Nasal High Flow Therapy: Neonates
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INTRODUCTION
• Nasal high flow (NHF) therapy is increasingly being used as an alternative form of respiratory support in neonatal intensive care units (NICU) in preterm infants with respiratory illnesses (Manley et al. 2016; Dysart et al. 2016). Continuous positive airway pressure (CPAP) has previously been regarded as the gold-standard for noninvasive support in this population. NHF is a form of noninvasive respiratory support that uses conditioned (heated and humidified), gas flow applied via small nasal cannulae. The following mechanisms of action are associated with NHF when used at effective flow rates.

MECHANISMS OF ACTION

Washout of dead space
• NHF allows for a very effective flushing of the nasopharyngeal dead space, resulting in alveolar ventilation being a higher fraction of minute ventilation (the volume of gas inhaled or exhaled from the lungs per minute) (Dysart et al. 2009, Manley et al. 2013).
• The flow of gas during NHF flushes CO₂ from the nasopharynx, facilitating clearance of CO₂ and improving oxygenation by creating a reservoir of fresh gas in the airway.

Improved mechanics
• NHF uses gas that is humidified (100% relative humidity) and adequately heated (maintained at 34-37°C) which reduces conductance and pulmonary compliance compared with the use of dry, cooler gas (Dysart et al. 2009).
• The use of gas that is already warmed and humidified presumably reduces the metabolic energy that might have been expended had the inspired gases been cooler or drier (Dysart et al. 2009).

Reduction in the work of breathing
• The distensibility of the nasopharynx results in an increased resistance on inspiration compared with expiration.
• NHF provides gas flow rates that meet or exceeds the peak inspiratory flow, thereby leading to a reduction of inspiratory resistance. This translates to a decrease in the resistive work of breathing (Dysart et al. 2009).
• The work of breathing with NHF (air flow rates of 3-5 L/min) was comparable to that with CPAP set to 6 cm H₂O, according to a study in 18 preterm infants (Saslow et al. 2006).

Provision of distending airway pressure
• Providing distending pressure to the lungs improves ventilatory mechanics by optimizing lung compliance and assists with gas exchange by maintaining the patency of the alveoli (Dysart et al. 2009).
• Initial data from premature infants showed that increasing NHF flow rates resulted in increased pharyngeal pressures (Wilkinson et al. 2008).
  • Pressures generated in the nasopharynx with NHF were within the range of commonly used CPAP pressures.
  • Appropriate prong-to-nares ratio is essential to achieve adequate, but not excessive, positive pressure support (Sivieri et al. 2013).
• When similar end-expiratory pressures were applied, there was no difference in breathing pattern, gas exchange, lung mechanics or work of breathing between NHF and CPAP, according to a study in 20 preterm infants with mild to moderate respiratory distress (Lavizzari et al. 2014).

INTRODUCTION

• Preterm infants are prone to respiratory failure and often require mechanical ventilation through an endotracheal tube after birth. Once these infants are extubated, traditionally Continuous Positive Airway Pressure (CPAP) has been used as the standard of care for noninvasive respiratory support. However, there is increasing evidence that Nasal High Flow (NHF) therapy is a suitable alternative form of noninvasive respiratory support in infants ≥28 weeks GA.

• To date there have been a number of Randomized Controlled Trials (RCTs) comparing the use of NHF to CPAP for post-extubation support in preterm infants. Of particular interest are the following three RCTs that have also been included in a Cochrane Review meta-analysis by Wilkinson et al (2016):

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Manley et al. 2013</th>
<th>Collins et al. 2013</th>
<th>Yoder et al. 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>303 infants &lt;32 weeks GA</td>
<td>132 infants &lt;32 weeks GA</td>
<td>432* term and preterm Infants &gt;28 GA or &gt;1000 g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study design</th>
<th>Multicentre RCT Non-inferiority trial (20% margin)</th>
<th>Single-centre RCT</th>
<th>Multicentre RCT</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>NHF flow rate</th>
<th>5-8 L/min</th>
<th>4-8 L/min</th>
<th>3-8 L/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPAP cmH2O</td>
<td>5-8 cmH2O</td>
<td>4-8 cmH2O</td>
<td>5-8 cmH2O</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Treatment failure within 7 days</td>
<td>Extubation failure within 7 days</td>
<td>Extubation failure within 72 hours</td>
</tr>
</tbody>
</table>

*226 preterm infants were randomized to post-extubation treatment. 125 preterm infants were randomized to primary treatment. Subgroup analysis are unavailable.

