Guidelines For Non-Invasive Primary Respiratory Support For Premature Neonates < 32 Weeks With RDS Clinical Pathway
This pathway is intended as a guide for physicians, physician assistants, nurse practitioners and other healthcare providers. It should be adapted to the care of specific patients based on the patient’s individualized circumstances and the practitioner’s professional judgment.
Guidelines For Non-Invasive Primary Respiratory Support For Patients With Respiratory Distress Syndrome (RDS) Clinical Pathway

Rationale

Non-invasive ventilation and CPAP to support premature infants with respiratory distress syndrome (RDS) has been proven to be safe and effective resulting in minimized lung damage associated with mechanical ventilation and the risk of bronchopulmonary dysplasia (BPD). Initial non-invasive support trial prior to intubation and surfactant administration has become the standard of care for premature infants breathing spontaneously \(^1\)\(^-\)\(^3\). In order to optimize the chances of adequate oxygenation and ventilation with noninvasive strategies it is important to optimize the efficacy of non-invasive ventilation systems available for premature infants according to their size and respiratory physiology. Despite efforts to maintain premature infants on non-invasive ventilation a subset of them will still require mechanical ventilation/surfactant administration and will fail attempts of initial non-invasive support (failure rate reported is 25-50\%) \(^4\).

Therefore, it is also important to establish objective criteria for intubation and surfactant administration for premature infants who demonstrate respiratory failure despite being initially supported by non-invasive ventilation. This clinical pathway aims to establish standardized practice for respiratory support for premature neonates born under 32 weeks gestation, who are at the highest risk for RDS as a cause for their respiratory failure.
Definitions:

1. Continuous positive airway pressure (CPAP) refers providing positive end expiratory pressure (PEEP) to the nasal and or oral orifices via a nasal interface. Pressure can be generated by a ventilator, a flow driver or under water seal (bubble system) 5.

2. Nasal Intermittent Positive Pressure Ventilation (NIPPV) refers to providing a combination of the application CPAP with intermittent pressure increases applied at the nose, without an endotracheal tube. It is ventilator driven and it can be synchronized or non-synchronized. 5

3. Bi-level CPAP is often included under the umbrella of NIPPV. This mode also combines CPAP with intermittent pressure increases via a nasal interface, but describes alternating high and low levels of CPAP. Throughout both levels the infant breathes independently. Bi-level CPAP has also been called nasal BiPAP and biphasic nasal CPAP 5

4. Heated High Flow Nasal Cannula (HHFNC) refers to providing a blend of oxygen and air by a flow generator, active heated humidifier, single heated circuit, and nasal cannula to the nares 6.

5. Short binasal prongs are sealing nasal interfaces used to deliver CPAP or NIPPV

6. Nasal masks are sealing nasal interfaces used to deliver CPAP or NIPPV

7. Nasal cannulas are long non-sealing interfaces used to delivery HHFNC, CPAP or NIPPV (Ram cannula®, Fisher Paykel®)
Background / Published Data and Levels of Evidence

1. CPAP versus Surfactant and Mechanical ventilation

There are several trials comparing initial support with CPAP versus surfactant administration and mechanical ventilation, however there are **no trials comparing NIPPV with surfactant + MV**

The three largest trials published have used different criteria for definition of intubation/failure of CPAP:

<table>
<thead>
<tr>
<th>Study</th>
<th>Gestational age of infants, weeks</th>
<th>CPAP arm, n</th>
<th>Criteria for intubation</th>
<th>Criteria for surfactant treatment</th>
<th>Infants intubated in CPAP arm</th>
<th>Infants treated with surfactant in CPAP arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>COIN [19]</td>
<td>25–28</td>
<td>307</td>
<td>FiO2 &gt;0.60</td>
<td>Local guidelines</td>
<td>46%</td>
<td>38%</td>
</tr>
<tr>
<td>SUPPORT [20]</td>
<td>24–27</td>
<td>603</td>
<td>Hemodynamic instability, acidosis or ( \text{FiO2} &gt;0.50 )</td>
<td>When intubated surfactant given if age &lt;48 h</td>
<td>83%</td>
<td>67%</td>
</tr>
<tr>
<td>VON DRM [21]</td>
<td>26–29</td>
<td>223</td>
<td>Repeated apneas, hypercapnia &gt;65 mm Hg, ( \text{FiO2} &gt;0.40 \text{discretionary}/&gt;0.60 mandatory )</td>
<td>When intubated surfactant given if supplemental oxygen required</td>
<td>45%</td>
<td>45%</td>
</tr>
</tbody>
</table>

