Clinical Practice Guidelines

Non-invasive Respiratory Support for Newborns

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National Neonatology Forum, India
Guideline Development Group (Alphabetical)

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**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), 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 the developing lung of preterm infant. These injuries lead to an arrest in alveolarization and scarring from fibrosis.

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 (CPAP), 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 decreases the need for mechanical ventilation, use of surfactant and lung injury leading to BPD. There are guidelines from the European expert panel on the management of RDS and American Academy of Pediatrics on non-invasive ventilatory strategies in preterm neonates. National Neonatology Forum, India (NNF) had published guidelines on the use of CPAP in neonates in 2010. With more evidence from recently published randomized controlled trials and growing interest with other non-invasive modalities like HFNC and NIPPV, there was a felt need to update these guidelines and to provide recommendations suited to the Indian context.

The Guideline Development Group short-listed 14 questions pertaining to the use of non-invasive respiratory strategies in neonates to be of highest priority. Thirteen of these questions focus on issues related to use of CPAP, HFNC and NIPPV among preterm for various settings like respiratory distress syndrome (RDS), apnea of prematurity and post-extubation period. One of them is a background question on predictors of failure of CPAP and the other addresses the use of CPAP in term neonates with meconium aspiration syndrome. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used for grading the quality of evidence after adaptation to the relevant working area. The quality of evidence for an outcome was graded as high, moderate, low or very low. After grading the available studies for each outcome, recommendations were formulated, based on the summary and quality of evidence, balance between benefits and harms, values and preferences of policy-makers, health-care providers and parents, feasibility and resource use and whether costs are justifiable relative to benefits in Indian settings.

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 /context specific** if the benefits outweigh the harms in some situations but not in others (indicated in the document as appropriate). Table 1 lists the summary of key recommendations of the guidelines.
Table 1: Summary of recommendations for non-invasive respiratory support for newborns

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Recommendations</th>
<th>Strength of recommendations</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Initial respiratory support for preterm neonates with or at risk of RDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>All preterm neonates with respiratory distress should be managed with continuous positive airway pressure (CPAP)</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Comment: There is a small but possible risk of air-leak in neonates started on CPAP therapy. Facilities offering CPAP support should have expertise to monitor such neonates to avoid complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Continuous positive airway pressure (CPAP) should be administered at or immediately after the onset of respiratory distress in preterm neonates.</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>3.</td>
<td>Heated humidified high flow nasal canula (HFNC) is not recommended for the management of preterm neonates with or at risk of respiratory distress syndrome (RDS)</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>4.</td>
<td>Nasal intermittent positive pressure ventilation (NIPPV) delivered by a ventilator using synchronised or non-synchronised methods may be used as the primary mode in preterm neonates with or at risk of RDS</td>
<td>Strong, Conditional</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Applicable to settings with optimal availability of ventilators and trained manpower</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Extreme preterm neonates (gestation &lt;28 weeks) should not be routinely intubated in the delivery room; intubation and ventilation should be reserved only for those with severe perinatal asphyxia requiring resuscitation</td>
<td>Strong, Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Applicable in settings with high antenatal steroid coverage and adequate expertise in managing extreme preterm neonates</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. Early rescue surfactant should be administered along with CPAP in preterm neonates with respiratory distress syndrome (RDS)

Comment: Units offering surfactant therapy should have equipment to offer mechanical ventilation, blood gas analysis, chest X-ray and skilled newborn care for adequate monitoring.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Non-invasive respiratory support for preterm neonates with apnea of prematurity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>a. CPAP therapy should be initiated in preterm neonates with apnea of prematurity in conjunction with methylxanthines.</td>
</tr>
<tr>
<td>Low</td>
<td>b. NIPPV (both synchronized and non-synchronised) may be used for frequent and severe apneic episodes, if adequate expertise and equipment are available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength</th>
<th>Non-invasive respiratory support for preterm neonates in post-extubation setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Preterm very low birth weight neonates being extubated after a brief period of ventilation should be weaned off either to CPAP or NIPPV.</td>
</tr>
<tr>
<td>Low to moderate</td>
<td>Comment: If adequate expertise and equipment are available, NIPPV (both synchronized and non-synchronised) might preferably be used, particularly in neonates at high risk of CPAP failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength</th>
<th>Non-invasive respiratory support for late preterm and term neonates with meconium aspiration syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak</td>
<td>Continuous positive airway pressure (CPAP) may be employed as the primary mode of respiratory support in late preterm and term neonates with meconium aspiration syndrome (MAS)</td>
</tr>
<tr>
<td>Low</td>
<td>Comment: Facilities offering CPAP support should have the expertise to monitor such neonates for air-leak.</td>
</tr>
</tbody>
</table>
## CPAP devices, nasal interfaces, initial pressure and weaning strategies

<table>
<thead>
<tr>
<th></th>
<th>Pressure generators</th>
<th>Weak</th>
<th>Low to very low</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.</td>
<td><strong>Pressure generators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bubble CPAP, rather than ventilator CPAP or variable flow device, may preferably be used in preterm neonates requiring continuous positive airway pressure for any indication</td>
<td>Weak</td>
<td>Low to very low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Nasal interface</th>
<th>Strong</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td><strong>Nasal interface</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPAP should be delivered by either short binaural prongs or nasal masks in neonates</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td><strong>Comment:</strong> If available, nasal masks may be preferred, particularly in neonates at high risk of nasal injury</td>
<td></td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>Initial pressures</th>
<th>Weak</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.</td>
<td><strong>Initial pressures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Preterm neonates with respiratory distress syndrome (RDS) may be initiated on CPAP pressures of 5 cm H₂O</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>b. Preterm very low birth weight neonates being extubated to CPAP, after a brief period of ventilation may be initiated on pressures of 6 cm H₂O or more</td>
<td>Weak</td>
<td>Very low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Weaning</th>
<th>Weak</th>
<th>Low</th>
</tr>
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<tbody>
<tr>
<td>13.</td>
<td><strong>Weaning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preterm very low birth weight neonates being weaned off from CPAP may preferably be weaned off by sudden discontinuation of CPAP rather than CPAP cycling</td>
<td>Weak</td>
<td>Low</td>
</tr>
</tbody>
</table>
Non-invasive respiratory support for newborns

Introduction

Respiratory distress is a common symptom affecting up to 7% of all term infants and a higher percentage of preterm infants (30%)\(^6\). Respiratory distress is a common cause of neonatal intensive care unit (NICU) admission (15-30%) among neonates and the major contributor (45%) of neonatal deaths among preterm neonates\(^6\). According to the National Neonatal Perinatal Database of India (NNPD) for the year 2002-03, transient tachypnea of newborn (3.2% of all live births), meconium aspiration syndrome (1.3%) and respiratory distress syndrome (1.2%) were the three common causes of respiratory morbidity among inborn neonates admitted to various hospitals that formed part of the Consortium\(^7\).

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, 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. The risk of BPD among preterm neonates ≤ 30 weeks gestation is around 50%\(^8\). There is paucity of data from India on the burden of BPD among preterm neonates. A recent report cites a conservative estimate of (11%) among neonates < 33 weeks gestation with an average survival rate of 63%\(^9\).

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 (CPAP), 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\(^10\). Among various non-invasive strategies, there is greater interest with the use of NIPPV and HFNC either for greater efficacy, ease of use and patient comfort. There are guidelines from the European\(^1\) expert panel on the management of RDS and the American Academy of Pediatrics\(^2,3\) on non-invasive ventilatory strategies in preterm neonates. The National Neonatology Forum, India (NNF) had published guidelines on the use of CPAP in neonates in 2010\(^4\). With more evidence from recently published randomized controlled trials and growing interest with other non-invasive modalities, there was a felt need to update these guidelines and to provide recommendations suited to the Indian context.

Scope of the guidelines and target audience

Scope

The Guideline Development Group identified 17 research questions about the use of non-invasive respiratory strategies in neonates to be of highest priority. Fifteen of these questions focus on priority issues related to the use of CPAP, HFNC and NIPPV among preterm neonates beginning with birth and subsequently for various settings like respiratory distress syndrome...
Non-invasive respiratory support for newborns

(RDS), apnea of prematurity and post-extubation period. One of them is a background question on predictors of failure of CPAP and the other addresses the use of CPAP in term neonates with meconium aspiration syndrome. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used for grading the quality of evidence after adaptation to the relevant working area. The quality of evidence for an outcome was graded as high, moderate, low or very low. After grading the available studies for each outcome, recommendations were formulated based on the summary and quality of evidence, balance between benefits and harms, values and preferences of policymakers, health-care providers and parents, feasibility and resource use and whether costs are justifiable relative to benefits in Indian settings.

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 India.

METHODOLOGY

Questions relevant to clinical practice

The Guideline Development Group (GDG) short-listed 14 questions about the use of non-invasive respiratory strategies in neonates to be of highest priority after survey amongst the GDG and a wider group of NNF members. Thirteen of these questions focus on priority issues related to the use of CPAP, HFNC and NIPPV among preterm neonates beginning with birth and subsequently for various settings like respiratory distress syndrome (RDS), apnea of prematurity and post-extubation period. One of them is a background question on predictors of failure of CPAP and the other addresses the use of CPAP in term neonates with meconium aspiration syndrome. Each of these questions deserved separate systematic reviews, taking into consideration the critical and important outcomes. The performed systematic reviews were peer reviewed by the GDG and also by external peer reviewers.

The following questions were identified to be of the highest priority:

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, what is the effect of continuous positive airway pressure (CPAP) when compared to oxygen therapy delivered by head box, facemask or nasal cannula on mortality and severe morbidities?
2. Among preterm neonates with RDS, what is the effect of early CPAP therapy when compared to delayed CPAP therapy on mortality and severe morbidities?

3. Among preterm neonates with RDS, what is the effect of high flow nasal cannula (HFNC) when compared to CPAP on mortality and severe morbidities?

4. Among preterm neonates with RDS, what is the effect of nasal intermittent positive pressure ventilation (NIPPV) when compared to CPAP on mortality and severe morbidities?

5. Among extreme preterm neonates with RDS, what is the effect of CPAP when compared to routine intubation and ventilation in the first few hours of life on mortality and severe morbidities?

6. Among preterm neonates with RDS, what is the effect of CPAP alone when compared to CPAP therapy with early rescue surfactant on mortality and severe morbidities?

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

7. Among neonates with apnea of prematurity, what is the effect of
   a. CPAP therapy compared with no CPAP therapy
   b. CPAP therapy compared with HFNC or NIPPV

   on the need for ventilation, mortality and severe morbidities?

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, what is the effect of
   a. continuous positive airway pressure (CPAP) therapy compared with no CPAP therapy
   b. high flow nasal cannula (HFNC) therapy compared with CPAP
   c. nasal intermittent positive pressure ventilation (NIPPV) therapy compared with CPAP

   on the need for additional ventilatory support, mortality, and severe morbidities?