RESULTS

1. No difference to rate of treatment failure

Treatment failure rates were not significantly different between neonates randomized to NHF or CPAP across all three RCTs. However, Collins et al. (2013) found that across both treatment groups, extubation failure was significantly greater in infants with a GA <28 weeks (P<0.001)

<table>
<thead>
<tr>
<th>Extubation Failure within 72 hours, %</th>
<th>Yoder et al. (2013)</th>
<th>NHF (n=212)</th>
<th>CPAP (n=220)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.8</td>
<td>8.2</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extubation Failure within 7 days, %</th>
<th>Collins et al. (2013)</th>
<th>NHF (n=67)</th>
<th>CPAP (n=65)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22</td>
<td>34</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Failure within 7 days, %</th>
<th>Manley et al. (2013)</th>
<th>NHF (n=152)</th>
<th>CPAP (n=151)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34.2</td>
<td>25.8</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
2. No difference to rate of reintubation

There was no significant difference between NHF and CPAP with respect to reintubation within 7 days in all three studies conducted by Collins et al. (2013) Manley et al. (2013) and Yoder et al. (2013)

<table>
<thead>
<tr>
<th>Study</th>
<th>NHF (n)</th>
<th>CPAP (n)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins et al. (2013)</td>
<td>10</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Manley et al. (2013)</td>
<td>17.8</td>
<td>25.2</td>
<td>NS</td>
</tr>
<tr>
<td>Yoder et al. (2013)</td>
<td>11</td>
<td>10</td>
<td>NS</td>
</tr>
</tbody>
</table>

3. Significant reduction in rates of nasal trauma

NHF was associated with significantly less nasal trauma than CPAP across all three studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>NHF (n)</th>
<th>CPAP (n)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoder et al. (2013)</td>
<td>9</td>
<td>16</td>
<td>0.047</td>
</tr>
<tr>
<td>Manley et al. (2013)</td>
<td>39.5</td>
<td>54.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Collins et al. (2013)</td>
<td>3.1</td>
<td>11.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

4. No difference in rates of other adverse outcomes i.e. death, pneumothorax, bronchopulmonary dysplasia (BPD)

Apart from significant differences in reported nasal trauma, there was no difference in the adverse events profile with NHF compared to CPAP.

CONCLUSION & KEY POINTS

- The evidence indicates that for preterm infants aged ≥28 weeks' GA, NHF and CPAP are associated with similar efficacy and safety.
- The use of NHF resulted in significantly lower rates of nasal trauma, with no additional risk of adverse events, compared to CPAP.
- For infants <28 weeks, there are limited data and insufficient evidence to change the current practice of using CPAP for post-extubation respiratory support.

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BACKGROUND

- Traditionally, invasive ventilation and noninvasive ventilation in the form of CPAP have been the standard treatment for premature infants requiring respiratory support after birth and initial stabilization. There is emerging evidence comparing the efficacy of CPAP with that of Nasal High Flow (NHF) therapy.

- Two non-inferiority, Randomized Controlled Trials (RCTs) have investigated the use of NHF compared with CPAP for the primary treatment of preterm neonates.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥29 weeks' GA</td>
<td>316</td>
<td>564</td>
</tr>
</tbody>
</table>

| Study design       | Single-center study in Italy | Multi center study in Australia and Norway |

| Non inferiority margin | 10% | 10% |

| NHF flow rate | 4-6 L/min | 6-8 L/min |

| CPAP cmH2O     | 4-6 cmH2O  | 6-8 cmH2O  |

| Type of CPAP   | SiPAP      | SiPAP, Bubble, Ventilator |

| Primary outcome | Intubation and mechanical ventilation | Failure of initial therapy |

| Surfactant use  | NHF 44.3% CPAP 46.2% | NHF 14.4% CPAP 10.5% |

| High usage/low threshold | Low usage/threshold not specified |

| Rescue therapy | “Rescue CPAP” was used for infants in the NHF group at clinician discretion | “Rescue CPAP” was used for infants in the NHF group who met the failure criteria |

A note on recruitment for Roberts et al.

Analysis of the primary outcome data from the first 515 recruited infants indicated a significant difference between groups (P<0.001). The trial was stopped since continued recruitment was extremely unlikely to indicate the non-inferiority of NHF to CPAP in terms of primary outcome.

RESULTS

Rate of treatment failure

Roberts et al. reported significantly higher rates of initial treatment failure in the NHF group, while Lavizzari et al. found that NHF was non-inferior to CPAP with regards to intubation and mechanical ventilation.

<table>
<thead>
<tr>
<th>Treatment Failure within 72 hours, %</th>
<th>NHF</th>
<th>CPAP</th>
<th>P-value</th>
<th>Risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts et al. (2016)</td>
<td>25.5</td>
<td>13.3</td>
<td>&lt;0.001</td>
<td>12.3% (95% CI, 5.8 to 18.7)</td>
</tr>
<tr>
<td>Lavizzari et al. (2016)</td>
<td></td>
<td></td>
<td></td>
<td>Not reported</td>
</tr>
</tbody>
</table>

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### The role of “Rescue CPAP” on the rate of intubation

The use of “Rescue CPAP” in both studies resulted in no significant difference to the rates of intubation between therapies. Lower rates of intubation were found among older preterm infants (>32 weeks’ GA).

<table>
<thead>
<tr>
<th>Intubation rates within 72 hours, %</th>
<th>NHF</th>
<th>CPAP</th>
<th>P-value</th>
<th>Risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts et al. (2016)</td>
<td>15.5</td>
<td>11.5</td>
<td>0.17</td>
<td>3.9% (95% CI, -1.7 to 9.6)</td>
</tr>
<tr>
<td>Lavizzari et al. (2016)</td>
<td>10.8</td>
<td>9.5</td>
<td>0.71</td>
<td>1.3% (95% CI, -6.0 to 8.6)</td>
</tr>
</tbody>
</table>

### Nasal trauma

Nasal trauma was significantly lower with NHF than with CPAP (Roberts et al.)

