Post Extubation Respiratory Support for Premature Infants Born Under 32 Weeks Gestation Clinical Pathway
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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 patient based on the patient’s individualized circumstances and the practitioner’s professional judgment.

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Rationale

A. To provide guidance on evidence-based strategies for respiratory support post-extubation for premature neonates born with GA under 332 weeks, status post respiratory failure and RDS who still have respiratory insufficiency
B. To provide guidance on evidence-based optimal respiratory support with goal to optimize extubation success
C. To provide guidance on evidence-based on objective parameters for reintubation of patients who fail to sustain adequate breathing on non-invasive support post extubation

Background/Published Data and Levels of Evidence

Minimizing the number of days on mechanical ventilation is a strategy to decrease development of important long term neurodevelopmental impairment in ELBW infants. It is important to optimize 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 and will fail attempts of extubation. Therefore, it is also important to establish objective criteria for reintubation of infants who have been extubated.

Goals of Non-invasive respiratory support are the Maintenance of adequate, not necessarily normal, gas exchange, oxygenation and growth with the least degree of side effects to skin integrity, neurodevelopment and physical comfort for patient and family

What is the respiratory support system with the best chances of success in maintaining extubation status?

In a Cochrane meta-analysis initially published in 2014 and updated in 2017 authors included a total of 10 RCTs enrolling a total of 1431 infants and comparing extubation of infants to NIPPV or NCPAP (5- synchronized form of NIPPV, 4- non-synchronized form and 1 used both methods; and of those 8 used NIPPV delivered by a ventilator, one used a bilevel device and one used both methods). When all studies were included, meta-analysis demonstrated a statistically and clinically significant reduction in the risk of meeting extubation failure criteria (typical RR 0.70, 95% CI 0.60 to 0.80; typical RD -0.13, 95% CI -0.17 to -0.08; NNTB 8, 95% CI 6 to 13; 10 trials, 1431 infants) and needing re-intubation (typical RR 0.76, 95% CI 0.65 to 0.88; typical RD -0.10, 95% CI -0.15 to -0.05; NNTB 10, 95% CI 7 to 20; 10 trials, 1431 infants)
favoring NIPPV. Graded evidence for these outcomes was determined moderate, as all trial interventions were unblinded. Although methods of synchronization varied (Graseby capsule or pneumotachograph/flow-trigger), the five trials that synchronized NIPPV showed a significant benefit for infants extubated to NIPPV in terms of prevention of extubation failure up statistically to one week after extubation. Unsynchronized. NIPPV also reduced extubation failure. NIPPV provided via a ventilator is more beneficial than that provided by bilevel devices in reducing extubation failure during the first week.

When comparing interventions, investigators found no significant reduction in rates of chronic lung disease (typical RR 0.94, 95% CI 0.80 to 1.10; typical RD -0.02, 95% CI -0.08 to 0.03) or death, and no difference in the incidence of necrotizing enterocolitis. Air leaks were reduced in infants randomized to NIPPV (typical RR 0.48, 95% CI 0.28 to 0.82; typical RD -0.03, 95% CI -0.05 to -0.01; NNTB 33, 95% CI 20 to 100). Evidence quality was graded as moderate (unblinded studies) or low (imprecision) for secondary outcomes.