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

9. Among term neonates with meconium aspiration syndrome (MAS), what is the effect of CPAP when compared to oxygen therapy delivered by headbox, facemask or nasal cannula on mortality and severe morbidities?

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?
Among neonates requiring CPAP therapy, what is the optimal CPAP device for use (as determined by a comparison of the efficacy and safety of commonly used CPAP devices) with regard to

10. Patient interfaces: nasal prongs vs. masks vs. nasopharyngeal prongs
11. Pressure generators: Bubble CPAP vs. ventilator CPAP vs. infant flow driver (IFD)
12. Initial pressure: low (5 cm H$_2$O) vs. higher (>5 cm H$_2$O)
13. Weaning: cycling vs. sudden cessation vs. others

**Predictors of CPAP failure**

14. Among preterm neonates with RDS, which group of neonates are more likely to fail CPAP?

**Outcomes of interest**

For each question, the following outcomes (critical and important) were considered. 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. Details of outcomes and their definitions are available in the online version.

**Critical**

- Neonatal mortality
- In-hospital mortality
- Bronchopulmonary dysplasia (BPD)
- Grade 3 or 4 intraventricular haemorrhage (IVH)
- Air leaks

**Important**

- Respiratory failure warranting mechanical ventilation
- Need for surfactant
- Failure of extubation
- Need for re-intubation
- Sepsis
- Necrotising enterocolitis (NEC)
- Retinopathy of prematurity (ROP)
- Duration of hospitalisation
- Nasal trauma
- Duration of oxygen therapy

**Selection of studies**

**Search strategy**

Using the assembled list of priority questions and critical outcomes from the scoping exercise, the guideline development group, 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 one year 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 2019). The reference lists of relevant articles were also searched to identify relevant studies.

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, and intention to treat analysis. 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.

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 research question, and a GRADE profile was prepared for each quantitative outcome. 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 the risk of bias, inconsistency, imprecision, indirectness and publication bias.

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. Four criteria were used for assessing limitations in the methods of included studies; 1) Selection bias was assessed by analysing how randomization and allocation concealment was done 2) 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. Measurement bias was 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 the risk of bias was low, else it was high.

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.

Indirectness

Rating of the quality of evidence was downgraded where there were serious or very serious concerns regarding the directness of the evidence, i.e. where there were important differences between the research reported and the context for which the recommendations are being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes.

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.

Publication bias

The 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

After grading the available studies for each outcome, recommendations were formulated based on the summary and quality of evidence, balance between benefits and harms, values and preferences of policy-makers, health-care providers and parents, feasibility and resource use and whether costs are justifiable relative to benefits in Indian settings. 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/context specific if the benefits outweigh the harms in some situations but not in others (indicated in the document as appropriate).
Document review

The GDG personally met on two occasions and prepared a draft of the full guideline document with revisions to accurately reflect the deliberations and decisions of the GDG participants. This draft guideline was then sent electronically to the GDG participants for further comments. The inputs of the peer reviewers were included in the guideline document and, further revisions were made to the guideline draft as needed. After the peer review process, the revised version was prepared.
Questions, Evidence summary and Recommendations

Practice Question 1: Among preterm neonates with RDS, what is the effect of CPAP when compared to oxygen therapy delivered by headbox, facemask or nasal cannula on mortality and severe morbidities?

Summary of evidence - values and benefits

- 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 from 2015 that included 6 randomized/quasi-randomized trials. No new studies were identified in the updated search for this review. Most of these studies were done during 1960-70s when antenatal steroid coverage was low (20-35%) and surfactant use was uncommon in contrast to the current era with higher rates of antenatal steroid coverage and greater availability of surfactant. All the studies were conducted in high-income countries and all except one in level-3 neonatal intensive care units (NICU). The type of CPAP used in the studies are uncommon now; two used negative-pressure chambers, two used face-mask CPAP and one used negative pressure for less severe illness and endotracheal CPAP for severe illness.

- Pooled analysis showed low-quality evidence of a reduction in the risk of mortality during the initial hospital stay RR 0.53; 95% CI (0.32-0.87) and need for mechanical ventilation; RR 0.72; 95% CI (0.56, 0.91) in the CPAP group compared to oxygen therapy alone. There was no difference in the rate of BPD and the need for surfactant therapy (Table 2 enlists the summary of findings for this comparison).

- There is low-quality evidence of higher risk of air leaks in the CPAP group; RR 2.64; 95% CI (1.39, 5.04). The risk of pneumothorax was 14% in the CPAP group and 6% in the oxygen therapy group. This increased risk of pneumothorax may be because of various reasons; low coverage of antenatal steroids and surfactant use, late initiation of CPAP (mean age of 3 hours in one study and 10 hours in others), delivery of distending pressures through a facemask and negative pressure chambers - delivery techniques which are obsolete today.

- There are no randomized controlled trials from low middle-income settings comparing CPAP with oxygen therapy. In a meta-analysis published in 2016, authors analysed the efficacy and safety of CPAP in low and middle income (LMIC) settings. Pooled analysis from four observational studies showed that CPAP therapy resulted in 66% reduction in in-hospital mortality (odds ratio 0.34, 95% CI: 0.14 to 0.82). One study from Fiji reported a 50% reduction in the need for mechanical ventilation following the introduction of bubble CPAP (RR 0.5, 95% CI 0.37 to 0.66). The incidence of air leaks varied from 0 to 7.2% (in nine studies from LMIC set up). This risk is much less compared to 14% in the pooled analysis from studies from the earlier era.

- The benefits of CPAP namely reduction in in-hospital mortality and need for mechanical ventilation far outweigh the small risk of pneumothorax. Hence, healthcare providers, policy-makers, and parents in both high-income and low-and middle-income countries are likely to give a high value to the use of CPAP. Also, CPAP is a non-invasive method and delivered through nasal interface (binasal prongs or masks).
• Studies from LMIC set up have shown bubble CPAP to be a highly cost-effective strategy compared to oxygen therapy.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with head box or free flow oxygen</td>
<td>Risk with CPAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>179 per 1,000 (57 to 156)</td>
<td>RR 0.52 (0.32 to 0.87)</td>
<td>355 (6 RCTs)</td>
<td>LOW ab</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia assessed with: Oxygen requirement at day 28 of life</td>
<td>45 per 1,000 (20 to 152)</td>
<td>RR 1.22 (0.44 to 3.39)</td>
<td>260 (3 RCTs)</td>
<td>VERY LOW b,c,d</td>
</tr>
<tr>
<td>Respiratory failure warranting mechanical ventilation</td>
<td>525 per 1,000 (294 to 478)</td>
<td>RR 0.72 (0.56 to 0.91)</td>
<td>314 (5 RCTs)</td>
<td>LOW b,c</td>
</tr>
<tr>
<td>Need for surfactant</td>
<td>269 per 1,000 (32 to 398)</td>
<td>RR 0.43 (0.12 to 1.48)</td>
<td>52 (1 RCT)</td>
<td>VERY LOW b,c,d</td>
</tr>
<tr>
<td>Any air-leak</td>
<td>61 per 1,000 (85 to 310)</td>
<td>RR 2.64 (1.39 to 5.04)</td>
<td>351 (6 RCTs)</td>
<td>LOW b,c</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

Explanations
a. Unclear or high risk of bias of random sequence generation and allocation concealment in two studies that had weight of >65% in pooled analysis
b. All studies are from high income countries. The use of antenatal steroids and surfactant was low in most studies - contrary to the current situation. The type of CPAP used in some studies is no longer used now.
c. Neither outcome assessors nor treatment team was blinded to group allocation
d. 95% confidence interval around the pooled estimate includes both 1) no effect and 2) appreciable benefit or appreciable harm
e. Single study
Practice Question 2: Among preterm neonates with RDS, what is the effect of early initiation of CPAP when compared to delayed initiation of CPAP on mortality and severe morbidities?

Summary of evidence - values and benefits

- The evidence for this review is derived from a Cochrane systematic review that examined the effect of early CPAP therapy as compared to delayed CPAP therapy for RDS in preterm neonates that included six trials. We identified one more eligible study from LMIC setting (Iran) for this review.

- The earlier six trials were conducted in the pre-surfactant era and required clinical and radiological evidence of RDS for trial entry. The FiO₂ required at entry ranged from 0.3 to 0.7 or more. Early CPAP was initiated at trial entry and, late CPAP was initiated at higher FiO₂ ranging from 0.5 up to 1.0. Thus, there was considerable variation and overlap in the criteria used for initiating early and late CPAP. In contrast, the recent Iranian study had early CPAP and delayed CPAP initiated based on time since birth (early initiated within 5 minutes, whereas delayed initiated 30 minutes after birth). Also, the CPAP therapy was used in adjunct with antenatal steroids and surfactant treatments.

- There is low-quality evidence that early CPAP reduces the need for mechanical ventilation (RR 0.55; 95% CI: 0.32 to 0.96) and surfactant (RR 0.64; 95% CI: 0.44 to 0.93), and the risk of sepsis (RR 0.46; 95% CI: 0.27 to 0.79) when compared to late CPAP in preterm neonates with RDS. No difference was observed in the risk of mortality or severe morbidities like BPD and air leaks (Table 3 enlists the summary of findings for this comparison).

- Health care providers and policy-makers are likely to give a high value to the benefits observed with early CPAP. It could also result in cost savings by reducing the need for ventilation and surfactant as well as by reducing the incidence of sepsis.
### Table 3: Summary of findings for early compared to delayed initiation of CPAP for Preterm neonates with RDS

**Patient or population:** Preterm neonates with RDS  
**Setting:** Hospital  
**Intervention:** Early  
**Comparison:** delayed initiation of CPAP

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with delayed initiation of CPAP</td>
<td>Risk with Early</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>53 per 1,000 (7 to 358)</td>
<td>RR 0.93 (0.13 to 6.81)</td>
<td>61 (2 RCTs)</td>
<td>★★★★★ LOW a,b</td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>188 per 1,000 (75 to 232)</td>
<td>RR 0.70 (0.40 to 1.24)</td>
<td>237 (7 RCTs)</td>
<td>★★★★★ MODERATE b,c</td>
<td></td>
</tr>
<tr>
<td>BPD assessed with: Oxygen requirement at day 28 of life</td>
<td>55 per 1,000 (7 to 217)</td>
<td>RR 0.70 (0.12 to 3.98)</td>
<td>108 (2 RCTs)</td>
<td>★★★★★ VERY LOW b,d,e</td>
<td></td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td>315 per 1,000 (101 to 303)</td>
<td>RR 0.55 (0.32 to 0.96)</td>
<td>165 (6 RCTs)</td>
<td>★★★★★ MODERATE a,d</td>
<td></td>
</tr>
<tr>
<td>Need for surfactant therapy</td>
<td>778 per 1,000 (342 to 723)</td>
<td>RR 0.64 (0.44 to 0.93)</td>
<td>72 (1 RCT)</td>
<td>★★★★★ LOW d</td>
<td></td>
</tr>
<tr>
<td>Air-leak</td>
<td>148 per 1,000 (55 to 283)</td>
<td>RR 0.84 (0.37 to 1.91)</td>
<td>144 (5 RCTs)</td>
<td>★★★★★ VERY LOW a,b,d</td>
<td></td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>667 per 1,000 (180 to 527)</td>
<td>RR 0.46 (0.27 to 0.79)</td>
<td>72 (1 RCT)</td>
<td>★★★★★ LOW a,f</td>
<td></td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

**Explanations**

a. Allocation concealment unclear in most studies  
b. 95% CI around pooled estimate includes both 1) no effect and 2) appreciable harm  
c. Allocation concealment mentioned in 2 studies with a combined weightage of >50%  
d. neither treatment team nor outcome assessors were masked to group allocation  
e. Only 2 and 3 events in the two groups (both groups combined)  
f. Single study
RECOMMENDATION 2

Continuous positive airway pressure (CPAP) should be administered at or immediately after the onset of respiratory distress in preterm neonates.