### Rate of adverse events

- There were no significant differences in the secondary outcomes between the NHF and CPAP groups, including the duration of respiratory support, need for surfactant, duration of hospitalization, enteral feeding, weight or adverse events.
- Both studies report surfactant use and neither observed a difference between CPAP and NHF. However, the use of surfactant appears to differ between studies.
- In Lavizzari et al., >44% of infants were briefly intubated for surfactant delivery. These infants continued in the study. In Roberts et al., the use of surfactant was much lower and it appears that all infants who received surfactant were classified as treatment failure.
- This difference between study populations is important to note when comparing outcomes between studies.

### CONCLUSION & KEY POINTS

- Compared to NHF, CPAP may be associated with a lower rate of initial treatment failure when used for primary treatment.
- However, the need to intubate does not appear to differ significantly between the two groups. This suggests that NHF may be a feasible option when CPAP is available as rescue therapy in preterm infants, especially for those more mature preterm infants.
- While CPAP continues to be the gold standard for primary treatment of preterm infants requiring noninvasive respiratory support, further research into the use of NHF in this neonate group is still warranted.
R4. Review: Consensus on implementing NHF

Roehr et al. 2016; Yoder et al. 2017

AIM

• To provide an overview of clinical data regarding Nasal High Flow (NHF) therapy in neonates

• To establish consensus on the mechanisms of action and the clinical indications for the use of NHF compared with Continuous Positive Airway Pressure (CPAP) in neonates

BACKGROUND

• CPAP is the current gold standard for providing noninvasive respiratory support to neonates with respiratory insufficiency

• NHF is an alternative form of respiratory support that uses conditioned (heated and humidified), high flows of gas applied via small nasal cannulae

• NHF is typically defined as flows of 2L/min or higher

• The high flows of gas leads to the effective washout of carbon dioxide, a reduction of inspiratory resistance in the upper airways and a reduction in the work of breathing (WOB)

METHODS

NHF therapy expert meeting (Roehr, et al.)

• A group of 24 international physicians with a particular interest in neonatal and pediatric NHF gathered in Oxford, United Kingdom in June 2015 to discuss the present state of research into the respiratory management of newborn infants and young infants

• Respiratory physiologists, epidemiologists and authors of publications and reviews on NHF also attended the meeting

• A summary of discussions from the meeting and treatment recommendations was published, based on the latest available evidence from RCTs and the collective experience of the attendees

Consensus questionnaire (Yoder, et al.)

• Seven international NHF clinical researchers were questioned regarding their approaches to initiation, escalation, weaning and discontinuing NHF

• A prospective, modified Delphi approach was taken to construct a series of tables that answered questions related to specific aspects of NHF practice

• Completed tables were reviewed independently by each investigator, the results were discussed and areas of consensus were determined
CONSENSUS AGREEMENT AND MEETING RECOMMENDATIONS

Humidification
There was strong consensus that NHF should be humidified (100% relative humidity) and adequately heated (maintained at 34-37° C)

Flow rate
• The maximum flow rate should be determined by the manufacturer’s design or approval
  • There was general agreement that the initial gas flow should start at 4-6 L/min for preterm and term infants

Nares occlusion
• When selecting an NHF interface, there should be allowance for the generous egress of gas around the cannula tip and from the nares by ensuring that the prong diameter is approximately half that of the nostril

Appropriate population for NHF
• Current evidence supports the application of NHF for:
  • Post-extubation support of neonates ≥ 28 weeks’ in lieu of nasal CPAP
  • As an alternative to CPAP for stable infants who continue to require respiratory support above the level of standard Oxygen therapy
  • There was general agreement, but not consensus, that NHF can be used as the primary mode of support for neonatal respiratory distress at the clinician’s discretion (based on the neonate’s GA and the level of oxygen support required)

Contraindications for NHF
• Infants with signs of severe respiratory distress (FiO₂ >0.7), severe apnea, significant active air leak, or craniofacial or airway anomalies should not be considered for NHF

Feeding
• Further study is required regarding the approaches to safe oral feeding in infants on NHF
• There is very limited evidence regarding the use of nasogastric or orogastric feeding tubes in in infants on NHF

Post-extubation
• Post-extubation (support initiated after a period of intubation with resolving respiratory distress) evidence comes from randomized, clinical trials involving more than 1100 preterm infants and meta-analyses
• NHF was as effective and as safe as nasal CPAP
  • Failure rates were similar and there was no increase in adverse events, air leaks, or durations of oxygen use or hospital stay with NHF
  • Comfort scores of neonates were similar, but care of the infant was easier with NHF
  • NHF was associated with reduced rates of nasal trauma and potentially a reduced incidence of pneumothorax in preterm infants
  • The authors note that the majority of infants enrolled in trials to fate have been >28 weeks GA
• The approach to either escalation or weaning NHF should be based on signs of distress or increase in WOB, as well as the FiO₂ needed to maintain targeted SpO₂
  • Typically, weaning is considered in infants who have been stable for 12-24 hours
  • FiO₂ should be weaned first to <0.3, followed by flow rates in decrements of 0.5 to 1 L/min and every 12 to 24 h as tolerated, guided by the WOB of the infant
  • There was no consensus as to when to stop NHF, with discontinuation occurring at flow rates between 1-4 L/min
  • Escalation of gas flow is recommended for increasing FiO₂ and WOB, to a maximum recommended flow rate of 8 L/min
  • Alternative approaches to noninvasive support should be considered in neonates requiring elevated FiO₂ (typically >0.40) or with increased WOB or distress

