evidence was graded as very low. Pooled analysis showed no significant difference in the duration of CPAP between the two groups.

**IFD vs. ventilator CPAP**
- **In-hospital mortality:** The quality of evidence was graded as moderate. Pooled analysis showed no significant difference in the risk of mortality before discharge in preterm neonates managed with IFD vs. ventilator CPAP.
- **Need for re-intubation (‘Extubation failure’):** The quality of evidence was graded as low. Pooled analysis showed a significant reduction in the need for re-intubation in preterm neonates who were extubated to IFD. For every 1000 neonates receiving IFD following extubation, 134 fewer neonates (95% CI: 47 fewer to 198 fewer) would have extubation failure and require mechanical ventilation.
- **Bronchopulmonary dysplasia:** The quality of evidence was graded as low. Pooled analysis showed no significant difference in the risk of BPD.
- **Air leaks:** The quality of evidence was graded as low. Pooled analysis showed no significant difference in the incidence of air leaks between the two groups.
- **Severe IVH:** The quality of evidence was graded as low. Pooled analysis showed no significant difference in the risk of severe IVH between the two groups.
- **Severe nasal injury:** The quality of evidence was graded as low. Pooled analysis showed significant reduction in the risk of severe nasal injury following use of IFD. For every 1000 neonates receiving IFD for either primary treatment of RDS or after extubation, 156 fewer neonates (95% CI: 108 fewer to 171 fewer) would have severe nasal injury.
• **Duration of CPAP:** The quality of evidence was graded as *low*. Pooled analysis showed no significant difference in the duration of CPAP between the two groups.

**Infant flow driver versus bubble CPAP**

• **In-hospital mortality:** The quality of evidence was graded as *moderate*. Pooled analysis showed no significant reduction in the risk of mortality before discharge in preterm neonates managed with IFD vs. bubble CPAP.

• **Need for ventilation (‘CPAP failure’):** The quality of evidence was graded as *low*. Pooled analysis showed no significant difference in the need for ventilation in preterm neonates with RDS who were managed with either of the CPAP methods.

• **Bronchopulmonary dysplasia:** The quality of evidence was graded as *moderate*. Pooled analysis showed no significant difference in the risk of BPD.

• **Pneumothorax:** The quality of evidence was graded as *low*. Pooled analysis showed no significant difference in the incidence of pneumothorax between the two groups.

• **Severe IVH:** The quality of evidence was graded as *low*. Pooled analysis showed no significant difference in the risk of severe IVH between the two groups.

• **Severe nasal injury:** The quality of evidence was graded as *moderate*. Pooled analysis showed significant reduction in the risk of severe nasal injury following use of IFD. For every 1000 neonates receiving IFD for either primary treatment of RDS or after extubation, 109 fewer neonates (95% CI: 48 fewer to 135 fewer) would have severe nasal injury.

• **Duration of CPAP:** The quality of evidence was graded as *low*. Pooled analysis showed significantly lesser duration of CPAP with IFD when compared to bubble CPAP. The mean reduction in CPAP duration was by 8.5 hours and this ranged from 2.8 hours to 14.3 hours lower with IFD as against bubble CPAP.

**Summary**

There is low to very low quality evidence that ventilator CPAP does not improve any of the critical outcomes when compared to bubble CPAP in preterm neonates. There is low quality evidence that infant flow driver (IFD) is associated with lower risk of extubation failure when compared to ventilator CPAP, but without any effect on hard outcomes such as mortality and BPD. There is also low quality evidence that the use of IFD CPAP compared to ventilator CPAP is associated with lower incidence of nasal injury. When compared with bubble CPAP, there is moderate quality evidence that IFD reduces the severe local (nasal) injury and low quality evidence that IFD reduces duration of CPAP in preterm neonates; no benefits were observed in other critical outcomes.