Strong recommendation, Low quality evidence for significant benefits in need for ventilation/surfactant and risk of sepsis but the consensus among experts for other beneficial effects of CPAP including cost-effectiveness.

Practice Question 3: Among preterm neonates, at risk of or with respiratory distress at birth, what is the effect High flow nasal cannula (HFNC) as compared to CPAP therapy as the primary mode of respiratory support on the need for mechanical ventilation, need for surfactant treatment, mortality, and severe morbidities?

Summary of evidence-values and benefits

- We identified three systematic reviews that addressed this question. We used data from the most recent review that included ten studies and an additional study from updated search.

- There is moderate-quality evidence that HFNC results in more treatment failures than CPAP (RR 1.93; 95% CI 1.51 to 2.5). There is moderate-quality evidence that there is no difference need for mechanical ventilation within 7 days of trial entry, partly because neonates failing HFNC were rescued using CPAP (Table 4 enlists the summary of findings for this comparison). There is moderate-quality evidence that there is no difference in mortality and very low-quality evidence that it does not lower BPD rates when compared to CPAP. There is moderate quality evidence that HFNC decreases the nasal trauma among these infants when compared to Nasal CPAP (RR 0.51; 95% CI 0.36-0.71) – for every 1000 neonates treated, 46 fewer neonates would have nasal trauma (95% CI 27 to 60). Most trials enrolled neonates > 28 weeks’ gestation.

- Health care providers are likely to be concerned regarding the high failure rates with HFNC and would need to be prepared with a backup CPAP. Parents and nurses generally prefer HFNC to CPAP as neonates are more comfortable with HFNC prongs.

- In a cost-effectiveness evaluation of CPAP and HFNC therapy, CPAP therapy was noted to be highly cost-effective and, units opting to buy a single therapy should choose CPAP over HFNC alone.
Table 4: Summary of findings for HFNC compared to CPAP for preterm infants as the primary respiratory support

**Patient or population:** preterm infants as the primary respiratory support  
**Setting:** Hospital  
**Intervention:** Heated humidified high flow nasal cannula (HFNC)  
**Comparison:** CPAP

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with CPAP</td>
<td>Risk with Heated humidified high flow nasal cannula (HFNC)</td>
<td>RR</td>
<td>No of participants (studies)</td>
</tr>
<tr>
<td>Failure of primary respiratory support (Treatment failure) assessed with: need for mechanical ventilation or need for CPAP in HFNC group follow up: mean 7 days</td>
<td>101 per 1,000</td>
<td>195 per 1,000 (153 to 253)</td>
<td>RR 1.93 (1.51 to 2.50)</td>
<td>2244 (8 RCTs)</td>
</tr>
<tr>
<td>Need for intubation and mechanical ventilation (Mechanical ventilation) follow up: mean 7 days</td>
<td>94 per 1,000</td>
<td>103 per 1,000 (80 to 133)</td>
<td>RR 1.10 (0.86 to 1.42)</td>
<td>2186 (7 RCTs)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (BPD)</td>
<td>33 per 1,000</td>
<td>44 per 1,000 (21 to 93)</td>
<td>RR 1.35 (0.64 to 2.85)</td>
<td>1461 (7 RCTs)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>5 per 1,000</td>
<td>6 per 1,000 (2 to 15)</td>
<td>RR 1.36 (0.38 to 3.32)</td>
<td>2168 (8 RCTs)</td>
</tr>
<tr>
<td>Air leak</td>
<td>42 per 1,000</td>
<td>35 per 1,000 (23 to 53)</td>
<td>RR 0.84 (0.55 to 1.26)</td>
<td>2183 (7 RCTs)</td>
</tr>
<tr>
<td>Nasal trauma</td>
<td>93 per 1,000</td>
<td>48 per 1,000 (34 to 66)</td>
<td>RR 0.51 (0.36 to 0.71)</td>
<td>1933 (7 RCTs)</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

Explanations
a. Unblinded studies  
b. Treatment failure included both need for back up CPAP in HFNC group or need for intubation  
c. 95% CI for the outcome is crossing the clinical decision
RECOMMENDATION 3

Heated humidified high flow nasal canula (HFNC) is not recommended for the management of preterm neonates with or at risk of respiratory distress syndrome (RDS).

Strong recommendation based on moderate quality of evidence against HFNC with higher risk of treatment failure, an important outcome and lack of benefit in reducing the need for ventilation, mortality and BPD and the consensus among experts for other beneficial effects of CPAP including cost-effectiveness.

Practice Question 4: Among preterm neonates, at risk of or with respiratory distress at birth, what is the effect nasal intermittent positive pressure ventilation (NIPPV) as compared to CPAP therapy as the primary mode of respiratory support on the need for mechanical ventilation, need for surfactant treatment, mortality, and severe morbidities?

Summary of evidence-values and benefits

- We identified a Cochrane systematic review\textsuperscript{43} that included 10 RCTs\textsuperscript{44-53}. In the updated search, we identified 6 new eligible studies\textsuperscript{54-58}. These form the basis of this review.

- There is high-quality evidence that NIPPV reduces the risk of critical outcome namely, mortality (RR 0.65, 95% CI 0.46 to 0.91) and moderate-quality evidence that it reduces the need for mechanical ventilation (RR 0.73, 95% CI 0.62 to 0.87) within 7 days of trial entry, an important outcome when compared to CPAP as the primary mode of respiratory support among preterm infants (Table 5). There is low-quality evidence that NIPPV does not decrease BPD, pneumothorax, ROP and IVH (all grades) when compared to Nasal CPAP. Regardless of the population (a receipt of the surfactant or not before randomization), results showed no difference in the incidence of pneumothorax between NIPPV and CPAP groups (RR 0.83, 95%CI 0.50 to 1.37). Pooled results showed a reduction in NEC (RR 0.53, 95%CI 0.30 to 0.91) although none of the individual trials showed this benefit.

- **Type of device:** The benefits in a reduction in mechanical ventilation and mortality were observed when NIPPV was administered via a ventilator than using bi-level devices.

- **Synchronization:** Non-synchronized devices showed a reduction in the need for mechanical ventilation, and synchronized devices showed a trend toward benefit. Non-synchronized devices also showed benefit in mortality and BPD in subgroup analysis.
• Given the possible beneficial effects observed with NIPPV, especially the decrease in mortality, health care providers, policymakers and parents are likely to value the intervention high.
• NIPPV requires a ventilator or a bi-level CPAP machine and needs expertise and training. CPAP can be easily administered by nurses after training. Setting up a CPAP machine is easy compared to NIPPV.
• 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.

Table 5: Summary of findings for NIPPV compared to CPAP for preterm infants as the primary respiratory support

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for intubation and mechanical ventilation (Intubation) follow up: mean 7 days</td>
<td>249 per 1,000 (154 to 217)</td>
<td>RR 0.73 (0.62 to 0.87)</td>
<td>1745 (15 RCTs)</td>
<td>⬤⬤⬤◯ MODERATE a</td>
</tr>
<tr>
<td>Mortality during study period (Mortality)</td>
<td>91 per 1,000 (42 to 82)</td>
<td>RR 0.65 (0.46 to 0.91)</td>
<td>1691 (14 RCTs)</td>
<td>⬤⬤⬤⬤ HIGH</td>
</tr>
<tr>
<td>Chronic lung disease (CLD) assessed with: Oxygen need at 36 weeks PMA</td>
<td>136 per 1,000 (87 to 149)</td>
<td>RR 0.84 (0.64 to 1.10)</td>
<td>1403 (12 RCTs)</td>
<td>⬤⬤⬤◯ LOW b</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>33 per 1,000 (16 to 45)</td>
<td>RR 0.83 (0.50 to 1.37)</td>
<td>1776 (15 RCTs)</td>
<td>⬤⬤⬤◯ LOW b</td>
</tr>
<tr>
<td>Intraventricular hemorrhage assessed with: All grades</td>
<td>117 per 1,000 (83 to 157)</td>
<td>RR 0.98 (0.71 to 1.34)</td>
<td>1085 (10 RCTs)</td>
<td>⬤⬤⬤◯ LOW a,b</td>
</tr>
<tr>
<td>Necrotizing enterocolitis assessed with: Bells’ stage 2 or more</td>
<td>57 per 1,000 (17 to 52)</td>
<td>RR 0.53 (0.30 to 0.91)</td>
<td>1222 (10 RCTs)</td>
<td>⬤⬤⬤⬤ VERY LOW a,b,c</td>
</tr>
<tr>
<td>Retinopathy of Prematurity assessed with: Stage 3 or more</td>
<td>52 per 1,000 (30 to 117)</td>
<td>RR 1.14 (0.58 to 2.26)</td>
<td>529 (4 RCTs)</td>
<td>⬤⬤⬤◯ LOW a,b</td>
</tr>
</tbody>
</table>

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January 2020
Table 5: Summary of findings for NIPPV compared to CPAP for preterm infants as the primary respiratory support

**Patient or population:** preterm infants as the primary respiratory support  
**Setting:** hospital  
**Intervention:** NIPPV  
**Comparison:** CPAP

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with CPAP</td>
<td>Risk with NIPPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis assessed with: culture positive sepsis</td>
<td>144 per 1,000 (74 to 265)</td>
<td>138 per 1,000 (0.51 to 1.84)</td>
<td>220 (3 RCTs)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

**Explanations**

- a. Studies included a varied population of neonates with respect to surfactant therapy and the mode of surfactant administration before enrolment. Studies enrolling neonates without surfactant therapy showed in-consistency in outcome.
- b. Unblinded studies.
- c. Individual studies did not show any benefit and have wide confidence intervals.

**RECOMMENDATION 4**

Nasal intermittent positive pressure ventilation (NIPPV) delivered by a ventilator using synchronised or non-synchronised methods may be used as the primary mode in preterm neonates with or at risk of RDS where equipment and its expertise are available.

Strong Conditional recommendation based on the high-quality of evidence for benefits in one critical outcome with NIPPV namely a reduction in mortality and moderate quality evidence for reduction in the need for mechanical ventilation (an important outcome).