Primary treatment
• There was general agreement for NHF as the primary mode of support for neonatal respiratory distress, but GA and the requirement for oxygen support must be considered
  • Only limited evidence is available from clinical trials for this indication, including two randomized clinical trials which suggested no difference in efficacy between NHF and either nasal ventilation or nasal CPAP (Roberts et al, 2016; Lavizzari et al. 2016) and one randomized trial which found higher treatment failure with NHF than with CPAP (Roberts et al. 2016)

AREAS FOR FUTURE RESEARCH
• Further studies are required to:
  • Determine the safety and efficacy of NHF in various groups of infants including extremely preterm infants, and infants with other neonatal lung disorders (i.e., meconium aspiration, diaphragmatic hernia)
  • Compare different initial NHF gas flow rates
  • Evaluate different approaches to discontinuing NHF
  • Compare different NHF devices and cannula interfaces (i.e., dual versus single nasal prong cannulas)
  • Analyze the economics of NHF versus other noninvasive modes
  • Assess the efficacy and safety of NHF for initial delivery room stabilization and during neonatal transport
  • Assess the efficacy and safety of NHF in resource-limited countries
  • Develop and assess the use of NHF for post-discharge noninvasive support
  • Assess approaches to oral feeding on NHF

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**A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants**

**AIM**
- To determine whether Nasal High Flow (NHF) therapy increases the rate of successful extubation in premature infants following endotracheal positive pressure ventilation, compared with nasal Continuous Positive Airway Pressure (CPAP).

**METHOD**

**Patient group**
- 132 infants were randomized to either NHF (n=67) or nCPAP (n=65) and <32 weeks’ GA, stratified into two groups (<28 weeks vs ≥28 weeks’ GA)

**Study design**
- Single center RCT

**Primary outcome**
- Extubation failure within 7 days, defined as one or more of the following:
  - Apnea (respiratory pause >20 sec), >6 episodes in 6 hours or an episode requiring intermittent positive pressure ventilation; acidosis (pH <7.25 and PCO₂ >66 mmHg); sustained increase in FiO₂ of >15% from extubation
  - Patients were re-intubated at the treating physician’s discretion

**Secondary outcomes**
- Nasal trauma, duration of respiratory support, supplemental oxygen requirement, bronchopulmonary dysplasia
  - Nasal trauma was assessed at the internal and external nares, philtrum and septum, using the sum of thrice-daily nasal trauma score recordings from 0 (normal) to 3 (skin tear)

**Treatment regimen**
- NHF (Vapotherm) at a starting flow of 8L/min. Flow rate was weaned to a minimum of 4L/min OR
- nCPAP (Hudson Respiratory Care) at a starting positive end-expiratory pressure (PEEP) of 8cm H₂O or 7cm H₂O for FiO₂ values of >0.3 and <0.3, respectively; PEEP was weaned to a minimum of 5cm H₂O

**RESULTS**

**Primary outcome**
- NHF and nCPAP were associated with similar extubation failure rates at 7 days (see table)
  - Stratification of patients by GA (<28 weeks vs. ≥28 weeks) also showed no significant difference between NHF and nCPAP therapy in extubation failure rates at 7 days
  - Overall extubation failure rates were higher among infants born at <28 weeks’ GA than those born at 28–32 weeks (44% vs. 15%; P<0.001)
Secondary outcomes

- NHF was associated with significantly reduced nasal trauma compared with nCPAP
  - At 7 days after extubation, 20% of the infants randomized to nCPAP switched to NHF due to nasal trauma
  - No significant differences were seen in bronchopulmonary dysplasia (BPD) rates or the duration of supplemental oxygen and respiratory support:

<table>
<thead>
<tr>
<th>Variable</th>
<th>HFNC (n=67)</th>
<th>nCPAP (n=65)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extubation failure at 7 days (primary outcome), % pts.</td>
<td>22</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Apnoea, % pts.</td>
<td>21</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Acidosis, % pts.</td>
<td>0</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>FiO₂ increase &gt;15%, % pts.</td>
<td>10</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Nasal trauma score first week, mean (SD)</td>
<td>3.1 (7.2)</td>
<td>11.8 (10.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BPD at 36 weeks’ gestation, % pts.</td>
<td>36</td>
<td>43</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory support, mean completed weeks (SD)</td>
<td>33.5 (2.88)</td>
<td>34.3 (3.51)</td>
<td>NS</td>
</tr>
<tr>
<td>Supplemental oxygen, mean completed weeks (SD)</td>
<td>36.9 (2.54)</td>
<td>38.0 (3.26)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

NS, not significant; pts., patients; FiO₂, fraction of inspired oxygen; SD, standard deviation

CONCLUSION & KEY POINTS

NHF is associated with a similar rate of extubation failure at CPAP in premature infants ≥ 28 weeks’ GA

- Infants <28 weeks’ GA experienced a higher rate of extubation failure
- NHF is associated with significantly less nasal trauma compared with CPAP, with no additional risk of adverse events
High-flow nasal cannulae in very preterm infants after extubation