When comparing Bubble devices versus other pressure sources for nasal continuous positive airway pressure in preterm infants a Cochrane meta-analyses included 15 trials involving a total of 1437 infants. All trials were small (median number of participants 88). The methods used to generate the randomization sequence and ensure allocation concealment were unclear in about half of the trial reports. Lack of measures to blind caregivers or investigators was a potential source of bias in all of the included trials. The trials took place during the past 25 years in care facilities internationally, predominantly in India (five trials) and Iran (four trials). The studied pressure sources were commercially available bubble CPAP devices versus a variety of mechanical ventilator (11 trials) or Infant Flow Driver (4 trials) devices. Meta-analyses suggest that the use of bubble CPAP compared with mechanical ventilator or Infant Flow Driver CPAP may reduce the rate of treatment failure (RR 0.76, 95% confidence interval (CI) 0.60 to 0.95; (I² = 31%); RD -0.05, 95% CI -0.10 to -0.01; number needed to treat for an additional beneficial outcome 20, 95% CI 10 to 100; 13 trials, 1230 infants; low certainty evidence). The type of pressure source may not affect mortality prior to hospital discharge (RR 0.93, 95% CI 0.64 to 1.36 (I² = 0%); RD -0.01, 95% CI -0.04 to 0.02; 10 trials, 1189 infants; low certainty evidence). No data were available on neurodevelopmental impairment. Meta-analysis suggests that the pressure source may not affect the risk of pneumothorax (RR 0.73, 95% CI 0.40 to 1.34 (I² = 0%); RD -0.01, 95% CI -0.03 to 0.01; 14 trials, 1340 infants; low certainty evidence). Bubble CPAP likely increases the risk of moderate-severe nasal injury (RR 2.29, 95% CI 1.37 to 3.82 (I² = 17%); RD 0.07, 95% CI 0.03 to 0.11; number needed to treat for an additional harmful outcome 14, 95% CI 9 to 33; 8 trials, 753 infants; moderate certainty evidence). The pressure source may not affect the risk of bronchopulmonary dysplasia (RR 0.76, 95% CI 0.53 to 1.10 (I² = 0%); RD -0.04, 95% CI -0.09 to 0.01; 7 trials, 603 infants; low certainty evidence). AUTHORS’ CONCLUSIONS: Given the low level of certainty about the effects of bubble CPAP versus other pressure sources on the risk of treatment failure and most associated morbidity and mortality for preterm infants, further large, high-quality trials are needed to provide evidence of sufficient validity and applicability to inform context- and setting-relevant policy and practice 5

What is the respiratory support system with the best chances of success in maintaining extubation status in patients with apnea of prematurity?

In a Cochrane meta-analysis published in 2022, 18 studies were included with eight studies contributing to the primary outcome. All studies had a high risk of bias, with significant heterogeneity in definition and measurement of AOP. There was no difference in AOPs per hour
between NIPPV versus CPAP (weighted mean difference = -0.19; 95% confidence interval [CI]: -0.76 to 0.37; eight studies, 456 patients). However, in a post hoc analysis evaluating the presence of any AOP (over varying time periods), the pooled odds ratio (OR) was lower with NIPPV (OR: 0.46; 95% CI: 0.32-0.67; 10 studies, 872 patients). The author conclusion was that NIPPV was not associated with decrease in AOP frequency, although demonstrated lower odds of developing any AOP.

Is it acceptable to use Heated High flow nasal cannula instead of CPAP or NIPPV with sealing interfaces?

Heated humidified high-flow nasal cannula (HHHFNC) is gaining popularity as a mode of respiratory support 6. CPAP and NIPPV studies were performed utilizing short bi-nasal prongs or mask as interfaces designed to provide sealing of the nose, therefore minimizing pressure leakage 7.

There are 2 different types of heated high flow nasal cannula at ACH NICU: Ram cannula® and Vapotherm®. Ram cannula® are also called long nasal prong and the interface is not intended to provide a sealing to the nose. Vapotherm® cannulas deliver different levels of flow of liters per minute, with unpredictable pressures, whereas Ram cannula® can be connected to a ventilator and delivery PEEP or PEEP + rate. 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 8. 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 80% nares occlusion, even with closed mouth and full nasal prong insertion conditions. Therefore, Ram cannula® function as a HHFNC with a set PEEP 9.

A meta-analysis published in Pediatrics in 2015 10 has been recently updated comparing the efficacy and safety of HHHFNC compared with standard treatments for preterm infants being extubated (CPAP) identified included ten RCTs (n = 1,201), and the analysis of primary respiratory support included ten RCTs (n = 1,676). There were no statistically significant differences for outcomes measuring efficacy, including the primary outcome. There were statistically significant differences favoring HHHFNC versus nasal cannula positive airway pressure (NCPAP) for air leak (post-extubation, risk ratio [RR] 0.29, 95 percent confidence interval [CI] 0.11 to 0.76, I² = 0) and nasal trauma (post-extubation: 0.35, 95 percent CI 0.27 to 0.46, I² = 5 percent; primary respiratory support: RR 0.52, 95 percent CI 0.37 to 0.74; I² = 27 percent). Studies, included very few preterm infants with gestational age (GA) <28 weeks. Therefore conclusion is that HHHFNC may offer an efficacious and safe alternative to NCPAP for some infants but evidence is lacking for preterm infants with GA ≤28 weeks 6.