Comment: Applicable to settings with optimal availability of ventilators and trained manpower.
Practice Question 5: Among extremely preterm neonates (gestation <28 weeks) what is the effect of CPAP when compared to routine intubation and ventilation regardless of respiratory status in the first few hours of life on mortality and severe morbidities?

Summary of evidence - values and benefits

- Prophylactic nasal CPAP is defined as initiating CPAP within the first 5 to 15 minutes of life regardless of the respiratory status of the infant. Evidence for the role of prophylactic CPAP is derived from a recent Cochrane systematic review that included three RCTs compared prophylactic CPAP versus intubation in the delivery room. All these were parallel multi-centric RCTs conducted in high-income countries and enrolled neonates < 28 weeks gestation. The use of antenatal corticosteroids was quite high in all the three studies (>90%).

- There is moderate-quality evidence that prophylactic application of CPAP in extreme preterm infants (< 28 weeks gestation) results in small but clinically significant reduction in incidence of BPD (RR 0.89, 95% CI 0.79 to 0.99) and death or BPD (RR 0.89, 95% CI 0.81 to 0.97) (Table 6). Moreover, there is moderate-quality evidence of almost 50% reduction in the need of surfactant therapy (RR 0.54, 95% CI 0.40 to 0.73) and need of mechanical ventilation (RR 0.50, 95% CI 0.48-0.62) in infants managed with CPAP. There is no apparent harm with CPAP - the incidence of pneumothorax and severe intraventricular hemorrhage was similar between the two groups. The long-term outcomes are also reassuring with no significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months of corrected age in one study.

- Given the benefits without any apparent harm, health care providers, policymakers, and parents are likely to give a high value to the application of delivery room CPAP. Low and middle-income countries will be much more benefitted as compared to HICs in view of high incidence of RDS among very low birthweight infants and RDS being one of the important causes of neonatal mortality. Moreover, it is much easier for the nursing personnel to start and maintain CPAP with minimal training when compared to intubation and mechanical ventilation of extreme preterm neonates.

- The cost of CPAP delivery systems is much less as compared to invasive ventilation. Also, the use of CPAP will reduce the need of surfactant by almost half thus resulting in additional cost saving.
Table 6: Summary of findings for CPAP compared to Intubation and mechanical ventilation for preterm neonates in the delivery room

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with Intubation and mechanical ventilation</td>
<td>Risk with Prophylactic CPAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bronchopulmonary dysplasia at 36 weeks</strong>&lt;br&gt;assessed with: Oxygen requirement at 36 weeks PMA</td>
<td>381 per 1,000 (304 to 377)</td>
<td><strong>RR 0.89</strong>&lt;br&gt;(0.80 to 0.99)</td>
<td>2150 (3 RCTs)</td>
<td>⬤⬤⬤◯ MODERATE a</td>
</tr>
<tr>
<td><strong>Death or bronchopulmonary dysplasia (Death or BPD) assessed with: Death or oxygen dependency at 36 weeks' post-menstrual age</strong></td>
<td>470 per 1,000 (380 to 455)</td>
<td><strong>RR 0.89</strong>&lt;br&gt;(0.81 to 0.97)</td>
<td>2358 (3 RCTs)</td>
<td>⬤⬤⬤◯ MODERATE a</td>
</tr>
<tr>
<td><strong>In-hospital mortality assessed with: Neonatal Death during hospital stay</strong></td>
<td>126 per 1,000 (83 to 130)</td>
<td><strong>RR 0.82</strong>&lt;br&gt;(0.66 to 1.03)</td>
<td>2358 (3 RCTs)</td>
<td>⬤⬤⬤◯ MODERATE b</td>
</tr>
<tr>
<td><strong>Need for mechanical ventilation assessed with: Assisted ventilation</strong></td>
<td>982 per 1,000 (413 to 580)</td>
<td><strong>RR 0.50</strong>&lt;br&gt;(0.42 to 0.59)</td>
<td>1042 (2 RCTs)</td>
<td>⬤⬤⬤◯ MODERATE c</td>
</tr>
<tr>
<td><strong>Need for surfactant therapy</strong></td>
<td>107 per 1,000 (43 to 78)</td>
<td><strong>RR 0.54</strong>&lt;br&gt;(0.40 to 0.73)</td>
<td>2274 (3 RCTs)</td>
<td>⬤⬤⬤◯ LOW d,e</td>
</tr>
<tr>
<td><strong>Pneumothorax</strong></td>
<td>58 per 1,000 (39 to 171)</td>
<td><strong>RR 1.42</strong>&lt;br&gt;(0.68 to 2.98)</td>
<td>2357 (3 RCTs)</td>
<td>⬤⬤⬤◯ LOW b,d</td>
</tr>
<tr>
<td><strong>Intraventricular hemorrhage (Grade 3 or more)</strong></td>
<td>99 per 1,000 (63 to 148)</td>
<td><strong>RR 0.98</strong>&lt;br&gt;(0.64 to 1.50)</td>
<td>2301 (3 RCTs)</td>
<td>⬤⬤⬤◯ LOW b,d</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio

**Explanations**

a. Downgraded one level for serious imprecision because the 95% confidence interval includes appreciable benefit and the upper limit exceeds 0.9
b. Downgraded one level for serious imprecision because the 95% confidence interval includes appreciable benefit and harm/appreciable harm
c. Downgraded by 1 level due to lack of blinding and the fact that Control group intervention was assisted ventilation in 1 study
d. Unblinded studies. Outcome assessors unblinded
e. Marked heterogeneity between the studies.
RECOMMENDATION 5

Extreme preterm neonates (gestation <28 weeks) should not be routinely intubated in the delivery room; intubation and ventilation should be reserved only for those with severe perinatal asphyxia requiring resuscitation.

Strong, Conditional recommendation based on moderate-quality of evidence for benefits in two critical outcomes (BPD and death/BPD) and two important outcomes namely need for mechanical ventilation and surfactant).

Comment: Applicable in settings with high antenatal steroid coverage and adequate expertise in managing extreme preterm neonates

Practice Question 6: Among preterm neonates with RDS, what is the effect of CPAP alone when compared to CPAP therapy with early rescue surfactant on mortality and severe morbidities?

Summary of evidence- values and benefits

- Evidence for this review is based on an existing systematic review by Isayama et al. that included nine RCTs. No new eligible RCTs was identified in the updated search. Infants in the early InSurE group were intubated, given surfactant, and extubated to CPAP within 1 hour after intubation. Infants in the CPAP alone group continued to receive NCPAP initially and, were rescued by intubation followed by mechanical ventilation or InSurE based on pre-determined criteria. The role of Minimally Invasive Surfactant Therapy (MIST) or Least Invasive Surfactant administration (LISA) is not addressed in this review.

- The nine studies included in this systematic review were heterogenous with respect to maternal or infant characteristics (e.g, antenatal corticosteroid coverage (50% to 90%), gestational age (range from 25 to 35 weeks), timing of the intervention (from shortly after birth to 72 hours after birth), and back-up measures for CPAP failure.

- There is moderate-quality evidence that early rescue surfactant by InSurE in preterm infants with RDS reduces the need for mechanical ventilation (RR 0.71; 95% CI 0.54 to 0.92) (Table 7). A trend favouring InSurE therapy was noted with moderate-quality evidence for BPD (RR 0.86; 95% CI0.71 to 1.03) and death/BPD (RR 0.88; 95% CI0.76 to 1.02), and low quality of evidence for air-leak (RR 0.50; 95% CI 0.24 to 1.07). There was no difference in the mortality or severe intraventricular hemorrhage between the two groups. The results were similar for the subgroup of neonates who were symptomatic with RDS at the time of enrolment.

- Use of surfactant replacement therapy (SRT) in preterm neonates with RDS has shown to reduce mortality and air-leaks in low-and-middle-income countries (LMIC).

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However, there are concerns with the use of SRT with InSurE in LMIC where the expertise in such techniques and monitoring facilities may be limited.

- Given the benefits of InSurE therapy, health professionals, parents, and policy makers are going to give high value to this intervention provided skilled personnel and adequate support system for monitoring is available along with the surfactant. This is supported by the fact that surfactant has been included in the WHO Model List of Essential Medicines for Children75 and use of SRT in symptomatic preterm infants with RDS is one of the ‘conditional recommendation’ by WHO to improve preterm birth outcome76.

- The most important concern with SRT is the cost in LMICs settings. However, the incremental cost-effectiveness ratio is likely to be favourable if the quality-adjusted life years for survivors of preterm births are taken into account77.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with CPAP plus early rescue surfactant</td>
<td>Risk with CPAP alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or BPD</td>
<td>337 per 1,000 (256 to 344)</td>
<td>297 per 1,000 (256 to 344)</td>
<td>RR 0.88 (0.76 to 1.02)</td>
<td>1250 (6 RCTs) MODERATE a</td>
</tr>
<tr>
<td>BPD assessed with Oxygen</td>
<td>263 per 1,000 (187 to 271)</td>
<td>226 per 1,000 (187 to 271)</td>
<td>RR 0.86 (0.71 to 1.03)</td>
<td>1128 (6 RCTs) MODERATE a</td>
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<tr>
<td>requirement at 36 weeks PMA</td>
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<tr>
<td>Death assessed with In-hospital mortality</td>
<td>90 per 1,000 (60 to 119)</td>
<td>85 per 1,000 (60 to 119)</td>
<td>RR 0.94 (0.67 to 1.32)</td>
<td>1394 (7 RCTs) MODERATE b</td>
</tr>
<tr>
<td>Air-leak-yellow</td>
<td>56 per 1,000 (13 to 60)</td>
<td>28 per 1,000 (13 to 60)</td>
<td>RR 0.50 (0.24 to 1.07)</td>
<td>1547 (9 RCTs) VERY LOW a,c,d</td>
</tr>
<tr>
<td>Severe Intra-ventricular haemorrhage</td>
<td>44 per 1,000 (20 to 61)</td>
<td>34 per 1,000 (20 to 61)</td>
<td>RR 0.79 (0.45 to 1.39)</td>
<td>1325 (7 RCTs) MODERATE a</td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td>361 per 1,000 (195 to 332)</td>
<td>257 per 1,000 (195 to 332)</td>
<td>RR 0.71 (0.54 to 0.92)</td>
<td>1549 (9 RCTs) MODERATE e</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

Explanations
a. The 95% CIs of the relative risk estimates include an appreciable benefit and a null effect
b. The 95% CIs of the relative risk estimates include an appreciable benefit and harm
c. The risk of bias was serious because the sensitivity analyses using fixed-effect methods or excluding studies with a high risk of bias changed the results.
d. The inconsistency was serious for air leakage because the point estimate of RR in the study by Sandri et al was very different from the other studies. There were no overlaps of 95% CIs between the studies by Rojas et al and Sandri et al. In addition, the sensitivity analyses using the fixed-effect model or excluding the study by Sandri et al changed the significance of the results.
e. The confidence intervals of the study by Dunn et al does not overlap with that of Verder et al 1999 and Verder et al 1999. Moreover, the I2 (I square) value of the heterogeneity in Random effect Model is 73% with p value being 0.0003.
Non-invasive respiratory support for newborns

RECOMMENDATION 6

Early rescue surfactant should be administered along with CPAP in preterm neonates with respiratory distress syndrome (RDS).