AIM
- To compare the efficacy and safety of Nasal High Flow (NHF) therapy and nasal continuous positive airway pressure (nCPAP) for the noninvasive respiratory support of very preterm infants following extubation

METHOD
Patient group
- 303 infants <32 weeks’ GA

Study design
- Multicenter, randomized, non-inferiority trial with a non-inferiority margin of 20%

Primary outcome
- Treatment failure within 7 days of extubation

Secondary outcomes
- Reintubation during the 7 day primary endpoint period defined as; requirement for supplemental oxygen at a GA of 36 weeks; pneumothorax following study entry; total number of days of any respiratory support following study entry; duration of oxygen supplementation following study entry; length of hospital admission
- The incidence, cause, and need for a change of treatment as a result of nasal trauma were also documented

Treatment regimen
- NHF (Fisher & Paykel Healthcare) at a starting flow rate of 5–6 L/min
  - Infants who met the failure criteria were “rescued” with nCPAP; OR
- nCPAP (Fisher & Paykel Healthcare or Hudson Respiratory Care) at a starting pressure of 7cm H₂O. A mechanical ventilator or a “bubble” system was used to generate nCPAP
  - Infants who met the failure criteria were reintubated

RESULTS
Primary outcome
- NHF was non-inferior to nCPAP with regard to the primary outcome, treatment failure within 7 days of extubation (risk difference 8.4%; 95% confidence interval [CI] -1.9, 18.7; see table)
- There were no significant differences between NHF and nCPAP groups in terms of the reasons for treatment failure
  - 48% of infants that met the failure criteria on NHF were “rescued” with nCPAP and did not require reintubation

Secondary outcomes
- There was no significant difference between the NHF and nCPAP groups for the secondary outcome of reintubation within 7 days of extubation (risk difference -7.4%; 95% CI -16.6, 1.8; P=0.12)
- NHF was associated with significantly lower rates of nasal trauma compared with nCPAP
- No significant differences were seen between the two treatment groups for other secondary outcomes and serious adverse events

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<table>
<thead>
<tr>
<th>Primary outcome (% pts)</th>
<th>HFNC (n=152)</th>
<th>nCPAP (n=151)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure within 7 days of extubation</td>
<td>34.2</td>
<td>25.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Secondary outcomes**

<table>
<thead>
<tr>
<th></th>
<th>HFNC (n=152)</th>
<th>nCPAP (n=151)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reintubation within 7 days of extubation (% infants)</td>
<td>17.8</td>
<td>25.2</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen supplementation at GA of 36 weeks (% pts)</td>
<td>30.9</td>
<td>34.4</td>
<td>NS</td>
</tr>
<tr>
<td>Pneumothorax following study entry (% pts)</td>
<td>0.7</td>
<td>2.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Nasal trauma (% infants)**

<table>
<thead>
<tr>
<th></th>
<th>HFNC (n=152)</th>
<th>nCPAP (n=151)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any documented</td>
<td>39.5</td>
<td>54.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Leading to change of treatment</td>
<td>5.3</td>
<td>17.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Caused by randomized treatment</td>
<td>19.1</td>
<td>53.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Serious adverse events (% pts)**

<table>
<thead>
<tr>
<th></th>
<th>HFNC (n=152)</th>
<th>nCPAP (n=151)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax during randomized treatment</td>
<td>0.0</td>
<td>0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Death before discharge</td>
<td>3.3</td>
<td>4.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

pts, patients; IQR, interquartile range; NS, not significant.

### CONCLUSION & KEY POINTS

- NHF appears to have a similar efficacy and safety to CPAP when used post-extubation in infants ≥28 weeks’ GA
- NHF is associated with significantly less nasal trauma compared with nCPAP therapy, with no additional risk of adverse events
Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates

AIM
• To determine the safety and efficacy of Nasal High Flow (NHF) therapy versus nasal Continuous Positive Airway Pressure (nCPAP) when used as noninvasive respiratory support in neonates with respiratory dysfunction

METHOD
Patient group
• 432 infants between 28-42 weeks’ GA, with a birth weight ≥1000g

Study design
• Multicenter RCT
• Infants were stratified according to birth weight (1000-1999g and ≥2000g) and age at randomization (≤7 days vs >7 days)

Primary outcome
• Failure of study support mode (defined as the need for intubation within the first 72 hours of treatment)

Secondary outcomes
• Rates of bronchopulmonary dysplasia (BPD), total ventilator days, days on supplemental oxygen, need for delayed intubation

Treatment regimen
• NHF (Fisher & Paykel Healthcare, Vapotherm or Hudson Respiratory Care devices) at a starting flow determined by patient weight; 1000-1999g infants received 3 L/min, 2000-2999g infants received 4 L/min, and ≥3000g infants received 5 L/min OR
• nCPAP (bubble and Infant Flow nCPAP System, CareFusion) at a starting pressure of 5-6 cm H2O
• Oxygenation and ventilation targets were 85-98% for oxygen saturation (SpO2), and 40-65 mmHg for partial pressure of carbon dioxide (PCO2)