**Evidence to recommendation (Draft considerations)**

**Balance of benefits and harms:** There is moderate to very low quality evidence that ventilator CPAP, bubble CPAP and IFD perform equally with respect to critical outcomes like mortality and BPD in preterm neonates. There is low and moderate quality evidence that IFD reduces the risk of nasal injury when compared to ventilator CPAP and bubble CPAP, respectively in these infants. This finding needs to be interpreted carefully as the incidence of nasal injury depends on difference in the nasal interfaces, fixation technique, flow delivery mechanisms, humidification and nursing competence. IFD usually comes with its own prongs while prongs from other manufacturers are used with ventilators as well as bubble CPAP devices.
When compared to ventilator CPAP, there is low quality evidence to show that IFD is associated with lower incidence of extubation failure. The variable inspiratory and expiratory flow of IFD has been postulated to reduce work of breathing. Yet, one would desire that the finding be consistently shown across larger studies and varying populations to meaningfully change practices.

Overall, only a small number of studies that had enrolled only a few hundreds of infants were available for all the comparisons; therefore, confidence in these results is likely to be low.

Values and preferences: Health care providers and policy-makers in both high-income and low-and middle-income countries are likely to prefer IFD over ventilator and bubble CPAP, given the benefits observed in the risk of extubation failure and nasal injury. Nevertheless, the fact that bubble CPAP can be assembled indigenously would appeal to both health care providers as well as policy makers from resource restricted settings.

Costs: Both ventilators and IFD are quite expensive than bubble CPAP. It is difficult to justify the higher costs of these devices in the absence of evidence for significant benefits with either of them.

Draft recommendation

Bubble CPAP should preferably be used in preterm neonates requiring continuous positive airway pressure for any indication.

(Weak recommendation, based on low to very low quality evidence for no significant difference in critical outcomes and cost and availability considerations in low- and middle-income countries)
<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of studies</strong></td>
<td><strong>Design</strong></td>
<td><strong>Risk of</strong></td>
<td><strong>Inconsistency</strong></td>
<td><strong>Indirectness</strong></td>
</tr>
<tr>
<td>CPAP failure</td>
<td>1</td>
<td>randomised trials</td>
<td>serious¹</td>
<td>serious²</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (assessed with: Oxygen requirement at 36 weeks PMA)</td>
<td>1</td>
<td>randomised trials</td>
<td>serious⁴</td>
<td>serious²</td>
</tr>
<tr>
<td>Air leaks</td>
<td>2</td>
<td>randomised trials</td>
<td>serious⁵</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>Intraventricular hemorrhage (assessed with: stage 2 or more)</td>
<td>1</td>
<td>randomised trials</td>
<td>serious⁴</td>
<td>serious²</td>
</tr>
<tr>
<td>Nasal septal injury</td>
<td>1</td>
<td>randomised trials</td>
<td>serious¹</td>
<td>serious²</td>
</tr>
<tr>
<td>Duration of CPAP (hours) (Better indicated by lower values)</td>
<td>1</td>
<td>randomised trials</td>
<td>serious⁴</td>
<td>serious²</td>
</tr>
</tbody>
</table>
Outcome assessors were blinded but the investigators were not blinded.

Single study

95% CI around the pooled estimate includes both 1) no effect and 2) appreciable benefit or appreciable harm.

Outcome assessment was not blinded

Outcome assessment not blinded in the study(ies) with >50% weightage

Table 4 summarises the Grade profile summary for infant flow driver versus ventilator CPAP.

Table 4: Grade profile summary for ‘infant flow driver (IFD) vs. ventilator CPAP’

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>In-hospital mortality (assessed with: death before discharge )</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>randomised trials</td>
<td>no serious risk of bias¹</td>
<td>no serious inconsistency</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

| Extubation failure |
| 3 | randomised trials | Serious³ | Serious⁴ | Not serious | no serious imprecision | none | 54/209 (25.8%) | 83/210 (39.5%) | RR 0.66 (0.5 to 0.88) | 134 fewer per 1000 (from 47 fewer to 198 fewer) |

| Bronchopulmonary dysplasia (assessed with: Oxygen at 36 weeks PMA) |
| 3 | randomised trials | Serious¹ | no serious inconsistency | Not serious | Serious² | none | 119/269 (44.2%) | 107/269 (39.8%) | RR 1.11 (0.92 to 1.34) | 44 more per 1000 (from 32 fewer to 135 more) |

| Air leaks |
| 3 | randomised trials | Serious¹ | no serious inconsistency | Not serious | Serious² | none | 37/269 (13.8%) | 34/269 (12.6%) | RR 1.14 (0.76 to 1.71) | 18 more per 1000 (from |