The 5 largest published trials are:
1. Campbell: single-center, n=40, GA 27 weeks, BW 1Kg (HHFNC mean gas flow 1.6L/min vs CAPAP + 5-6) Results: HFFNC more likely to be re-intubated an also had more oxygen supplementation, apneic and bradycardic spells 11.
2. Collins: Single center Australian, n=132 <32 weeks, Mean BW 1.1kg (HHFNC 8L/Min vs CPAP +7-8 c, H2O) Results: not different in regards to reintubation prior to 7 days post-extubation, less nasal trauma on HHFNC.

3. Yoder: USA, n=432 28-42 weeks primary therapy or post-extubation. (BW >/=1Kg. Similar efficacy and safety)

4. Manley: 3 NICU Australia, n=303 <32 weeks (HHFNC 5-6L/min vs CPAP +7cmH2O) in a subgroup of preterm infants born <28 weeks HHFNC was inferior to CPAP with 7% vs 31% failure rate. Not inferior overall population and no difference in BPD or pneumothorax. Less nasal trauma in HHFNC.

What are the best settings for PEEP post extubation?

In a RCT, extubation failure in preterm infants (23-30 weeks GA; n=93) with residual lung disease (pre extubation FiO2 > 25%) was lower with CPAP range of 7-9 vs 4-6 cm H2O.

What are the criteria for Reintubation?

Definitions of extubation success in very premature infants vary widely. There are a number of studies comparing several different modes of NIV for premature infants with the primary outcome being extubation success within 7 days and all of them have set criteria to define extubation failure. According to all references above defined criteria for reintubation were:

1. Patients with residual lung disease (within first 6 weeks of life) indicated by 2 consecutive blood gases with PaCO2≥65 mm Hg with an increase greater than 15 mmHg above the PaCO2 at randomization; FiO2 requirement >.60 with an increase in ≥0.20 above the FiO2 required at randomization for more than 2 hours; Repeated episodes of apnea or bradycardia requiring bag reintubation Nasal breakdown requiring discontinuation of CPAP.
2. FiO2 > 0.2 above baseline to maintain saturation 88-92%; Ph < 7.2 and PaCO2>60 mmHg on arterial or capillary blood gas; more than one apneic episode requiring PPV within a 24 hour period; urgent intubation determined by attending physician.
3. Sustained increase of FiO2>0.15 from pre extubation,or Ph<7.25 and PaCO2>66mmHg or more than 6 episodes of apnea in 6 hours or 1 apnea requiring PPV.

When and how to discontinue respiratory support

Duration of noninvasive respiratory support exposure has not been associated with any positive or negative effect on the combined outcome of death or BPD in patients born at <29weeks gestation in a large retrospective cohort of 6268 preterm infants from the NICHD Neonatal Research Network. In a systematic review of weaning strategies sudden wean on ncpap was associated with a lower PMA at successful wean compared to pressure wean but also with a lower rate of successful wean at first attempt.

There is paucity of data to determine the best approach to weaning.
Prevention and Management of skin injury associated noninvasive respiratory support
Refer to “Care of the Patient on Non-Invasive ventilation (NIV)”
Clinical Management

A. RECOMMENDED SUPPORT AFTER EXTUBATION

• < 28 weeks - NIPPV with short bi-nasal prongs or mask sealing interface. Acceptable alternative CPAP with short bi-nasal prongs or mask (ventilator driven or bubble)

• ≥ 28 weeks – CPAP/NIPPV with short bi-nasal prongs or mask sealing interface or nasal cannula (HHFNC Vapotherm®, Ram cannula®)