RESULTS
Primary outcome
• There was no significant difference between groups in the primary outcome of failure of support within 72 hours (see table)
• There were no significant differences in the reasons for early failure and intubation between groups: Increasing respiratory distress (83% in the NHF and nCPAP groups), increased FiO2 (39% in the NHF group and 50% in the nCPAP group) and severe apnea (22% in the NHF group and 11% in the CPAP group)
Secondary outcomes

- Infants managed with nCPAP had fewer days of any positive pressure support, and a shorter duration of study mode support compared to infants managed with heated humidified NHF (see table)
- At 7 days post-study entry, significantly more infants receiving NHF remained on the treatment than on nCPAP
  - There were no differences in the other endpoints measured
- Adverse events were similar between groups, and rates of failure were also similar between different devices used

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heated humidified NHF</th>
<th>nCPAP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for reintubation, % pts</td>
<td>15</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Remaining on therapy 7 days post-study entry, % pts</td>
<td>23</td>
<td>9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPD, % pts</td>
<td>20</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>Median days on positive pressure support</td>
<td>6</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median days on study mode</td>
<td>4</td>
<td>2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median days on supplemental O₂</td>
<td>10</td>
<td>8</td>
<td>NS</td>
</tr>
</tbody>
</table>

BPD, bronchopulmonary dysplasia, NS, not significant; O₂, oxygen; pts, patients

CONCLUSIONS & KEY POINTS

- NHF appears to have a similar efficacy and safety to CPAP when used post-extubation in infants ≥28 weeks’ GA
- There were no significant differences to the rate of adverse events between groups, and rates of failure were also similar between different devices used
Heated, humidified high-flow nasal cannula vs nasal continuous positive airway pressure for respiratory distress syndrome of prematurity: a randomized clinical non-inferiority trial

**AIM**
- This trial investigated whether primary treatment with Nasal High Flow (NHF) therapy is non-inferior to Continuous Positive Airway Pressure (CPAP) in preterm infants with mild to moderate respiratory distress syndrome (RDS)

**METHOD**

**Patient group**
- Preterm infants 29 to <37 weeks’ GA (GA) requiring noninvasive respiratory support for mild to moderate RDS

**Study design**
- Non-inferiority RCT with a margin of non-inferiority of 10% (determined by the absolute risk difference in the primary outcome)

**Primary outcome**
- Requirement for mechanical ventilation (MV) within 72 hours from commencing noninvasive respiratory support
  - Criteria for MV:
    - Persistent fraction of inspired oxygen ($\text{FiO}_2$) >0.4 to a target oxygen saturation ($\text{SpO}_2$) of 86-93% after surfactant
    - Severe apnea (>4 apnea episodes/hour or 2 apnea episodes/hour requiring positive pressure ventilation [PPV])
    - Acidosis (persistent partial pressure of carbon dioxide [$\text{PaCO}_2$] >70 mmHg, pH <7.2)

**Treatment regimen**
- NHF (Precision Flow, Vapotherm) starting flow 4-6 L/min OR
- nCPAP (SiPAP; Viasys Healthcare) starting pressure 4-6 cmH$_2$O
  - Switched from nCPAP to bilevel nCPAP in the following scenarios
    - >4 episodes of apnea/hour
    - >2 episodes/hour requiring PPV
    - Evidence of increased work of breathing
    - Bilevel CPAP started at a rate of 30 breaths/minute, inspiratory time 0.7-1 second, mean airway pressure of 6-8 cmH$_2$O
### RESULTS

**Intention to treat group**

- 316 infants enrolled between January 2012 and June 2014 randomized to receive either
  - NHF (n = 158, mean GA 33.1 weeks, 52.5% female) OR
  - nCPAP (n = 158, mean GA 33.0 week, 47.5% female)

**Primary outcome**

- Requirement for MV within 72 hours from commencing respiratory support was similar in both treatment groups (see table)
  - 10.8% with NHF and 9.5% with nCPAP. NHF was non-inferior to nCPAP in this patient group

**Secondary outcome**

- No significant differences in secondary outcomes between treatment groups
  - Includes duration of respiratory support, need for surfactant, adverse events, the duration of hospitalization, full enteral feeding, weight or exclusive breast feeding at discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NHF (n =158)</th>
<th>nCPAP (n = 158)</th>
<th>95% CI of risk difference or difference in medians</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV within 72 hours, n (%)</td>
<td>17 (10.8)</td>
<td>15 (9.5)</td>
<td>-6.0 to 8.6</td>
<td>0.71</td>
</tr>
<tr>
<td>Median age at start of MV (IQR), h</td>
<td>27.0 (8.0-36.0)</td>
<td>7.0 (3.0-19.0)</td>
<td>-24.5-0.00</td>
<td>0.06</td>
</tr>
<tr>
<td>Median duration of MV (IQR), d</td>
<td>3.2 (1.2-5.0)</td>
<td>3.0 (1.2-6.0)</td>
<td>-1.25-2.25</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of respiratory support (IQR), d</td>
<td>4.0 (2.0-6.0)</td>
<td>4.0 (2.0-7.0)</td>
<td>-1.0-0.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Surfactant requirement, n (%)</td>
<td>70 (44.3)</td>
<td>73 (46.2)</td>
<td>-9.8-13.5</td>
<td>0.73</td>
</tr>
<tr>
<td>Any adverse event, n (%)</td>
<td>28 (17.7)</td>
<td>28 (17.7)</td>
<td>-9.0-9.0</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