¹ Outcome assessors were blinded but the investigators were not blinded.
² Single study
³ 95% CI around the pooled estimate includes both 1) no effect and 2) appreciable benefit or appreciable harm.
⁴ Outcome assessment was not blinded
⁵ Outcome assessment not blinded in the study(ies) with >50% weightage
<table>
<thead>
<tr>
<th>Event</th>
<th>Randomised Trials</th>
<th>Serious</th>
<th>No Serious Inconsistency</th>
<th>Not Serious</th>
<th>Serious</th>
<th>None</th>
<th>CV</th>
<th>Event</th>
<th>Randomised Trials</th>
<th>Serious</th>
<th>No Serious Inconsistency</th>
<th>Not Serious</th>
<th>Serious</th>
<th>None</th>
<th>CV</th>
<th>Event</th>
<th>Randomised Trials</th>
<th>Serious</th>
<th>No Serious Inconsistency</th>
<th>Not Serious</th>
<th>Serious</th>
<th>None</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe intraventricular hemorrhage (assessed with: grade 3 and 4 IVH by USG)</td>
<td>2 randomised trials</td>
<td>Serious</td>
<td>no serious inconsistency</td>
<td>Not serious</td>
<td>Serious</td>
<td>none</td>
<td>13/219 (5.9%)</td>
<td>18/219 (8.2%)</td>
<td>RR 0.77 (0.4 to 1.47)</td>
<td>19 fewer per 1000 (from 49 fewer to 39 more)</td>
<td>⬤⬤◯◯ LOW</td>
<td>IMPORTANT</td>
<td></td>
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</tr>
<tr>
<td>Severe nasal injury</td>
<td>1 randomised trials</td>
<td>Serious</td>
<td>serious</td>
<td>Not serious</td>
<td>no serious imprecision</td>
<td>none</td>
<td>3/141 (2.1%)</td>
<td>24/135 (17.8%)</td>
<td>RR 0.12 (0.04 to 0.39)</td>
<td>156 fewer per 1000 (from 108 fewer to 171 fewer)</td>
<td>⬤⬤◯◯ LOW</td>
<td>IMPORTANT</td>
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</tr>
<tr>
<td>Duration of CPAP (measured with: total days on CPAP therapy; Better indicated by lower values)</td>
<td>3 randomised trials</td>
<td>Serious</td>
<td>no serious inconsistency</td>
<td>Not serious</td>
<td>Serious</td>
<td>none</td>
<td>269</td>
<td>269</td>
<td>-</td>
<td>MD 0.85 higher (0.85 lower to 2.54 higher)</td>
<td>⬤⬤◯◯ LOW</td>
<td>IMPORTANT</td>
<td></td>
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</tbody>
</table>