Strong recommendation based on the moderate-quality of evidence for a reduction in the need for mechanical ventilation with favourable trend towards a reduction in critical outcomes namely, BPD and, death or BPD.

Comment: Units offering surfactant therapy should have the equipment to offer mechanical ventilation, blood gas analysis, chest x-ray and skilled newborn care for adequate monitoring

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

Practice Question 7a: Among neonates with apnea of prematurity, what is the effect of CPAP therapy compared with no CPAP therapy on the need for ventilation, mortality, and severe morbidities?

Summary of evidence- values and benefits

- We did not find any RCT that compared the effect of CPAP with oxygen therapy by headbox or cannula in preterm neonates with apnea. A Cochrane systematic review\textsuperscript{78} included one RCT comparing CPAP therapy delivered using a face mask with theophylline for apnea among preterm infants\textsuperscript{79}. The quality of evidence was graded as very low. The requirement of mechanical ventilation was higher in the CPAP group, but there was no difference in in-hospital mortality. 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.

- Sequential application of CPAP therapy in preterm neonates has shown a reduction in mixed and obstructive apnea episodes, but no effect on central apnea episodes\textsuperscript{80}. The beneficial effects are postulated to be due to splinting of upper airway and relief of obstruction. Methylxanthine has been shown to reduce the incidence of apneic episodes and use of mechanical ventilation. Coupled with better longer-term outcomes and lower toxicity, caffeine is recommended as the drug of choice for the treatment of apnoea\textsuperscript{81}. CPAP therapy is generally administered in conjunction with methylxanthines.

- Despite the paucity of evidence and based on recommendations from the American Academy of Pediatrics\textsuperscript{82}, the GDG members recommend CPAP therapy for the management of apnea in preterm neonates considering the beneficial effects of CPAP.
Practice Question 7b: Among neonates with apnea of prematurity, what is the effect of HFNC therapy and NIPPV therapy as compared with CPAP therapy on the need for ventilation, mortality and severe morbidities among neonates with apnea of prematurity?

Summary of evidence-values and benefits

- Evidence for this review is based on a Cochrane review that compared NIPPV versus CPAP for apnea of prematurity that included two studies Lin 1998 and Ryan 1989. In the updated search, we identified 2 more studies, Gizzi 2014 and Pantalitschka 2009. No studies were identified that compared CPAP versus HFNC for apnea of prematurity.

- Ryan 1989 and Lin 1998 examined only short term (4 - 6 hours) effects of CPAP and NIPPV in reducing apneic events. Outcomes like the need for intubation beyond the trial period, in-hospital mortality, air leaks were not looked at. Gizzi et al. and Pantalitschka et al. were crossover RCTs. Gizzi et al compared flow-synchronized NIPPV, NIPPV and CPAP all delivered via a ventilator. The authors concluded that flow-synchronized NIPPV is more effective than NIPPV and CPAP in reducing the incidence of desaturations, bradycardias and central apnoea episodes.

- Pantalitschka et al compared 4 different modes; NIPPV via a conventional ventilator, NIPPV and NCPAP via a variable flow device, and CPAP delivered via a constant flow underwater bubble system. The authors concluded that a variable flow NCPAP device may be more effective than a conventional ventilator in NIPPV mode. Both examined short term outcomes (rates of apnea and desaturation) and had a small sample size. The outcomes were reported in the median and interquartile ranges and the distribution was skewed. Hence, they were not combined in a meta-analysis.

- There is very low-quality evidence from two older RCTs that non-synchronised NIPPV decreases the 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) as compared to nasal CPAP - a benefit of questionable clinical relevance (Table 8 enlists the summary of findings for the comparison between NIPPV and CPAP for 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. The role of Heated humidified nasal cannula in the management of apnea of prematurity is not known.

- Given the lack of clinically important benefits with NIPPV and the need for a ventilator to deliver the same, health care providers and policymakers are unlikely to give high value to NIPPV. The cost of variable flow device is higher than the bubble CPAP device.
Table 8: Summary of findings table for NIPPV compared to NCPAP for apnea of prematurity

| Patient or population: | apnea of prematurity |
| Setting: | Hospital |
| Intervention: | NIPPV |
| Comparison: | NCPAP |

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of therapy: intubation</td>
<td>28 per 1,000 (0 to 190)</td>
<td>RR 0.30 (0.01 to 6.84)</td>
<td>74 (2 RCTs)</td>
<td>☐☐☐☐ VERY LOW a,b,c</td>
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<tr>
<td>Rate of apnea (events/hr) assessed with: cardiopulmonary monitoring</td>
<td>The mean rate of apnea (events/hr) was 0</td>
<td>MD 0.1 lower (0.53 lower to 0.33 higher)</td>
<td>-</td>
<td>40 (1 RCT)</td>
<td>☐☐☐☐ VERY LOW c,d,e</td>
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<tr>
<td>Change in rate of apnea (events/hr)</td>
<td>The mean change in rate of apnea (events/hr) was 0</td>
<td>MD 1.19 lower (2.31 lower to 0.07 lower)</td>
<td>-</td>
<td>34 (1 RCT)</td>
<td>☐☐☐☐ VERY LOW c,d,e</td>
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</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

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

Explanations
a. The interventions in both the studies were unblinded. However, the outcome assessors were blinded. While both studies (n=74) reported this outcome, but only one infant (randomised to NCPAP) needed intubation (Lin 1998).
b. The 95% CI is crossing the line of equivalence and also the threshold for clinical decision.
c. Investigators unblinded to intervention, but blinded for outcome assessment.
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What should be the mode of non-invasive respiratory support among preterm infants who are extubated following a period of intubation and mechanical ventilation?

Practice Question 8a: Among preterm neonates being extubated following a period of intubation and mechanical ventilation what is the effect of CPAP therapy compared with no CPAP therapy on the need for additional ventilatory support, mortality, and severe morbidities?

Summary of evidence - values and benefits

- The recommendations are based on a Cochrane systematic review that addressed the above question and included nine studies. No new studies were identified in the updated search.
- There is low-quality evidence that CPAP decreases the incidence of treatment failure (RR 0.62; 95% CI 0.51 to 0.76) when compared to no CPAP in neonates who were extubated from mechanical ventilation. There was no difference in the rates of reintubation and ventilation or BPD in these infants. No information was available for other critical outcomes including, mortality and air leaks (Table 9a).

Practice Question 8b: Among preterm neonates being extubated following a period of intubation and mechanical ventilation, what is the effect of HFNC therapy compared to CPAP therapy on the need for additional ventilatory support, mortality, and severe morbidities?

Summary of evidence - values and benefits

- We found a recent 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. A total of 10 studies involving 1,201 preterm neonates were included in the review.
- There is very low-quality evidence that high flow nasal cannula (HFNC) reduces the incidence of air leaks (RR 0.29; 95% CI 0.11 to 0.76) when compared to CPAP. 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 (RR 0.35; 95% CI 0.27 to 0.46) (Table 9b).

Practice Question 8c: Among preterm neonates being extubated following a period of intubation and mechanical ventilation (P), what is the effect of NIPPV compared to CPAP therapy on the need for additional ventilatory support, mortality, and severe morbidities?

Summary of evidence - values and benefits

- We identified one Cochrane review on NIPPV versus CPAP therapy following extubation in preterm neonates (Lemyre 2017). The review had identified 10 trials enrolling a total of 1431 neonates. On updating search, two more studies were found to be eligible for inclusion in the review. Only five trials synchronised NIPPV delivery – three trials used the Infant Star ventilator with Star Synch abdominal capsule while two used more recent ventilators.
- There is low to moderate-quality evidence that NIPPV reduces the risk of two critical outcomes namely, in-hospital mortality (RR 0.70; 95% CI 0.49 to 0.99) and air leaks (RR 0.65; 95% CI 0.42 to
0.98) but does not reduce the risk of the other critical outcome – bronchopulmonary dysplasia. There is moderate-quality evidence that NIPPV reduces the incidence of extubation failure requiring re-intubation (RR 0.69; 95% CI 0.60 to 0.79) in the first week following extubation (Table 9c). Benefits were noted both with synchronized and non-synchronized NIPPV.

Evidence to recommendations

- 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.
- 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 widespread availability in most settings in India.
- 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.
- Cost-minimisation analysis by Fleeman et al for National Health Services (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). The threshold analysis showed that if the lifespan of the machines reaches 6.8 years, then CPAP becomes the less costly option.
- 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.
- 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.
Table 9a: Summary of findings for the comparison CPAP versus no CPAP in preterm neonates following extubation from mechanical ventilation

**Patient or population:** Preterm neonates following extubation from mechanical ventilation  
**Setting:** Hospital (neonatal intensive care unit)  
**Intervention:** CPAP  
**Comparison:** no CPAP

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for mechanical ventilation in the post extubation period</td>
<td>Risk with no CPAP</td>
<td>314 per 1,000 (217 to 339)</td>
<td>Risk with CPAP</td>
<td>273 per 1,000 (217 to 339)</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>Risk with no CPAP</td>
<td>438 per 1,000 (223 to 333)</td>
<td>Risk with CPAP</td>
<td>272 per 1,000 (223 to 333)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (BPD) assessed with: Oxygen requirement at 28 days of life</td>
<td>Risk with no CPAP</td>
<td>424 per 1,000 (343 to 526)</td>
<td>Risk with CPAP</td>
<td>424 per 1,000 (343 to 526)</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

**Explanations**  
a. 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  
c. P for heterogeneity <0.05
Table 9b: Summary of findings for HFNC compared to CPAP in preterm neonates extubated after a period of endotracheal intubation and mechanical ventilation

**Patient or population:** preterm neonates extubated after a period of endotracheal intubation and mechanical ventilation  
**Setting:** Hospital  
**Intervention:** HFNC  
**Comparison:** CPAP

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-hospital mortality (Mortality)</strong></td>
<td>25 per 1,000 (8 to 41)</td>
<td>RR 0.71 (0.31 to 1.60)</td>
<td>1020 (7 RCTs)</td>
<td>⬤⬤⬤◯ MODERATE a,b</td>
</tr>
<tr>
<td><strong>Pulmonary air leaks</strong></td>
<td>29 per 1,000 (3 to 22)</td>
<td>RR 0.29 (0.11 to 0.76)</td>
<td>1037 (7 RCTs)</td>
<td>⬤◯◯◯ VERY LOW c,d,e</td>
</tr>
<tr>
<td><strong>Bronchopulmonary dysplasia (BPD) assessed with:</strong> oxygen supplementation at 36 weeks</td>
<td>233 per 1,000 (163 to 247)</td>
<td>RR 0.86 (0.70 to 1.06)</td>
<td>1130 (8 RCTs)</td>
<td>⬤⬤◯◯ LOW b,c</td>
</tr>
<tr>
<td><strong>Respiratory failure requiring re-intubation assessed with:</strong> within 3 days of extubation</td>
<td>135 per 1,000 (110 to 256)</td>
<td>RR 1.24 (0.81 to 1.89)</td>
<td>478 (5 RCTs)</td>
<td>⬤◯◯◯ VERY LOW b,c,d</td>
</tr>
<tr>
<td><strong>Nasal trauma</strong></td>
<td>356 per 1,000 (96 to 164)</td>
<td>RR 0.35 (0.27 to 0.46)</td>
<td>860 (7 RCTs)</td>
<td>⬤⬤⬤◯ MODERATE c</td>
</tr>
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</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