• PEEP 5-9 cmH₂O, Flow 2-8 L/min, NIPPV rate 20-40, PIP 10-15 above PEEP (max 25) It 0.5-1.0

• Patients post surfactant administration with residual lung disease still requiring FiO₂ >0.25 prior to extubation, start PEEP 7-9 cmH₂O

B. REINTUBATION CRITERIA S/P RDS/SURFACTANT ADMINISTRATION
(One or more of the following):

• Any 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)

  • < 3 weeks old - FiO₂ > 0.60 or >0.20 from prior to extubation on CPAP for > 1 hour to maintain SpO₂ 90-95% OR PaCO₂ > 65 and pH < 7.2 X 2 blood gases (30-60 min apart)

  • ≥ 3 weeks old – FiO₂>60-70% or >0.20 PaCO₂>70, and pH < 7.2X 2 blood gases (30-60 min apart)

• Worsening clinical status (Septic shock, NEC, pulmonary hemorrhage, acute pulmonary hypertension, etc.)

• Severe apnea requiring bag-mask ventilation X 2 in 1 hour, despite adequate caffeine therapy, PEEP/NIPPV
Summary

ELBW and VLBW infants are at increased risk for the development of bronchopulmonary dysplasia in part due to prolonged mechanical ventilation. Optimization of NIV therapies with adequate support system according to patient size and objective criteria for reintubation may minimize prolonged mechanical ventilation and subsequently development of BPD

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)
### RECOMMENDED RESPIRATORY SUPPORT FOR PATIENT READY TO EXTUBATE

#### Gestational Age at birth

<table>
<thead>
<tr>
<th>&lt; 28 weeks</th>
<th>≥28 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mode: NIPPV</td>
<td>• Mode: NIPPV or CPAP or HHFNC</td>
</tr>
<tr>
<td>• Interface: short bi-nasal prongs or mask*</td>
<td>• Interface: short bi-nasal prongs or mask or nasal cannula (Ram cannula®, Vapotherm®, Fisher Paikel®)</td>
</tr>
<tr>
<td>• Pressure source: ventilator</td>
<td>• Pressure source: any</td>
</tr>
<tr>
<td>Acceptable alternative:</td>
<td></td>
</tr>
<tr>
<td>• Mode: CPAP</td>
<td></td>
</tr>
<tr>
<td>• Interface: short bi-nasal prongs or mask*</td>
<td></td>
</tr>
<tr>
<td>• Pressure source: ventilator on bubble</td>
<td></td>
</tr>
</tbody>
</table>

**PEEP****: 5-9 cmH₂O, Flow: 2-8 L/min, NIPPV rate 20-40, PIP 10-15 above PEEP It 0.5-1.0

* Exception to use of Ram cannula® or Vapotherm® in babies <28 weeks prior to reintubation: nasal breakdown. For such cases always consult skin team.

** Patients with FiO₂ >0.25 prior to extubation, start PEEP 7-9 cmH₂O
REINTUBATION CRITERIA FOR PATIENTS S/P RDS/SURFACTANT ADMINISTRATION

Severe apnea requiring bag-mask ventilation X 2 in 1 hour

OR

Respiratory failure

< 3 weeks old
- FiO₂ > 0.60 or >0.20 from prior to extubation on support for > 1 hour to maintain SpO₂ 90-95%
- PaCO₂ > 65 and pH < 7.2 X 2 blood gases (30-60 min apart)

≥ 3 weeks old
- FiO₂ > 60-70% or >0.20 from prior to extubation on CPAP for > 1 hour to maintain SpO₂ 90-95%
  OR
- PaCO₂ > 70, and pH < 7.2X 2 blood gases (30-60 min apart)

AND

√ Adequate infant position
√ Management of airway obstruction (stridor)
√ Clearing of airway (mouth, nostril, pharynx, neck)
√ Adequate caffeine therapy
√ Maximum NIV support settings
√ Optimal delivery of NIV pressures with sealing interface
√ Optimal atelectasis treatment
√ Correction of metabolic acidosis
√ Treatment of any underlying condition

YES

REINTUBATION

NO

CONTINUE MONITORING
References


Disclaimer

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The ultimate judgment regarding care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

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