1 Intervention not blinded but objective outcome
2 95% CI around the pooled estimate includes both 1) no effect and 2) appreciable benefit or appreciable harm.
3 Intervention/outcome assessment not blinded
4 Test for heterogeneity - P<0.05 or I² ≥60%
5 single study
Table 5 summarises the Grade profile summary for infant flow driver versus bubble CPAP.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality (assessed with: Death before discharge)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td><strong>3</strong></td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
<td>21/208 (10.1%)</td>
<td>RR 1.02 (0.60 to 1.73)</td>
<td>2 more per 1,000 (from 41 fewer to 74 more)</td>
<td>⨁⨁◯</td>
</tr>
<tr>
<td>CPAP failure (as assessed with 7 days of CPAP)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>randomised trials</td>
<td>serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>43/298 (14.4%)</td>
<td>RR 0.88 (0.56 to 1.38)</td>
<td>20 fewer per 1,000 (from 72 fewer to 62 more)</td>
<td>⨁◯◯</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (assessed as oxygen requirement at 36 weeks postmenstrual age)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
<td>33/149 (22.1%)</td>
<td>RR 1.54 (0.86 to 2.75)</td>
<td>84 more per 1,000 (from 22 fewer to 272 more)</td>
<td>⨁⨁◯</td>
</tr>
<tr>
<td>Air leaks</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>randomised trials</td>
<td>serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>5/298 (1.7%)</td>
<td>RR 1.24 (0.35 to 4.40)</td>
<td>3 more per 1,000</td>
<td>⨁◯◯</td>
</tr>
</tbody>
</table>
### Intraventricular Hemorrhage (as assessed by grade 2 or more in USG)

<table>
<thead>
<tr>
<th></th>
<th>randomised trials</th>
<th>seriou s c</th>
<th>not serious</th>
<th>not serious</th>
<th>serious b</th>
<th>none</th>
<th>16/229 (7.0%)</th>
<th>13/227 (5.7%)</th>
<th>RR 1.24 (0.58 to 2.64)</th>
<th>14 more per 1,000 (from 24 fewer to 94 more)</th>
<th>⨁⨁◯◯</th>
<th>LOW</th>
<th>IMPORTANT</th>
</tr>
</thead>
</table>

### Moderate to Severe Nasal Injury (as assessed by well designed scoring systems or uniform clinical criteria)

<table>
<thead>
<tr>
<th></th>
<th>randomised trials</th>
<th>seriou s c</th>
<th>not serious</th>
<th>not serious</th>
<th>not serious</th>
<th>none</th>
<th>7/139 (5.0%)</th>
<th>24/156 (15.4%)</th>
<th>RR 0.29 (0.12 to 0.69)</th>
<th>109 fewer per 1,000 (from 135 fewer to 48 fewer)</th>
<th>⨁⨁◯</th>
<th>MODERATE</th>
<th>IMPORTANT</th>
</tr>
</thead>
</table>

### Duration of CPAP (hours)

<table>
<thead>
<tr>
<th></th>
<th>randomised trials</th>
<th>seriou s c</th>
<th>serious d</th>
<th>not serious</th>
<th>not serious</th>
<th>none</th>
<th>170</th>
<th>161</th>
<th>-</th>
<th>MD 8.5 hours lower (14.3 lower to 2.8 lower)</th>
<th>⨁⨁◯</th>
<th>LOW</th>
<th>IMPORTANT</th>
</tr>
</thead>
</table>

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**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

**Explanations**

a. Intervention not blinded but objective outcome

b. 95% CI around the pooled estimate includes both 1) no effect and 2) appreciable benefit or appreciable harm.

c. Intervention not blinded with subjective outcome

d. I² ≥80% with p<0.05 for heterogeneity
NASAL INTERFACE

Summary of evidence
We identified one non Cochrane systematic review by King, et al, published in 2019 comparing the effect of nasal masks versus short binasal prongs to deliver CPAP in preterm neonates (King 2019). The review had identified 7 randomised controlled trials comparing nasal masks versus short binasal prongs in delivering CPAP. The authors of the review had searched the relevant databases till February 2019. We updated the search until July 2019 using terms: (infant, newborn) AND (continuous positive airway pressure or continuous distending pressure) in Pubmed. A total of 10 citations were identified, of which none were found to be eligible for inclusion in the review.

Of the 7 trials included, 4 trials enrolled only neonates requiring CPAP for the treatment of respiratory distress syndrome while 2 trials enrolled neonates requiring CPAP in the post extubation setting and one trial included neonates requiring CPAP in either setting. All 7 trails used the same pressure generator (CPAP device) in both groups. The make and brand of the nasal interface varied across trials. The make of the masks and short binasal prongs belonged to the same brand / company in 3 out of the 7 included trials whereas 4 trials used masks and prongs from different makes for comparison. (Table 1)

Random sequence generation was done in most trials and allocation concealment was appropriate in all 7 included trials. None of the included studies blinded the health care personnel to the intervention or to the outcome assessment. Loss to follow-up was minimal to nil in six of the seven included studies.