**CI:** Confidence interval; **RR:** Risk ratio

**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)
**Table 9c: Summary of findings for NIPPV compared to CPAP in in preterm neonates being extubated from mechanical ventilation**

**Patient or population:** in preterm neonates being extubated from mechanical ventilation  
**Setting:** Hospital  
**Intervention:** NIPPV  
**Comparison:** CPAP

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Risk with CPAP</td>
<td>Risk with NIPPV</td>
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</tr>
<tr>
<td><strong>In-hospital mortality</strong></td>
<td>97 per 1,000</td>
<td>68 per 1,000 (48 to 96)</td>
<td>RR 0.70 (0.49 to 0.99)</td>
<td>1338 (7 RCTs) MODERATE ab</td>
</tr>
<tr>
<td><strong>Pulmonary air leaks</strong></td>
<td>68 per 1,000</td>
<td>44 per 1,000 (29 to 67)</td>
<td>RR 0.65 (0.42 to 0.98)</td>
<td>1323 (7 RCTs) LOW bc</td>
</tr>
<tr>
<td><strong>Bronchopulmonary dysplasia (BPD) assessed with: oxygen supplementation at 36 weeks</strong></td>
<td>338 per 1,000</td>
<td>315 per 1,000 (271 to 369)</td>
<td>RR 0.93 (0.80 to 1.09)</td>
<td>1209 (7 RCTs) LOW c,d</td>
</tr>
<tr>
<td><strong>Respiratory failure post extubation</strong></td>
<td>394 per 1,000</td>
<td>272 per 1,000 (236 to 311)</td>
<td>RR 0.69 (0.60 to 0.79)</td>
<td>1604 (12 RCTs) MODERATE c,e</td>
</tr>
<tr>
<td><strong>Necrotising enterocolitis (NEC)</strong></td>
<td>114 per 1,000</td>
<td>99 per 1,000 (73 to 136)</td>
<td>RR 0.87 (0.64 to 1.19)</td>
<td>1315 (7 RCTs) LOW c,d</td>
</tr>
<tr>
<td><strong>Duration of hospitalisation (days)</strong></td>
<td>The mean duration of hospitalisation (days) was 0</td>
<td>MD 2.7 higher (0.01 higher to 5.4 higher)</td>
<td>-</td>
<td>244 (4 RCTs) LOW c,d</td>
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</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

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

**Explanations**

- **a.** Blinding of outcome assessment not done but outcome is objective  
- **b.** 95% CI does not cross the clinical decision threshold, but the optimal information size is not met  
- **c.** Blinding of outcome assessment not done in most studies  
- **d.** 95% CI crosses the clinical decision threshold between recommending and not recommending treatment  
- **e.** I² > 50% but 95% CI of all the studies overlap with each other
RECOMMENDATION 8

Preterm very low birth weight neonates being extubated after a brief period of ventilation should be weaned off either to CPAP or 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.

Comment: If adequate expertise and equipment are available, NIPPV (both synchronized and non-synchronised) might preferably be used, particularly in neonates at risk of CPAP failure.

Practice Question 9: Among term neonates with meconium aspiration syndrome (MAS), what is the effect of CPAP when compared to oxygen therapy delivered by headbox, facemask or nasal cannula on mortality and severe morbidities?

Summary of evidence- values and benefits

- The evidence for this review comes from a study by Pandita et al. There is low quality evidence that CPAP decreases the need for mechanical ventilation (2 [3.0%] vs. 17 [25.0%]); odds ratio, 0.09; 95% CI, 0.02-0.43; P = .002) in the first 7 days of life compared with no CPAP or oxygen therapy alone. There is very low-quality evidence that CPAP therapy is associated with less need for surfactant (3 [4.5%] vs. 11 [16.2%]; odds ratio, 0.24; 95% CI, 0.05-0.87). There was no difference in mortality between the two groups (Table 10).

- CPAP therapy 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.

- One third to half of the 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.

- 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.
Table 10: Summary of findings for CPAP compared to oxygen therapy (head box or nasal prong etc) for late preterm and term infants with meconium aspiration syndrome

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td>Risk with oxygen therapy (head box or nasal prong etc)</td>
<td>Risk with CPAP</td>
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<tr>
<td>In-hospital mortality (In-hospital mortality)</td>
<td>15 per 1,000 (0 to 110)</td>
<td><strong>5 per 1,000 (0.01 to 8.30)</strong></td>
<td>135 (1 RCT)</td>
<td>⬤⬤◯◯ LOW a</td>
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<td>Need for mechanical ventilation</td>
<td>250 per 1,000 (7 to 125)</td>
<td><strong>29 per 1,000 (0.02 to 0.43)</strong></td>
<td>135 (1 RCT)</td>
<td>⬤⬤◯◯ LOW b,c</td>
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<tr>
<td>Air leak</td>
<td>0 per 1,000 (0 to 0)</td>
<td><strong>0 per 1,000 (0.12 to 77.20)</strong></td>
<td>135 (1 RCT)</td>
<td>⬤⬤◯◯ VERY LOW a,d</td>
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<tr>
<td>Need for surfactant therapy</td>
<td>162 per 1,000 (10 to 144)</td>
<td><strong>44 per 1,000 (0.05 to 0.87)</strong></td>
<td>135 (1 RCT)</td>
<td>⬤⬤◯◯ LOW a,d</td>
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</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

Explanations
a. CI for the Odds ratio is very wide. Optimal information size is less
b. The need for mechanical ventilation was assessed within 7 days of enrolment. Neonates in oxygen therapy were initially rescued with CPAP prior to intubation.
c. Optimal information size is less

RECOMMENDATION 9

Continuous positive airway pressure may be employed as the primary mode of respiratory support in late preterm and term neonates with meconium aspiration syndrome.

Weak recommendation based on low quality of evidence for benefit in two important outcomes namely: the need for mechanical ventilation and surfactant therapy with CPAP and consensus among experts for beneficial effects with CPAP.

Comment: Facilities offering CPAP support should have the expertise to monitor such neonates for air-leak.
What should be the characteristics of optimal CPAP device for use as determined by a comparison of the efficacy and safety of commonly used CPAP devices?

Practice Questions 10-13: Among neonates requiring CPAP therapy, what is the optimal CPAP device for use (as determined by comparison of the efficacy and safety of commonly used CPAP devices)?

- Pressure generators: Bubble vs. ventilator vs. variable flow device
- Patient interfaces: nasal prongs vs. masks vs. nasopharyngeal prongs.
- Initial pressure: ≤5 cm vs. > 5 cm H₂O
- Weaning: cycling vs. sudden cessation vs. others

Practice Question 10: Bubble CPAP vs. ventilator CPAP vs. variable flow device

Summary of evidence -values and benefits

- The evidence for this review is derived from a Cochrane systematic review by DePaoli et al.120, published in 2008 that included two studies121,122 comparing the effects of different CPAP devices. On updating the search, we identified seven new studies.
  - Ventilator versus Bubble CPAP- 3 studies123-125
  - Infant flow driver versus ventilator CPAP- 4 studies121,122,126,127
  - Infant flow driver versus bubble CPAP- 4 studies128-131

- There is low to very low-quality evidence that ventilator CPAP does not improve any of the critical or important outcomes when compared to bubble CPAP in preterm neonates (Table 1a).

- There is low-quality evidence that infant flow driver (IFD) is associated with a lower risk of extubation failure when compared to ventilator CPAP (RR 0.66; 95% CI 0.5 to 0.88), but without any effect on hard outcomes such as mortality and BPD (Table 1b).

- There is also low-quality evidence that the use of IFD CPAP compared to ventilator CPAP is associated with a lower incidence of nasal injury (RR 0.12; 95% CI 0.04 to 0.39). When compared with bubble CPAP, there is moderate-quality evidence that IFD reduces the duration of CPAP in preterm neonates; no benefits were observed in other critical outcomes (Table 1c).

- The benefit of reduction in nasal injury needs to be interpreted carefully as the incidence of nasal injury depends on nasal interfaces, fixation technique, flow delivery mechanisms, humidification and nursing competence.

- 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.

- 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.

NNF India Evidence-based Clinical Practice Guidelines January 2020
### Table 11a: Summary of findings for Ventilator CPAP compared to bubble CPAP in preterm neonates

**Patient or population:** preterm neonates with respiratory distress  
**Setting:** Hospital  
**Intervention:** ventilator CPAP  
**Comparison:** bubble CPAP

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<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td>Risk with bubble CPAP</td>
<td>Risk with ventilator CPAP</td>
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</table>
| CPAP failure | 133 per 1,000 (39 to 1,000)            | 200 per 1,000 (39 to 1,000) | RR 1.50 (0.29 to 7.73) | 30 (1 RCT) | ⬤◯◯◯   VERY LOW  
| Bronchopulmonary dysplasia assessed with: oxygen requirement at 36 weeks PMA | 500 per 1,000 (8 to 277) | 375 per 1,000 (170 to 835) | RR 0.75 (0.34 to 1.67) | 32 (1 RCT) | ⬤◯◯◯   VERY LOW |
| Air leaks | 32 per 1,000 (8 to 277) | 48 per 1,000 (8 to 277) | RR 1.50 (0.26 to 8.59) | 62 (2 RCTs) | ⬤◯◯◯   LOW |
| Intraventricular hemorrhage assessed with: Grade 3 or 4 IVH on USG brain | 63 per 1,000 (4 to 915) | 63 per 1,000 (4 to 915) | RR 1.00 (0.07 to 14.64) | 32 (1 RCT) | ⬤◯◯◯   VERY LOW |
| Nasal septal injury | 267 per 1,000 (3 to 507) | 29 per 1,000 (3 to 507) | RR 0.11 (0.01 to 1.90) | 30 (1 RCT) | ⬤◯◯◯   VERY LOW |
| Duration of CPAP | The mean duration of CPAP was 0 MD 3.91 lower (18.03 lower to 10.23 higher) | - | 30 (1 RCT) | ⬤◯◯◯   VERY LOW |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