HFNC, heat humidified high flow nasal cannula; IQR, interquartile range; nCPAP, nasal continuous positive airway pressure (includes bilevel nCPAP)

### CONCLUSIONS & KEY POINTS

- NHF was non-inferior to CPAP as primary respiratory support for preterm infants 29 to <37 weeks’ GA with mild to moderate RDS
- NHF and nCPAP showed similar efficacy and safety in this patient group
Nasal high-flow therapy for primary respiratory support in preterm infants

AIM
• To compare the efficacy of nasal high flow (NHF) therapy and nasal continuous positive airway pressure (nCPAP) as primary respiratory support for preterm infants with respiratory distress

METHOD
Patient group
• Preterm infants 28 weeks to <37 weeks’ GA, <24 hours old, with early respiratory distress
  • No prior endotracheal ventilation or surfactant replacement therapy
  • No urgent need for intubation or ventilation, no major congenital abnormality or pneumothorax

Study design
• Multi center non-inferiority RCT with a margin of non-inferiority of 10% (determined by the absolute risk difference in the primary outcome)
  • Nine NICUs in Australia and Norway
  • Infants stratified by GA (<32 weeks vs ≥32 weeks) and study center

Primary outcome
• Treatment failure within 72 hours from randomization
  • Failure was determined if an infant receiving maximal support (NHF 8 L/min or nCPAP 8 cmH2O) met one or more of the following criteria:
    • Fraction of inspired oxygen (FiO2) ≥0.4
    • pH ≤7.2 plus partial pressure of carbon dioxide (PaCO2) >60 mmHg (8.0 kPa)
    • ≥2 episodes of apnea requiring positive pressure ventilation (PPV) within a 24-hour period or ≥6 episodes requiring any intervention within a 6-hour period
    • Urgent need for intubation and mechanical ventilation

Secondary outcomes
• Reason(s) for treatment failure, use of mechanical ventilation within 72 hours from randomization or at any time during admission, nasal trauma, other complications including complications of prematurity and other measures of neonatal health and respiratory support use, cost of care

Adverse events
• Serious adverse events were defined as death before hospital discharge, pneumothorax or other air leak during treatment
Treatment regimen

- NHF (Optiflow Junior; Fisher and Paykel Healthcare or Precision Flow; Vapotherm) at a starting flow rate of 6-8 L/min
  - Infants who met the criteria for treatment failure could receive nCPAP as rescue therapy (initiated at 7-8 cmH₂O)
  - Infants with continued treatment failure were intubated and ventilated OR
- nCPAP at a starting pressure 6-8 cmH₂O
  - Infants with treatment failure were intubated and ventilated

RESULTS

Study cessation

- Analysis of primary outcome data from the first 515 recruited infants (278 in the NHF group and 286 in the CPAP group) indicated a statistically significant difference between treatment groups
  - Continued recruitment was considered highly unlikely to show non-inferiority of NHF to nCPAP

Primary outcome

- Treatment failure within 72 hours of randomization was significantly higher with NHF than nCPAP
  - 25.5% with NHF versus 13.3% with nCPAP (Risk difference 12.3% points, 95% confidence interval 5.8-18.7; P <0.001)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NHF (n = 278)</th>
<th>nCPAP (n = 286)</th>
<th>Risk difference (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary intent-to-treat analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure within 72 hours</td>
<td>71 (25.5)</td>
<td>38 (13.3)</td>
<td>12.3 (5.8-18.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GA &lt;32 weeks’</td>
<td>46 (32.9)</td>
<td>27 (18.1)</td>
<td>14.7 (4.8-24.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>GA ≥32 weeks’</td>
<td>25 (18.1)</td>
<td>11 (8.0)</td>
<td>10.1 (2.2-18.0)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Per-protocol analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure within 72 hours</td>
<td>64 (24.2)</td>
<td>36 (12.9)</td>
<td>11.3 (4.8-17.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Positive values favor the nCPAP group, and negative values favor the NHF group. Apparent discrepancies in some of the risk differences are due to rounding. nCPAP, nasal continuous positive airway pressure; NHF, nasal high flow therapy; wk, weeks.
Secondary outcomes

- Intubation rate at 72 hours did not differ significantly between treatment groups
  - 15.5% with NHF versus 11.5% with nCPAP (use of nCPAP as rescue therapy may explain this finding)
- Median duration of respiratory support was 1 day longer with NHF (4 vs 3 days; P = 0.005)
- Supplemental oxygen requirement was more common with NHF (78.1% vs 69.6%; P = 0.02)
- The overall rate of adverse events, including rate of death, overall frequency of pneumothorax or other air leak from the lung, was similar between treatment groups
  - However, nasal trauma was significantly lower with NHF than with nCPAP (8.3% vs 18.5%; P < 0.001)

CONCLUSIONS

- Primary support with CPAP resulted in a significantly lower rate of treatment failure compared with NHF in preterm infants with respiratory distress
- However there was no significant difference in the observed rate of intubation (secondary outcome) between treatment groups, suggesting that the use of NHF with “rescue CPAP” may result in similar rates of intubation
GLOSSARY

95% CONFIDENCE INTERVAL: A statistical measure showing that 95% of the results for that parameter lie within the range quoted.