In-hospital mortality: A total of six studies involving 665 neonates reported this outcome. The quality of evidence was graded as moderate. There was no significant reduction in the risk of mortality in neonates who received CPAP through nasal masks compared to short binasal prongs (RR 0.91; 95% CI 0.59 to 1.38).

CPAP failure: Five studies involving 576 neonates reported this outcome. The quality of evidence was graded as low. There was a significant reduction in the incidence of CPAP failure requiring re-intubation and mechanical ventilation in the nasal mask group (RR 0.72; 95% CI 0.53 to 0.97).

Nasal injury (All grades): Six studies involving 665 neonates reported this outcome. The quality of evidence was graded as low. There was a significant reduction in the incidence of nasal injury (all grades) in neonates who received CPAP through nasal masks compared to short binasal prongs (RR 0.71; 95% CI 0.59 to 0.85).
**Nasal injury (Severe):** Four studies involving 396 neonates reported this outcome. The quality of evidence was graded as *moderate*. There was a significant reduction in the incidence of severe nasal injury in neonates who received CPAP through nasal masks compared to short binasal prongs (RR 0.27; 95% CI 0.16 to 0.46).

**Bronchopulmonary dysplasia (BPD):** Five studies involving 547 neonates reported this outcome. The quality of evidence was graded as *low*. No significant difference was observed in the risk of BPD between the neonates who received CPAP through nasal mask and short binasal prongs (RR 0.75; 95% CI 0.48 to 1.22).

**Air leaks:** Three studies involving 387 neonates reported this outcome. The quality of evidence was graded as *moderate*. No significant difference was observed in the risk of air leaks between nasal masks and short binasal prongs (RR 0.70; 95% CI 0.27 to 1.82).

**Duration of CPAP:** Five studies involving 548 neonates reported this outcome. The quality of evidence was graded as *low*. No significant difference was observed in the duration of CPAP between the nasal masks and short binasal prongs (mean difference: 0.33 days; 95% CI -0.37 to 1.03).

**Evidence to recommendation (Draft considerations)**

**Balance of benefits and harms:** There is low quality evidence that using nasal masks to deliver CPAP reduces the incidence of two important outcomes – CPAP failure within 72 hours as well as nasal injury of all grades compared to short binasal prongs. There is moderate quality evidence that nasal CPAP delivered using nasal masks reduces severe nasal injury. However, both nasal masks and short binasal prongs are similar with regard to the other important outcomes such as bronchopulmonary dysplasia, air leaks and duration of CPAP.

**Values and preferences:** The current evidence shows that the use of nasal mask in preferable to short binasal prongs for administering CPAP in preterm neonates with respiratory distress or neonates being extubated from mechanical ventilation. While doing this, the preferences, skills and comfort of nurses should be taken into consideration. Efforts to reduce nasal injury should be continued.

**Costs:** The cost of nasal masks is almost similar to the cost of short binasal prongs. The cost of other disposables such as nasal tubings and CPAP circuits are also similar with both the interfaces.