The European Consensus Guidelines on the management of respiratory distress syndrome updated in 2019 states the following:

- Babies with RDS should be given rescue surfactant early in the course of the disease. A suggested protocol would be to treat babies who are worsening when \( \text{FiO2} >0.30 \) on CPAP pressure of at least 6 cm H2O
- CPAP should be started from birth in all babies at risk of RDS, such as those <30 weeks’ gestation who do not need intubation for stabilization
- The system delivering CPAP is of little importance; however, the interface should be short binal prongs or mask with a starting pressure of about 6–8 cm H2O. Positive end-expiratory pressure (PEEP) can then be individualized depending on clinical condition, oxygenation and perfusion.
- CPAP with early rescue surfactant is considered optimal management for babies with RDS.

2. NIPPV versus CPAP

**A Meta-analysis published in 2016 (n=1527)**

Primary outcome = need for intubation and mechanical ventilation any time before discharge; secondary outcomes: BPD, pneumothorax, IVH, NEC, ROP, PDA, total time of nasal support, duration of hospitalization, death before discharge
6 studies included: 3 randomizations prior to surfactant administration, 3 randomizations after surfactant administration

The conclusion was that NIPPV could not decrease the need for invasive ventilation both in the subgroup of infants whose GA ≤ 30 weeks or BW < 1,500 g and the subgroup of infants with BW of >30 weeks or BW > 1,500 g.

More recently, a systematic review and network meta-analysis of 35 studies 10, including 4078 neonates concluded that NIPPV was more effective in decreasing the requirement of MV than CPAP. (risk ratios [95% credible interval]: 0.60 [0.44, 0.77]) and HFNC [0.66 (0.43, 0.97)]. Surface under the cumulative ranking curve (SUCRA) for NIPPV, BiPAP, HFNC, and CPAP were 0.95, 0.59, 0.32, and 0.13.

- For the outcome of treatment failure, both NIPPV and BiPAP were more efficacious compared to CPAP and HFNC (0.56 [0.44, 0.71] {NIPPV vs CPAP}, 0.69 [0.51, 0.93] {BiPAP vs CPAP}, 0.42 [0.30, 0.63] {NIPPV vs HFNC}, 0.53 [0.35, 0.81] {BiPAP vs HFNC}). The SUCRA for NIPPV, BiPAP, CPAP, and HFNC were 0.96, 0.70, 0.32, and 0.01.
- NIPPV was associated with a reduced risk of air leak compared to BiPAP and CPAP (0.36 [0.16, 0.73]; 0.54 [0.30, 0.87], respectively).
- NIPPV resulted in lesser incidence of bronchopulmonary dysplasia or mortality when compared to CPAP (0.74 [0.52, 0.98]).
- Nasal injury was lesser with HFNC compared to CPAP (0.15 [0.01, 0.60]).

A review of studies by Ruegger et all 11 concluded that there is clear evidence that NIPPV is superior to CPAP as primary respiratory support for the prevention of respiratory failure in preterm infants with RDS.

- Ventilator-generated, synchronized NIPPV is most effective to prevent respiratory failure.
- Results show no reduction in mortality overall or within subgroups.
- Longer-term pulmonary benefits include a reduction in BPD, but only with ventilator-generated, synchronized NIPPV. A table with levels of support utilized in each study is available.

The studies included in the systematic reviews and meta-analysis are all small, therefore the level of evidence is low to medium.
3. CPAP vs. HHFNC

The most recent systematic review and meta-analysis included a total of 1830 patients demonstrated an increase of 34% (RR=1.34, 95% CI 1.01 to 1.68, I²=16.2%) of treatment failure using HFNC compared with CPAP. Secondary outcome meta-analysis showed lower rate of nasal injuries using HFNC compared with CPAP (RR=0.48, 95% CI 0.31 to 0.65, I²=0.0%). There were no significant differences in the rates of other secondary outcomes: intubation, surfactant therapy, air leak syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis and retinopathy of prematurity. Heterogeneity was not significant for all meta-analyses (p>0.05). Meta-regression did not show any influence of gestational age and weight at birth, HFNC flow rate, type of CPAP generator or use of surfactant.