100% RELATIVE HUMIDITY (RH): The maximum amount of water a gas can hold at a given temperature.

BRONCHOPULMONARY DYSPLASIA (BPD): A form of chronic lung disease that develops in premature neonates treated with oxygen and positive-pressure ventilation.

BUBBLE CONTINUOUS POSITIVE AIRWAY PRESSURE (BCPAP): Continuous positive airway pressure therapy delivered via a bubble generator.

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP): A technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilatory circuit.

DEAD SPACE: A volume of gas that does not participate in gas exchange, is common to both the inspiratory and expiratory passages. There are different types of “dead space” including:

- Alveolar dead space: Volume of gas ventilating unperfused alveoli that has no blood perfusion (shunt or pulmonary embolism).
- Anatomic dead space: Volume of gas within the conducting zone of the lungs and upper airway. (Amount of volume that does not enter the alveoli.)
- Mechanical dead space: Expired air that is re-breathed through connecting tubing.
- Physiological dead space: Anatomic and alveolar dead space.

DISTENDING PRESSURE: Pressure applied to the lungs to expand them. Can be applied using continuous positive or negative airway pressure to create a partial vacuum.

ENDOTRACHEAL TUBE (ETT): A tube inserted through the mouth or nose into the trachea to maintain an unobstructed airway.

EXTUBATION: Withdrawing an endotracheal tube (ETT) from a patient’s airway.

FRACTION OF INSPIRED OXYGEN (FIO2): The proportion of oxygen in the air that is inspired.

FULL-TERM: An infant born between 37 and 40 weeks gestation.

FUNCTIONAL RESIDUAL VOLUME (FRC): The volume in the lungs at the end-expiratory position.

GA: Gestational Age – Period of time between conception and birth.

HEATED, HUMIDIFIED GAS: Air that has been heated and humidified prior to delivery by non-invasive ventilation, typically to 37°C and 100% relative humidity.

HYPERCAPNIA: The presence of an abnormally high level of carbon dioxide in the circulating blood.

INFANT: Children greater than 1 month to 2 years of age.

INTUBATION: The insertion of an ETT or tracheostomy tube into the trachea.

LOW BIRTH WEIGHT (LBW): Birth weight less than 2500g.

LUNG COMPLIANCE: The ease of lung expansion.

MECHANICAL VENTILATION (MV): The use of an invasive artificial airway to mechanically assist or replace spontaneous breathing, when patients cannot do so on their own.

MINUTE VENTILATION (VE): The volume of gas that moves in and out of the lungs in one minute; it is calculated by multiplying the exhaled tidal volume by the respiratory rate.

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP): A technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilator circuit.

NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION (NIPPV): A method of noninvasive ventilation that provides positive pressure to the back of the nose that is transferred to the lungs with intermittent breaths from a ventilator.

NEONATE: Premature infants or newborns less than 30 days old.

NICU: Neonatal Intensive Care Unit.

NON-INFEIORITY TRIAL: A trial that is designed to determine whether the effect of a new treatment is not worse than a standard treatment.

NONINVASIVE VENTILATION (NIV): The delivery of ventilatory support without the need for an invasive artificial airway.

OXYGEN SATURATION (SPO2): Oxygen saturation as measured by pulse oximetry.

PARTIAL PRESSURE OF CARBON DIOXIDE (PCO2): The part of total blood gas pressure exerted by carbon dioxide gas; a measure of how much carbon dioxide is dissolved in the blood and how well carbon dioxide is able to move out of the body.
PARTIAL PRESSURE OF OXYGEN (PAO2):
The part of total blood gas pressure exerted by oxygen gas; a measure of how much oxygen is dissolved in the blood and how well oxygen is able to move from the airspace of the lungs into the blood

PEDIATRIC:
Referring to children up to 21 years of age; usually found in the PICU.

PICU:
Pediatric Intensive Care Unit

PNEUMOTHORAX:
Air or gas in the pleural space

POSITIVE END EXPIRATORY PRESSURE (PEEP):
The amount of pressure above atmospheric pressure present in the airway at the end of the expiratory cycle during mechanical ventilation

POSITIVE END INSPIRATORY PRESSURE (PIP):
The highest pressure applied to the lungs during inspiration

PRETERM:
An infant born before 37 weeks gestation regardless of their weight. They can be further divided into:

• Moderate to late preterm
  32 to <37 weeks gestation

• Very preterm
  28 to <32 weeks gestation

• Extremely preterm
  <28 weeks gestation

RESPIRATORY DISTRESS SYNDROME (RDS):
A lung disease of the newborn, most frequently occurring in premature infants, that is caused by abnormally high alveolar surface tension as a result of a deficiency in lung surfactant; also called hyaline membrane disease

RESPIRATORY RATE:
The amount of breaths over a specified time period

SURFACTANT:
A substance produced in the lungs that tends to reduce the surface tension of the fluid in the lungs and helps make the small air sacs in the lung (alveoli) more stable

TIDAL VOLUME (VT):
Volume of air inspired or expired with each normal breath. The amount of gas delivered to a patient in one breath.

WORK OF BREATHING (WOB):
The force required to expand the lung against its elastic properties
Notes
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