**Draft recommendation**
<table>
<thead>
<tr>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>nasal mask s</th>
<th>short binasal pron gs</th>
<th>Relat ive (95% CI)</th>
<th>Absol ute (95% CI)</th>
<th>Certain ty</th>
<th>Importa nce</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Hospital mortality</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 randomised trials</td>
<td>not serious a</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
<td>36/3</td>
<td>28 (11.0 %)</td>
<td>40/3</td>
<td>37 (11.9 %)</td>
<td>RR 0.91 (0.59 to 1.38)</td>
<td>11 fewer per 1,000 (from 49 fewer to 45 more)</td>
</tr>
<tr>
<td>CPAP failure within 72 hours (assessed with: Need for intubation)</td>
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<tr>
<td>5 randomised trials</td>
<td>serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
<td>54/2</td>
<td>87 (18.8 %)</td>
<td>77/2</td>
<td>89 (26.6 %)</td>
<td>RR 0.72 (0.53 to 0.97)</td>
<td>75 fewer per 1,000 (from 125 fewer to 8 fewer)</td>
</tr>
<tr>
<td>Nasal injury (all grades) (assessed with: Standard nasal injury assessment tools)</td>
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<tr>
<td>6 randomised trials</td>
<td>serious c</td>
<td>serious d</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>100/329</td>
<td>30.4 %</td>
<td>142/336</td>
<td>42.3 %</td>
<td>RR 0.71 (0.59 to 0.85)</td>
<td>123 fewer per 1,000 (from 173 fewer to 63 fewer)</td>
</tr>
<tr>
<td>Nasal injury (severe grades) (assessed with: Standard nasal injury assessment tools)</td>
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</tr>
<tr>
<td>4 randomised trials</td>
<td>serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>14/196</td>
<td>7.1%</td>
<td>57/200</td>
<td>28.5 %</td>
<td>RR 0.27 (0.16 to 0.46)</td>
<td>208 fewer per 1,000 (from 239 fewer to 154 fewer)</td>
</tr>
</tbody>
</table>

Bronchopulmonary dysplasia (assessed with: the need for respiratory support at 36 weeks postmenstrual age)
<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>nasal masks</th>
<th>short binasal prongs</th>
<th>Relat. (95% CI)</th>
<th>Absolut. (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>randomised trials</td>
<td>serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>serious b</td>
<td>none</td>
<td>10/195 (5.1%)</td>
<td>22/200 (11.0%)</td>
<td>RR 0.75 (0.48 to 1.22)</td>
<td>58 fewer per 1,000 (from 85 fewer to 6 fewer)</td>
<td>⬤ ⬤ ⬤</td>
<td>LOW</td>
</tr>
</tbody>
</table>

**Air leaks**

| 3              | randomised trials | not serious a | not serious | not serious | serious b | none | 7/193 (3.6%) | 10/194 (5.2%) | RR 0.70 (0.27 to 1.82) | 15 fewer per 1,000 (from 38 fewer to 42 more) | ⬤ ⬤ ⬤ | MODERATE | IMPORTANT |

**Duration of CPAP (follow up: mean 56 days; assessed with: days)**

| 5              | randomised trials | serious c | not serious | not serious | serious b | none | 271          | 277          | MD 0.33 days higher (0.37 lower to 1.03 higher) | ⬤ ⬤ ⬤ | LOW | IMPORTANT |

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

**Explanations**

a. Although all the studies were not blinded for intervention, we have not downgraded the quality of evidence considering that the outcome is a "hard outcome"

b. The 95% CI crosses the threshold for change in clinical decision

c. None of the studies were blinded to intervention, few studies were not blinded for outcome assessment. Considering that the outcome is not a "hard" outcome, the quality of evidence has been downgraded in view of lack of blinding

d. 95% CI of studies not overlapping, heterogeneity indicated by I² = 83% for the meta analysis
References:
Among preterm neonates with RDS, which group of neonates are more likely to fail CPAP?

**Objective**
To identify the predictors of CPAP failure among preterm neonates with RDS.

**Methods**

**Participants**
Symptomatic preterm infants (i.e. those born before 37 completed weeks’ gestation) having respiratory distress syndrome

**Exposure**
Continuous Positive Airway Pressure (CPAP) delivered by any mode irrespective of the type CPAP pressure generator (generator (bubble/infant flow driver/ventilator for CPAP) or nasal interface (nasal mask, nasal prongs, nasopharyngeal tubes) used with or without surfactant therapy via InSurE.