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

**Explanations**

a. Outcome assessors were blinded but investigators were not blinded  
b. Single study  
c. 95% CI includes 1) no effect and 2) appreciable benefit or appreciable harm  
d. Outcome assessment was not blinded  
e. Outcome assessment was not blinded in the study with > 50% weightage
Table 11b: Summary of findings for Variable flow CPAP compared to ventilator CPAP for preterm neonates with respiratory distress

**Patient or population:** preterm neonates with respiratory distress  
**Setting:** Level 2 or 3 NICU  
**Intervention:** variable flow CPAP  
**Comparison:** ventilator CPAP

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<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
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<tr>
<td></td>
<td>Risk with ventilator CPAP</td>
<td>Risk with variable flow CPAP</td>
<td>RR</td>
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<tr>
<td>In hospital mortality New outcome assessed with: death before discharge</td>
<td>71 per 1,000</td>
<td>102 per 1,000 (59 to 177)</td>
<td>1.45 (0.84 to 2.50)</td>
<td>538 (3 RCTs)</td>
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<td>Extubation failure</td>
<td>395 per 1,000</td>
<td>261 per 1,000 (198 to 348)</td>
<td>0.66 (0.50 to 0.88)</td>
<td>419 (3 RCTs)</td>
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<td>Bronchopulmonary dysplasia assessed with: Oxygen requirement at 36 weeks’ PMA</td>
<td>398 per 1,000</td>
<td>442 per 1,000 (366 to 533)</td>
<td>1.11 (0.92 to 1.34)</td>
<td>538 (3 RCTs)</td>
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<td>Air leaks</td>
<td>126 per 1,000</td>
<td>144 per 1,000 (96 to 216)</td>
<td>1.14 (0.76 to 1.71)</td>
<td>538 (3 RCTs)</td>
</tr>
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<td>Severe Intraventricular haemorrhage assessed with: Grade 3 and 4 IVH by USG brain</td>
<td>82 per 1,000</td>
<td>63 per 1,000 (33 to 121)</td>
<td>0.77 (0.40 to 1.47)</td>
<td>438 (2 RCTs)</td>
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<td>Severe nasal injury</td>
<td>178 per 1,000</td>
<td>21 per 1,000 (7 to 69)</td>
<td>0.12 (0.04 to 0.39)</td>
<td>276 (1 RCT)</td>
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<td>Duration of CPAP assessed with: Total days on CPAP therapy</td>
<td>The mean duration of CPAP was 0</td>
<td>MD 0.85 higher (0.85 higher to 2.54 higher)</td>
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<td>538 (3 RCTs)</td>
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</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*  
CI: Confidence interval; RR: Risk ratio; MD: Mean difference

**Explanations**  
a. Intervention not blinded but objective outcome  
b. 95% CI around the pooled estimate includes 1) no effect and 2) no appreciable benefit or appreciable harm  
c. Intervention as well as outcome assessment not blinded, subjective outcome  
d. Test for heterogeneity I² > 60%  
e. Single study
Table 11 c: Summary of findings for Variable flow CPAP compared to bubble CPAP for preterm neonates with respiratory distress

**Patient or population:** preterm neonates with respiratory distress  
**Setting:** Level 2 or level 3 NICU  
**Intervention:** variable flow CPAP  
**Comparison:** bubble CPAP

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<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects(\ast) (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
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<td><strong>In-hospital mortality</strong> (assessed with: Death before discharge)</td>
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<td><strong>Risk with bubble CPAP</strong></td>
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</table>
**RECOMMENDATION 10**

Bubble CPAP, rather than ventilator CPAP or variable flow device, may 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 but the consensus among experts on cost and availability considerations in low- and middle-income countries.

---

**Question 11: nasal interface - masks vs. Prongs**

**Summary of evidence - values and benefits**

- A systematic review by King, et al, published in 2019 comparing the effect of nasal masks versus short bi-nasal prongs and included seven RCTs. Four of these trials enrolled only neonates requiring CPAP for the treatment of RDS while 2 trials enrolled neonates requiring CPAP in the post-extubation setting and one trial included neonates requiring CPAP in either setting. All 7 trials used same pressure generator in both groups. The make and brand of the nasal interface varied across trials.

- There is low-quality evidence that using nasal masks reduces the incidence of two important outcomes – CPAP failure within 72 hours as well as the nasal injury of all grades compared to short bi-nasal prongs. There is moderate-quality evidence that nasal masks reduce severe nasal injury. However, both nasal masks and short bi-nasal prongs are similar with regard to the other important outcomes such as bronchopulmonary dysplasia, air leaks and duration of CPAP.
With either interface, the preferences, skills and comfort of nurses should be taken into consideration. The cost of nasal masks is almost similar to the cost of short bi-nasal prongs. The cost of other disposables such as nasal tubing and CPAP circuits are also similar to both the interfaces.

Table 12: Summary of findings for nasal masks compared to short binasal prongs for administering CPAP

**Patient or population:** administering continuous positive airway pressure in preterm neonates with RDS  
**Setting:** Level 2 or level 3 NICU  
**Intervention:** nasal masks  
**Comparison:** short binasal prongs

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with short binasal prongs</td>
<td>Risk with nasal masks</td>
<td>RR</td>
<td>No. of participants (studies)</td>
</tr>
<tr>
<td>In Hospital mortality (Mortality)</td>
<td>119 per 1,000 (70 to 164)</td>
<td>108 per 1,000 (70 to 164)</td>
<td>RR 0.91 (0.59 to 1.38)</td>
<td>665 (6 RCTs)</td>
</tr>
<tr>
<td>CPAP failure within 72 hours (CPAP failure) assessed with: Need for intubation</td>
<td>266 per 1,000 (141 to 258)</td>
<td>192 per 1,000 (141 to 258)</td>
<td>RR 0.72 (0.53 to 0.97)</td>
<td>576 (5 RCTs)</td>
</tr>
<tr>
<td>Nasal injury (all grades) (Nasal injury) assessed with: Standard nasal injury assessment tools</td>
<td>423 per 1,000 (249 to 359)</td>
<td>300 per 1,000 (249 to 359)</td>
<td>RR 0.71 (0.59 to 0.85)</td>
<td>665 (6 RCTs)</td>
</tr>
<tr>
<td>Nasal injury (severe grades) (Nasal injury) assessed with: Standard nasal injury assessment tools</td>
<td>285 per 1,000 (46 to 131)</td>
<td>77 per 1,000 (46 to 131)</td>
<td>RR 0.27 (0.16 to 0.46)</td>
<td>396 (4 RCTs)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia (BPD) assessed with: the need for respiratory support at 36 weeks postmenstrual age</td>
<td>110 per 1,000 (25 to 105)</td>
<td>52 per 1,000 (25 to 105)</td>
<td>RR 0.47 (0.23 to 0.95)</td>
<td>395 (4 RCTs)</td>
</tr>
<tr>
<td>Air leaks (Air leaks)</td>
<td>52 per 1,000 (14 to 94)</td>
<td>36 per 1,000 (14 to 94)</td>
<td>RR 0.70 (0.27 to 1.82)</td>
<td>387 (3 RCTs)</td>
</tr>
<tr>
<td>Duration of CPAP assessed with: days follow up: mean 56 days</td>
<td>The mean duration of CPAP was 0 days</td>
<td>MD 0.33 days higher (0.37 lower to 1.03 higher)</td>
<td>-</td>
<td>548 (5 RCTs)</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).  
CI: Confidence interval; RR: Risk ratio; MD: Mean difference
Table 12: Summary of findings for nasal masks compared to short binausal prongs for administering CPAP

<table>
<thead>
<tr>
<th>Patient or population:</th>
<th>administering continuous positive airway pressure in preterm neonates with RDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting:</td>
<td>Level 2 or level 3 NICU</td>
</tr>
<tr>
<td>Intervention:</td>
<td>nasal masks</td>
</tr>
<tr>
<td>Comparison:</td>
<td>short binausal prongs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with short binausal prongs</td>
<td>Risk with nasal masks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

RECOMMENDATION 11

CPAP should be delivered by either short binausal prongs or nasal masks in neonates.

Strong recommendation based on moderate-quality evidence of no difference in critical outcomes such as bronchopulmonary dysplasia and air leaks and important ones like duration of CPAP.

Comment: If available, nasal masks may be preferred, particularly in neonates at high risk of nasal injury

Question 12: Initial CPAP pressures- Low vs. High

Summary of evidence-values and benefits

- We included trials for lower initial pressure (≤ 5 cm H2O) versus higher initial pressure (> 5 cm H2O) for two comparisons- initial respiratory support after birth and following MV and endotracheal extubation. We identified two randomized trials eligible for inclusion. Murki et al140 studied two different CPAP levels for initial respiratory support after birth and Buzella et al141 studied two different CPAP levels in the post-extubation setting.

- For initial respiratory support: There is low-quality evidence from a single trial140 that initiation of CPAP at higher pressure (7 cm of water) does not translate into clinically
relevant outcomes like the need for mechanical ventilation and surfactant, in-hospital mortality and BPD when compared initiation at 5 cm water or lower in preterm neonates with RDS. There was no increased risk of air leak in this study (Table 13a). In a systematic review\textsuperscript{10} that compared prophylactic CPAP versus intubation in the delivery room for extremely preterm neonates, a subgroup analysis was done for the outcome of pneumothorax based on the level of initiation of CPAP. Two studies\textsuperscript{59,61} initiated CPAP at 5 cmH\textsubscript{2}O, and one\textsuperscript{60} at 8 cm H\textsubscript{2}O. The risk of pneumothorax was noted to be higher with 8 cm H2O (RR 3.07, 95% CI 1.47 to 6.40, one study, 610 infants). Hence clinicians need to execute caution when using higher initial pressures.

- Post-extubation setting: There is very low-quality evidence from a single trial\textsuperscript{141} that initiation of CPAP at higher pressure (7-9 cm) post-extubation decreases the rates of extubation failure and need for re-intubation; especially among those with birth weight 500-750 grams compared to the low pressure of 4-6 cm water. The increased risk of air leak later during the study period among high CPAP pressure group needs to be investigated (Table 13b).

- Given the lack of benefit in clinical outcome and the concerns with pneumothorax, health care providers are likely to consider initiating CPAP with pressures of 5 cm H\textsubscript{2}O for neonates with RDS. In the post-extubation setting, health care providers may consider initiating CPAP at higher pressures among extremely preterm neonates. The cost of CPAP, whether initiated at low or higher pressure, should remain the same.

### Table 13a: Summary of findings for high compared to low CPAP pressure for preterm infants who require CPAP for RDS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects\textsuperscript{*} (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for mechanical ventilation within 7 days of enrolment</td>
<td>Risk with low CPAP pressure: 217 per 1,000 (122 to 385)</td>
<td>Risk with High: 215 per 1,000 (122 to 385)</td>
<td>RR 0.99 (0.56 to 1.77)</td>
<td>271 (1 RCT)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>101 per 1,000 (71 to 142)</td>
<td>RR 0.9 (0.7 to 1.4)</td>
<td>271 (1 RCT)</td>
<td>MODERATE \textsuperscript{c}</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>36 per 1,000 (14 to 40)</td>
<td>RR 0.7 (0.4 to 1.1)</td>
<td>271 (1 RCT)</td>
<td>LOW \textsuperscript{a,c}</td>
</tr>
<tr>
<td>Surfactant</td>
<td>493 per 1,000 (394 to 986)</td>
<td>RR 1.2 (0.8 to 2.0)</td>
<td>271 (1 RCT)</td>
<td>LOW \textsuperscript{a,c}</td>
</tr>
<tr>
<td>BPD assessed with: Oxygen dependency at 36 weeks PMA</td>
<td>36 per 1,000 (22 to 80)</td>
<td>RR 1.1 (0.6 to 2.2)</td>
<td>271 (1 RCT)</td>
<td>LOW \textsuperscript{a,c}</td>
</tr>
</tbody>
</table>

\textsuperscript{*}The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio
Table 13a: Summary of findings for high compared to low CPAP pressure for preterm infants who require CPAP for RDS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>№ of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with low CPAP pressure</td>
<td>Risk with High</td>
<td></td>
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</table>

Explanations
a. Unblinded study.
b. The criteria for mechanical ventilation were many and some are subjective
c. 95% confidence limits include both benefit and harm GRADE Working Group grades of evidence

Table 13b: Summary of findings for high compared to low CPAP pressure for post extubation setting among preterm neonates

High compared to low CPAP pressure for post extubation setting among preterm neonates

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>№ of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with low CPAP pressure</td>
<td>Risk with High</td>
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<td></td>
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</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio
Table 13b: Summary of findings for high compared to low CPAP pressure for post extubation setting among preterm neonates

High compared to low CPAP pressure for post extubation setting among preterm neonates

**Patient or population:** post extubation setting among preterm neonates  
**Setting:** Hospital settings  
**Intervention:** High  
**Comparison:** low CPAP pressure

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>№ of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with low CPAP pressure</td>
<td>Risk with High CPAP</td>
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</tbody>
</table>

Explanations

a. Unblinded study and extubation failure included subjective criteria also  
b. Downgraded one level due to serious imprecision because the 95% confidence interval includes both appreciable benefit and harm/appreciable harm  
c. Downgraded one level for serious imprecision because the 95% confidence interval is wide  
d. Unblinded study and the decision to intubation was based on clinician’s decision  
e. Unblinded study

**RECOMMENDATION 12**

a. Preterm neonates with respiratory distress syndrome (RDS) may be initiated on CPAP pressure of 5 cm H2O.  
   Weak recommendation based on low quality of evidence for lack of benefit and concerns with risk of air leaks at higher pressure.

b. Preterm very low birth weight neonates being extubated to CPAP, after a brief period of ventilation may be initiated on pressure of 6 cm H2O.  
   Weak recommendation based on very low quality of evidence for benefit of reducing extubation failure and need for re-intubation.
Practice Question 13: Among neonates requiring CPAP therapy, what is the optimal CPAP weaning strategy on mortality and severe morbidities?

Summary of evidence- values and benefits

- Weaning of CPAP may involve the following possible strategies; stopping CPAP completely and remaining off CPAP, gradually decreasing CPAP pressures before stopping CPAP, cycling of CPAP: alternating between on and off periods, stopping CPAP and starting blended oxygen via a nasal cannula or HFNC or a combination of above strategies. We identified 13 RCTs\(^{105,142-152}\) that examined the various CPAP weaning strategies, but for the comparison of sudden CPAP cessation vs. cycling, we found only Rastogi 2013\(^{147}\) and Todd 2012\(^{151}\) suitable for meta-analysis.
- There is low-quality evidence from two studies that sudden cessation of CPAP results in lesser BPD (RR 0.20; 95% CI 0.08 to 0.50) and other important outcomes; time to wean CPAP, lesser total duration on CPAP, oxygen requirement, duration of hospitalisation and earlier discontinuation of CPAP in corrected age (Table 14). Both the studies had a protocolized method of weaning CPAP after neonates are deemed stable on minimal settings and specified failure criteria when weaning was deferred. More evidence is required on other strategies of weaning CPAP (weaning pressures on CPAP, change to HHHFNC etc).
- Given the benefits of sudden cessation of CPAP, health care providers are likely to choose this method in preference to CPAP cycling. The sudden CPAP cessation may in-fact lead to lesser cost of care as evidenced by lesser duration on CPAP, earlier discontinuation of CPAP, oxygen duration, days of hospitalisation and lesser BPD.

Table 14: Summary of findings for sudden cessation compared to CPAP cycling for weaning CPAP treatment in preterm neonates

<table>
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<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with CPAP cycling</td>
<td>Risk with Sudden cessation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to wean CPAP</td>
<td>The mean time to wean CPAP was 0</td>
<td>MD 5.5 lower (7.99 lower to 3.01 lower)</td>
<td>-</td>
<td>125 (1 RCT)</td>
</tr>
<tr>
<td>Corrected age at CPAP cessation</td>
<td>The mean corrected age at CPAP cessation was 0</td>
<td>MD 2.2 lower (2.39 lower to 1.85 lower)</td>
<td>-</td>
<td>181 (2 RCTs)</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>The mean duration of hospital stay was 0</td>
<td>MD 15.29 lower (15.57 lower to 15.02 lower)</td>
<td>-</td>
<td>181 (2 RCTs)</td>
</tr>
<tr>
<td>Total days on CPAP</td>
<td>The mean total days on CPAP was 0</td>
<td>MD 14.2 lower (14.48 lower to 13.92 lower)</td>
<td>-</td>
<td>125 (1 RCT)</td>
</tr>
</tbody>
</table>
Table 14: Summary of findings for sudden cessation compared to CPAP cycling for weaning CPAP treatment in preterm neonates

Patient or population: Weaning CPAP treatment in preterm neonates
Setting: Hospital
Intervention: Sudden cessation
Comparison: CPAP cycling

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of oxygen therapy</td>
<td>The mean duration of oxygen therapy was 0</td>
<td>MD 21.7 lower (26.9 lower to 16.5 lower)</td>
<td>-</td>
<td>125 (1 RCT)</td>
</tr>
<tr>
<td>BPD at 36 weeks PMA</td>
<td>420 per 1,000</td>
<td>127 per 1,000 (55 to 266)</td>
<td>OR 0.20 (0.08 to 0.50)</td>
<td>125 (1 RCT)</td>
</tr>
<tr>
<td>Successful wean at first attempt</td>
<td>429 per 1,000</td>
<td>465 per 1,000 (231 to 713)</td>
<td>OR 1.16 (0.40 to 3.32)</td>
<td>56 (1 RCT)</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; MD: Mean difference; OR: Odds ratio

Explanations
a. Investigators & outcome assessors unblinded  b. Single RCT  c. Results not consistent across studies

RECOMMENDATION 13

Preterm very low birth weight neonates being weaned off from CPAP may preferably be weaned off by sudden discontinuation of CPAP rather than CPAP cycling.

Weak recommendation based on low quality of evidence for benefits in one critical outcome and five important outcomes.
Question 14: Among preterm neonates with RDS, which group of neonates are more likely to fail CPAP?

Salient findings

- CPAP success is defined as being successfully treated with CPAP for at least 72 hours of life and CPAP failure as the need for intubation and mechanical ventilation within the first 72 hours or in the first 7 days of life.
- We identified 18 studies for this narrative review. The studies varied in design, population (a majority enrolled very low birth weight neonates), disease condition (most enrolled neonates with RDS and others included respiratory distress due to other etiologies also), the type of CPAP generator, nasal interface, maximal pressure settings and treatment with surfactant.
- CPAP failure criteria also varied; but included a combination of high FiO₂ requirement, inadequate ventilation as evidenced by blood gas analysis, frequent or severe episodes of apnea requiring management or worsening respiratory distress.
- The overall CPAP failure rate varied from 20-40% in studies from LMIC settings. CPAP failure rates are higher (50% or more) among extremely preterm neonates < 28 weeks gestation and those with birth weights <750 g.

- Risk factors for CPAP failure include:
  - Antenatal: lack of or incomplete coverage of antenatal steroids
  - Neonatal: Low gestational age (<28 weeks), birth weight (<1000 g), Need for resuscitation at birth
  - The severity of RDS as evidenced by higher respiratory distress scores, chest X-ray findings, higher level of oxygen requirement, blood gas parameters indicative of poor ventilation, oxygenation indices and clinical estimation of low surfactant pool size.
  - Presence of co-morbidities like air leak, hemodynamically significant patent ductus arteriosus (PDA), sepsis, intractable apnea, severe grades of intraventricular hemorrhage and necrotizing enterocolitis.

- Predictive scores for CPAP failure: Pillai et al devised a composite score to predict CPAP failure based on gestational age at birth, preterm premature rupture of membranes (PPROM) and receipt of antenatal steroids (ANS). Final weighted score was given as: 20 (gestation <28 weeks) + 18 (PPROM) + 18 (no ANSs) + 11 (product of CPAP pressure and FiO₂ at initiation >1.28). Each variable was assigned a value of ‘1’ if present and ‘0’ if absent. The final score was ≥18 predicted CPAP failure with 75% sensitivity and 70% specificity; the positive and negative likelihood ratios were 2.46 and 0.36, respectively.

- Increasing CPAP success rates: Administration of early rescue surfactant by InSurE technique (moderate-quality evidence for a reduction in the need of mechanical ventilation), quality of nursing and supportive care, experience of the unit in using CPAP, ongoing Quality Improvement Project for improving CPAP efficacy and safety.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOP</td>
<td>Apnea of prematurity</td>
</tr>
<tr>
<td>BPD</td>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CLD</td>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>ELBW</td>
<td>Extremely low birth weight</td>
</tr>
<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>
</tr>
<tr>
<td>FHNC/HHFNC</td>
<td>Heated, humidified, high-flow nasal cannula</td>
</tr>
<tr>
<td>IFD</td>
<td>Infant flow driver</td>
</tr>
<tr>
<td>CLD</td>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>ER</td>
<td>Excessive respiratory effort</td>
</tr>
<tr>
<td>FiO2</td>
<td>Fractional inspired oxygen concentration</td>
</tr>
<tr>
<td>GDG</td>
<td>Guideline development group</td>
</tr>
<tr>
<td>HFNC/HHFNC</td>
<td>Heated, humidified, high-flow nasal cannula</td>
</tr>
<tr>
<td>IFD</td>
<td>Infant flow driver</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>NIMV</td>
<td>Non-invasive mechanical ventilation</td>
</tr>
<tr>
<td>NIPPV</td>
<td>Non-invasive positive pressure ventilation</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PICO</td>
<td>Population, intervention, comparison, outcome</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RDS</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>ROP</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SGA</td>
<td>Small-for-gestational age</td>
</tr>
<tr>
<td>VLBW</td>
<td>Very low birth weight</td>
</tr>
<tr>
<td>WMD</td>
<td>Weighted mean difference</td>
</tr>
</tbody>
</table>
References


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