The largest study (HIPSTER trial) published in the NEJM, 2016 (n=564, GA≥28 weeks, international, multicenter) comparing HHFNC vs nCPAP for primary respiratory support for RDS showed treatment failure within 72 hours of life higher on HHFNC (25.5% vs.13.3% CI 5.8-18.7; p<0.001)

An additional trial at JAMA, 2016 (n=316, 29-36 weeks, single center, Italy) showed failure of therapy not different between the groups. The use of HHHFNC was noninferior to nCPAP with regard to the primary outcome: failure occurred in 10.8% vs 9.5% of infants, respectively (95% CI of risk difference, -6.0% to 8.6% [within the noninferiority margin]; P = .71). Significant between-group differences in secondary outcomes were not found between the HHHFNC and nCPAP/BiPAP groups, including duration of respiratory support (median [interquartile range], 4.0 [2.0 to
6.0] vs 4.0 [2.0 to 7.0] days; 95% CI of difference in medians, -1.0 to 0.5; P = .45), need for surfactant (44.3% vs 46.2%; 95% CI of risk difference, -9.8 to 13.5; P = .73), air leaks (1.9% vs 2.5%; 95% CI of risk difference, -3.3 to 4.5; P = .70), and bronchopulmonary dysplasia (4.4% vs 5.1%; 95% CI of risk difference, -3.9 to 7.2; P = .79).

Conclusions and relevance: In this study, HHHFNC showed efficacy and safety similar to those of nCPAP/BiPAP when applied as a primary approach to mild to moderate RDS in preterm infants older than 28 weeks’ GA.

4. Ram cannula® versus short bi-nasal prongs:

A study comparing pressures set on the ventilator to the pressures achieved on an artificial lung model demonstrated that the pressures set on the ventilator are much higher than the pressures reaching the lungs for both systems. However, the degree of pressure difference is much higher with the Ram cannula® because there must be a leak to allow exhalation. In addition, there is much higher resistance offered by the Ram cannula® of any size when compared to the short bi-nasal prongs.

Another study done on lung model concluded that the Ram cannula® interface connected to a ventilator in NCPAP mode failed to deliver set CPAP levels when applied using the manufacturer recommended 60-80% nares occlusion, even with closed mouth and full nasal prong insertion conditions. Therefore, Ram cannula® function as a HHFNC with a set PEEP.

5. Pressure generating systems

Bubble versus other CPAP forms were compared in a systematic review and meta-analysis in 2020. A total of 12 studies were included in the analysis (n=1194 subjects)

- The risk of the primary outcome (CPAP failure within 7 days) was lower with bubble CPAP (0.75; 95% CI 0.57 to 0.98; 12 studies, 1194 subjects, I²=21%).

- Among secondary outcomes, only nasal injury was higher with use of bubble CPAP (risk ratio (RR) 2.04, 95% CI 1.33 to 3.14; 9 studies, 983
subjects; $I^2=42\%$) whereas no differences in mortality (RR 0.82, 95% CI 0.47 to 1.92; 9 studies, 1212 subjects, $I^2=20\%$) or bronchopulmonary dysplasia (BPD) (RR 0.8, 95% CI 0.53 to 1.21; 8 studies, 816 subjects, $I^2=0\%$) were noted.

The studies included in the systematic reviews and meta-analysis include patients who received bubble CPAP as primary therapy for RDS or secondary mode of support post extubation). Studies are all small, therefore the level of evidence is low to medium.

In a systematic review and meta-analysis by Martin et al, to examine the evidence for the efficacy and safety of bubble CPAP in neonates with RDS in low- and middle-income settings, CPAP for respiratory distress in infants <28 days of age in hospitals in low- and middle-income countries) were assessed. Outcomes included need for mechanical ventilation, complications and mortality. In three studies, the initial use of bubble CPAP compared with oxygen therapy, followed by mechanical ventilation if required, reduced the need for mechanical ventilation by 30%-50%. In another three trials comparing bubble CPAP with ventilator CPAP, mortality and complication rates were similar, while meta-analysis of CPAP failure in these same trials showed a lower failure rate in the bubble CPAP groups (p <0.003). There is evidence that bubble CPAP is safe and reduces the need for mechanical ventilation. Further research into the efficacy of bubble CPAP in low-income and middle-income countries is needed.  

Clinical Management

SUGGESTED PRIMARY NON-INVASIVE SUPPORT

All premature infants <32 weeks gestation breathing spontaneously and showing clinical signs of respiratory distress syndrome with intact nose should be placed on short binyal prongs or mask and be supported with CPAP or NIPPV. The suggested settings for CPAP are PEEP of 5-6 cmH$_2$O. The suggested settings for NIPPV are: rate of 20-30, PIP 16-25 and PEEP 5-6 cmH$_2$O. Settings should be adjusted according to each patient clinical status and work of breathing and once determined to be adequate. No escalation of settings based on subsequent suboptimal blood gases is recommended, except for FiO2. The purpose of no escalation is to avoid delays in surfactant administration if indicated.

The pressure generation system can be a ventilator, flow driver or under water seal (bubble).

Intubation for surfactant administration is indicated if failure of CPAP or NIPPV therapy.
• Failure of non-invasive respiratory support criteria:
  o One or more of the following criteria met despite appropriate measures (position of infant, clearing of airway - nostril, pharynx, neck-, adequate caffeine therapy, atelectasis, metabolic acidosis, other underlying conditions)
    ▪ Severe apnea requiring recurrent bag-mask ventilation, or
    ▪ Hypercarbia indicated by 2 consecutive blood gases with \( \text{PaCO}_2 > 60 \text{ mm Hg and PH} < 7.2 \) (30-60 minutes apart), or
    ▪ Increasing \( \text{FiO}_2 \) requirement beyond 30% for 2 hours to keep saturations between 90-95%
    ▪ Nasal breakdown requiring discontinuation of short binasal prongs or mask

Summary

Among preterm infants with GA lower than 32 weeks, spontaneously breathing and with RDS avoiding mechanical ventilation with non-invasive respiratory support is beneficial to prevent mechanical ventilation associated lung injury and therefore BPD, however, a trial of non-invasive respiratory support (CPAP or NIPPV) should not delay surfactant therapy if respiratory failure is present.

Glossary

- HHFNC – Heated high flow nasal cannula
- CPAP - Continuous positive airway pressure
- NIPPV – Nasal intermittent positive pressure ventilation or Noninvasive positive pressure ventilation
- NIV – Noninvasive ventilation
- BPD- Bronchopulmonary dysplasia
- ELBW- Extremely low birth weight
- VLBW – Very low birth weight
- PPV – positive pressure ventilation
- PEEP- Positive end expiratory pressure
- ELGANS -Extremely low gestational age neonates (<28 weeks)
References


download .nbib. .


Appendix
Noninvasive primary respiratory support for patient with RDS

GA < 32 weeks
and
Spontaneously breathing
and
RDS
and
Intact nose

Short binasal prongs or mask; CPAP (ventilator driven, bubble or infant driver) or NIPPV
Suggested range of settings: PEEP 5-6 cmH₂O; if NIPPV – rate 20-30, PIP 16-25 cmH₂O
Adjust settings as needed according to patient clinical status and physical exam
No escalation of settings is recommended to avoid delays in surfactant administration

Success
- Maintenance of adequate oxygenation and ventilation despite level of retractions, grunting
- No apnea requiring PPV
- Intact nasal bridge and septum

Continue CPAP or NIPPV

Failure
**Failure Criteria**
Respiratory failure
- Increasing FiO₂ beyond 30% to maintain SpO₂ 90-95% ≥ 2 hours
  or
- PaCO₂ > 60 and pH < 7.2 X 2 blood gases (30-60 min apart)
  or
- Nasal septum or bridge breakdown
  or
Severe apnea
- Recurrent need for bag-mask ventilation

Intubate and give surfactant

Aim for extubation as soon as possible and follow Non-invasive support for patients with RDS post surfactant administration guidelines when ready for extubation.
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<th>Clinical Pathway Team</th>
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<tbody>
<tr>
<td>Guidelines For Non-Invasive Primary Respiratory Support For Premature Neonates &lt; 32 Weeks With RDS Clinical Pathway</td>
</tr>
<tr>
<td>Johns Hopkins All Children’s Hospital</td>
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