**Outcome**
Predictors of CPAP failure
Failure of CPAP has been defined as the need of reintubation and mechanical ventilation within first week of life. Reintubation and mechanical ventilation can be due to any of the following condition in isolation or combination despite of maximum CPAP settings (pressure 6-8 cm H2O and FiO2 0.4-0.8) with or without InSurE:

1) Respiratory acidosis
2) Hypoxia
3) Recurrent apnoea, prolonged apnoea or apnoea requiring bag and mask ventilation
4) Shock or hypotension requiring vasopressors
5) Worsening respiratory distress

**Results**

**Literature search:**
1) The last search was done in May 2017 while updating chapter entitled ‘Failure & Success of CPAP’ published in the ‘CPAP book’. This search was an unstructured literature search and was done only in Pubmed database and via cross references of the various articles obtained. The total studies included were 12.
2) The above literature search was updated for NNF CPG on 25-07-2019.
3) Database searched: Pubmed
4) Date of search: 25-07-2019
5) Search strategy used:
   a) Step 1: An unstructured search was done using the words CPAP/continuous Positive airway pressure, newborn/neonate/infant and failure. A formal search was not done as it is going to be narrative review rather than systematic review as meta-analysis is not possible.
   b) Step 2: Relevant cross-references from the retrieved articles (from the 1st step) including the latest articles published in year 2018 (review article in Clinics in Perinatology) and 2019 (original study) were retrieved and eligible articles were included.
   c) Step 3: Also, the articles highlighted under the box ‘similar articles’ in Pubmed after entering the titles of eligible articles retrieved from step 1 and 2 were screened and included, if relevant.
6) Total number of new studies added: 6
7) Following new information from the old studies apart from the new studies has also been retrieved and updated to help in making better evidence based decision:
   a) Criteria used to define CPAP failure
b) Timeline for assessing CPAP failure
c) Maximum settings of CPAP used before declaring CPAP failure
d) Timing/age (in hour) of CPAP initiation
e) Clinical status of infants at time of enrolment (prophylactic CPAP or only to symptomatic neonates)
f) Availability of surfactant replacement therapy (SRT) including prophylactic SRT & InSurE
g) Type of nasal interface used apart from the CPAP generator
h) Odds ratio (adjusted if available) with confidence intervals of the various predictors
i) Positive predictive value of various predictors wherever available

Pooled effect
We identified 18 studies including six new studies. Meta-analysis was not possible for this research question. Thus, eighteen studies were included (Table 1) for this narrative review. The details are as follows:

1) **Type of studies**: Eighteen studies have been included out of which 10 are retrospective cohort, five are prospective cohort, two being RCTs and one is a case-control study.

2) **Type of population**: Overall, majority of the studies have enrolled very low birth weight infants (VLBW). Two studies have enrolled extreme preterm infants & six each have enrolled infants <30 weeks and <32 weeks respectively. Two each have enrolled infants from 28-34 weeks and 28-37 weeks respectively.

3) **Status of infants at the time of enrolment**: Six studies each have enrolled symptomatic infants with respiratory distress syndrome (RDS) or respiratory distress probably due to any cause. Three studies have enrolled all infants irrespective of the respiratory status at birth. The information is not clear for remaining three studies.

4) **Type of CPAP generator used**: Twelve out of 18 studies provide this information. Bubble CPAP system was used in five studies and infant flow driver/variable flow system in three studies. One each study have used ventilator CPAP and indigenous CPAP. One RCT has compared bubble versus ventilator CPAP and another one compared infant flow driver with ventilator CPAP. Information is missing from remaining six studies.

5) **Type of nasal interface used**: The information is lacking in half of the studies. Majority of the remaining studies have used short binasal prongs including Hudson, Fisher & Paykel and Argyle prongs. One study each has used nasopharyngeal prongs and nasal mask apart from the short binasal prongs.

6) **Maximum CPAP settings used**:
   a) Pressure: Four studies have used a maximum pressure of 8 cm H2O, three have used 7 cm H2O and two studies have used a maximum pressure of 6 cm of H2O. The information is missing in remaining half of the studies.
   b) Fraction of inspired oxygen (FiO2): There is no information in half of the studies about the maximum FiO2 used before labelling CPAP failure. In remaining, majority (six) of the studies shave taken a cut-off of 0.6 before labelling CPAP failure. One study each have taken a higher cut-offs of 0.7, 0.8 and 0.9 respectively.

7) **Criteria for CPAP failure**: CPAP failure has been defined as the need for intubation and mechanical ventilation at different time points during the first week of life. Reintubation and mechanical ventilation was done due to any of the following condition in isolation or combination despite of maximum CPAP settings with or without InSurE:
   a) Respiratory acidosis
   b) Hypoxia
   c) Recurrent apnoea, prolonged apnoea or apnoea requiring bag and mask ventilation
   d) Shock or hypotension requiring vasopressors
e) Worsening respiratory distress

8) **Provision of surfactant replacement therapy (SRT):** The information about the availability of surfactant replacement therapy (SRT) is available in 16 out of 18 studies. InSurE (Intubation-surfactant-extubation) was done in 10 studies and SRT followed by continued mechanical ventilation was observed in six studies. There was a provision for prophylactic surfactant apart from rescue SRT in two studies for infants <25 weeks and <27 weeks respectively.

9) **Timeline for assessing CPAP failure:** In 11 out of 18 studies, the CPAP failure was assessed within first 72 hours of life. Two studies have assessed within first 48 hours and three in first one week of life. The information is missing in remaining two studies.

10) **CPAP failure rate:** The overall CPAP failure rate varied from 20-40% based on the type of infants enrolled. With as high as 50% in infants <750 g.

Thus, the CPAP failure rate will depend upon multiple factors including population studied (gestation & weight), maximum CPAP settings (pressure & FiO2) used and the criteria used to define CPAP failure. Based on the above evidence, the important predictors of CPAP failure among preterm infants with RDs are:

<table>
<thead>
<tr>
<th>Factors</th>
<th>Important</th>
<th>Less important</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal</td>
<td>No or partial exposure to antenatal steroids</td>
<td>Born by LSCS</td>
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<tr>
<td></td>
<td></td>
<td>Premature rupture of membrane</td>
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<tr>
<td></td>
<td></td>
<td>Pregnancy induced hypertension</td>
</tr>
<tr>
<td>Perinatal</td>
<td>Low gestational age (&lt;28 weeks)</td>
<td>Low APGAR score at 5 minutes</td>
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<tr>
<td></td>
<td>Low birth weight (&lt;1000 g)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male gender</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Need of positive pressure ventilation at birth</td>
<td></td>
</tr>
<tr>
<td>Postnatal</td>
<td>Moderate to severe RDS on first chest radiograph</td>
<td>Downe’s or Silverman Anderson score &gt;6 to 7 after 15-20 minutes of starting CPAP</td>
</tr>
<tr>
<td></td>
<td>FiO2 &gt;0.3 in first 2 hours of life and &gt;0.4 in first 4 hours of life</td>
<td>Pneumothorax during CPAP</td>
</tr>
<tr>
<td></td>
<td>(A-a) DO2 &gt;180 in initial ABG</td>
<td>Presence of PDA</td>
</tr>
<tr>
<td></td>
<td>a/A &lt; 0.18-0.44 in initial ABG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PaO2/FiO2 &lt;150 in initial ABG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis or pneumonia during CPAP therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RDS requiring surfactant</td>
<td></td>
</tr>
</tbody>
</table>

It is important to note that few additional factors are also equally important while delivering CPAP, which may affect the CPAP success rate. However, these factors have not been addressed in the above studies. Some of these factors are as follows:

1) Administration of early rescue surfactant by InSurE (see section Preterm with RDS - need to see the results of updated systematic review being undertaken for NNF-CPG)
2) Quality of nursing and supportive care
3) Experience of the unit in using CPAP
4) Ongoing ‘Quality Improvement Project’ for improving CPAP efficacy & safety
5) Type of CPAP generator (see section CPAP devices - need to see the results of updated systematic review being undertaken for NNF-CPG)
6) Type of nasal interface (see section CPAP devices - need to see the results of updated systematic review being undertaken for NNF-CPG)
References:


