Non invasive respiratory support in the NICU

Why Interface Matters

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– General Manager
Introduction

Trend towards more noninvasive care

- The patterns of respiratory support in neonatal critical care are changing, with more preterm infants being managed with non invasive therapies

![Diagram showing change in respiratory support methods](image)

- Invasive Ventilation: > 40 years research
- CPAP: > 10 years research
- NHF: > 10 years research
CPAP – the “gold standard”

- Delivered with a sealed interface, using a dual limb circuit and often, a bubble generator
- Mainstay of respiratory support in the NICU
- Better alternative to routine intubation\(^1\)
- With early rescue surfactant administration if required\(^2\)
- Extensive evidence base to guide practice\(^3\) - 7

3. Finer et al. NEJM. 2010 (SUPPORT)
4. Morley et al. NEJM. 2008 (COIN)
7. Sandri et al. Neonatology. 2008 (CURPAP)
Physiological effects:
- maintains lung expansion
- reduces end-expiratory alveolar collapse
- maintains functional residual capacity
- decreases work of breathing
- conserves surfactant
- improves gas exchange
Disadvantages of CPAP

- Bulky interface
- Labour intensive and requires highly skilled nurses to manage the baby and equipment
- Air leak syndrome
- Nasal trauma

Figure. Classification of nasal injury as described by Fischer et al. (A) stage I – persistent redness, (B) stage II – bleeding, superficial ulcers or erosions, (C) stage III – deep tissue injury.
Nasal High Flow – the “new kid on the block”

- Delivered with an unsealed interface, using a single limb circuit
- Increasing prevalence:
  - According to the 2017 ANZNN report, 33.0% of all level III registrants received NHF compared to 8.1% in 2009
  - Increasing evidence base guiding practice
  - Ease of use and parental preference over CPAP frequently cited

1. ANZNN Report 2017
3. Roberts et al. NEJM 2016
5. Manley et al. NEJM. 2019
NHF mechanisms of action

Physiological effects:
- decreases work of breathing
- Increases end expiratory lung volume
- improves oxygenation
- improves mucosal integrity and mucociliary clearance
Why does interface choice matter?
Characteristics of a flow vs pressure interface

Pressure interface
- Sealed interface
- Prescribe pressure
- Larger tubes lower resistance to flow

Flow interface
- Unsealed interface
- Prescribe flow
- Narrower tubes increase resistance to flow
CPAP – Pressure Based Therapy Considerations

- Pressure based therapy
  - Set and control the pressure

- Surfactant deficient babies may require more pressure
  - Helps maintain FRC

- Needs to be sealed
  - Any leak will result in a drop in pressure

- Dead space needs to minimised

- Tube diameters influence WOB
  - Small Diameters increase both inspiratory and expiratory WOB
Why does interface choice matter?

Non sealing / small bore interface
- Poor design for delivering CPAP/ NIPPV
  - Small bore tubing with high resistance to flow \(^1\)
  - CPAP / NIPPV pressures are significantly lower than intended \(^2, 3\)
  - Pressures transmitted are similar to Nasal High Flow
- Unknown / variable flow delivery
- High instrumental dead space

Sealing / wide bore interface
- Accurate delivery of pressure waveform
- Low resistance to flow
- Low instrumental dead space
- More challenging to manage the seal and avoid nasal trauma

\(^1\) Green et al. Arch Dis Child Fetal Neonatal Ed. 2019
\(^2\) Gerdes et al. Pediatric Pulmonology. 2015.
\(^3\) Mukerji and Belik.. J Perinatol. 2015
Benchtop airway models and simulation

- 3D Printing from Skull library
- Airway replica from CT scans
- Pressure sensors measuring at different parts of the airway
- Lung simulator
Pressure delivery during simulated breathing
Some patients respond to “CPAP” through non sealed cannula?

- If there is a leak at the interface, what is the pressure in the patient?
  - If you set 10 cmH₂O at the ventilator, maybe 2-3 cmH₂O at the patient
  - This will depend on nostril occlusion and interface size
  - Non-sealed interfaces deliver a low level of positive airway pressure

- If there is an intentional leak at the interface, there must be a positive flow to the patient
  - What is the flowrate?
  - Depending on leak and interface size, the net flow could be 6-8lpm
  - Non-sealed interfaces deliver a net positive flow to the patient
What are the clinical implications?

• Are some infants being intubated when non-sealed CPAP or NIPPV is failing?
  − If those babies had received higher pressures, or accurate waveforms, could they have avoided escalation?
  − If units think non-sealed interfaces deliver true CPAP / NIPPV, are they intubating patients who could have been managed with a sealed interface?
  − Are we seeing higher BPD rates in these units?
Randomized controlled trial comparing RAM cannula with short binasal prong CPAP (SBP)
- 126 premature infants with RDS, randomised soon after birth
- within 72 hours, RAM cannula group showed a significantly higher need for invasive ventilation and surfactant:
  - Intubation: 32.8% (RAM) vs 9.6% (SBP), \( p = 0.002 \)
  - Surfactant: 42.2% (RAM) vs 19.3% (SBP), \( p = 0.007 \)
Why shouldn’t I just seal my “non sealing” cannula?

- High device deadspace
  - The fresh gas is back at the y-piece

- Work of breathing
  - The long narrow tubes increase expiratory effort (like breathing through a straw)

- Skin breakdown
  - No opportunity to rest the skin
CPAP and NHF in the NICU

An evidence based approach
Evidence based guidance: CPAP and NHF in neonates

Pathways of care

- **POST-EXTUBATION SUPPORT**
  - < 28 weeks GA: CPAP
  - ≥ 28 weeks GA: NHF + Rescue CPAP

- **PROLONGED CPAP**
  - < 28 weeks GA: CPAP
  - ≥ 28 weeks GA: CPAP, then NHF once stable at the clinician’s discretion

- **PRIMARY TREATMENT**
  - < 28 weeks GA: CPAP
  - ≥ 28 weeks GA: CPAP or NHF + Rescue CPAP

This information collates data from published literature. It does not overrule expert clinical judgement and gestational age alone should not determine individual patient management.

Evidence based guidance: CPAP and NHF in neonates

STABILIZATION AT BIRTH

POST-EXTUBATION SUPPORT

< 28 weeks GA: CPAP

≥ 28 weeks GA: NHF + Rescue CPAP

Evidence: STRONG SUPPORT e.g. Cochrane Review

PROLONGED CPAP

< 28 weeks GA: CPAP

≥ 28 weeks GA: CPAP, then NHF once stable at the clinician’s discretion

Evidence: STRONG SUPPORT e.g. consensus of published expert opinion

PRIMARY TREATMENT

< 28 weeks GA: CPAP

≥ 28 weeks GA: CPAP or NHF + Rescue CPAP

Evidence: GENERAL SUPPORT e.g. emerging RCT data and consensus of published expert opinion

This information collates data from published literature. It does not overrule expert clinical judgement and gestational age alone should not determine individual patient management.

RCTs comparing CPAP & NHF in the preterm population

24 Publications

46% Randomized controlled trials (11)
8% In vitro studies (2)
21% Observational studies (5)
8% General reviews (2)
4% Systematic reviews (1)
4% Clinical reports (1)
8% Physiological studies (2)

7 Studies assessed safety
2 Studies assessed comfort
14 Studies used FPH products
11 Randomized controlled trials

Total population (n=1505)
- 5 post-extubation support RCTs
- 5 primary support RCTs
- 1 post-extubation and primary support RCTs

5 Registered ongoing RCTs comparing NHF & CPAP

CPAP & NHF delivery

There is an increasing body of evidence comparing the efficacy of CPAP & NHF for different applications in the preterm population. All RCTs have used nasal cannula to deliver NHF, however a range of CPAP generators were used:

<table>
<thead>
<tr>
<th>CPAP &amp; NHF delivery</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable flow</td>
<td>7</td>
</tr>
<tr>
<td>Ventilator driven</td>
<td>5</td>
</tr>
<tr>
<td>Bubble CPAP</td>
<td>5</td>
</tr>
<tr>
<td>Did not specify</td>
<td>3</td>
</tr>
</tbody>
</table>

Data compiled from PubMed search conducted in March 2019.
### CPAP & NHF for post-extubation support

#### High flow nasal cannula for respiratory support in preterm infants.

**Wilkinson et al. 2016. Cochrane Reviews**

Wilkinson et al. analyzed the efficacy and safety of NHF therapy in premature newborn infants. A subset of six post-extubation RCTs were investigated:

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Number</th>
<th>Center</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manley et al. 2013</td>
<td>N Engl J Med.</td>
<td>&gt; 303</td>
<td>Single center in Australia</td>
<td>Treatment failure within 7 days</td>
</tr>
<tr>
<td>Campbell et al. 2006</td>
<td>J Perinatol.</td>
<td>&gt; 40</td>
<td>Single center in USA</td>
<td>Need for intubation</td>
</tr>
<tr>
<td>Collins et al. 2013</td>
<td>J Pediatr.</td>
<td>&gt; 132</td>
<td>Single center in Australia</td>
<td>Treatment failure within 7 days</td>
</tr>
<tr>
<td>Mostafa - Gharehbagi et al. 2015</td>
<td>Zahedan J Res Med Sci.</td>
<td>&gt; 85</td>
<td>Single center in Iran</td>
<td>Treatment failure within 3 days</td>
</tr>
<tr>
<td>Liu et al. 2016</td>
<td>Chinese J Pediatr.</td>
<td>&gt; 256</td>
<td>Single center in China</td>
<td>Treatment failure within 7 days</td>
</tr>
<tr>
<td>Yoder et al. 2013</td>
<td>Pediatrics.</td>
<td>&gt; 432</td>
<td>Centers: 4 in USA, 1 in China</td>
<td>Need for intubation within 72 hours</td>
</tr>
</tbody>
</table>
### Results

**Meta-analysis of post-extubation data shows that compared to CPAP, infants on NHF experienced:**

<table>
<thead>
<tr>
<th>No difference in rate of treatment failure</th>
<th>No difference in rate of reintubation</th>
<th>No difference in rates of other adverse outcomes i.e. death, pneumothorax, BPD</th>
<th>Significant reduction in rates of nasal trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; Typical relative risk: 1.21, 95% CI 0.95 to 1.55</td>
<td>&gt; Typical relative risk: 0.91, 95% CI 0.68 to 1.20</td>
<td>&gt; Typical relative risk: 0.64, 95% CI 0.51 to 0.79</td>
<td>&gt; Typical risk difference: -0.14, 95% CI -0.20 to -0.08</td>
</tr>
<tr>
<td>&gt; Data from 5 studies, 786 infants</td>
<td>&gt; Data from 6 studies, 934 infants</td>
<td></td>
<td>&gt; Data from 4 studies, 645 infants</td>
</tr>
</tbody>
</table>

Flow and pressure settings, an overview of RCTs

Setting Flow

Recent guidance from leading experts suggests that NHF should be initiated between 4-6 L/min. Neonatal RCTs demonstrate starting flow rates within a similar range:

0 1 2 3 4 5 6 7 8 9

POST-EXTUBATION RCTs

Collins et al. 2013 <32 weeks GA
Manley et al. 2013 Premature and neonatal cannula
Infant cannula
Yoder et al. 2013 <2kg
2-3 kg
>3kg

PRIMARY TREATMENT RCTs

Roberts et al. 2017 ≥28 weeks
Lavizzari et al. 2016 ≥29 weeks

Setting Pressure

Neonatal RCTs comparing NHF to CPAP have initiated CPAP levels between 5-7 cm H₂O.

0 1 2 3 4 5 6 7 8 9

Starting Minimum Maximum

Clinical evidence for NHF for **primary treatment**

**Roberts et al. 2016**
- 564 infants
- 4 centers in Australia, 5 centers in Norway
- Primary outcome: Treatment failure within 72 hours

**Lavizzari et al. 2016**
- 316 infants
- Single center in Italy
- Primary outcome: Intubation and mechanical ventilation within 72 hours

**Manley et al. 2019**
- 754 infants
- Multicentre study in Australian special care nurseries
- Primary outcome: Treatment failure within 72 hours

**Yoder et al. 2013**
- 432 infants (125 enrolled in primary treatment arm)
- 4 centers in USA, 1 center in China
- Primary outcome: Need for intubation within 72 hours

**Shin et al. 2017**
- 85 infants
- Single center in Korea
- Primary outcome: Treatment failure

**Murki et al. 2018**
- 272 infants
- Multi center in India
- Primary outcome: Treatment failure within 72 hours

Nasal high-flow therapy for primary respiratory support in preterm infants (HIPSTER)

**STUDY**

This study compared the efficacy of NHF and CPAP therapies as primary respiratory support for preterm infants with respiratory distress.

**METHOD**

Randomized controlled trial
- 4 centers in Australia and 5 centers in Norway
- 564 infants ≥ 28 weeks GA, < 24 hours old, with early respiratory distress
- Non-inferiority trial design with a margin of 10%

**NHF**
- Starting flow of 6-8 L/min

**nCPAP**
- Starting pressure 6-8 cmH₂O

**Primary outcome**
- Treatment failure within 72 hours

**KEY POINTS**

- First RCT to investigate NHF for primary treatment in infants.
- Primary outcome: Treatment failure within 72 hours
- Secondary outcome: Intubation

RESULTS

NHF
- Therpay Success: 207/278 (74.5%)
  - Failure criteria: 71/278 (25.5%)
  - ‘Rescure’ CPAP: 7-8 cmH₂O
  - Intubation: 43 (15.5%)

CPAP
- Therpay Success: 248/286 (86.7%)
  - Failure criteria: 38/286 (13.3%)
  - 5 did not get intubated
  - Intubation: 33 (11.5%)

PRIMARY OUTCOME:
Treatment failure favored CPAP by a margin >10%, therefore NHF is not non-inferior (P value <0.001).

SECONDARY OUTCOME:
There was no significant difference in the rate of intubation between therapies.
Lavizzari et al. 2016

JAMA Pediatrics

Heated, humified high-flow nasal cannula vs. CPAP for respiratory distress syndrome of prematurity: a randomized clinical noninferiority trial

STUDY

This study compared the efficacy of NHF and CPAP therapies as primary respiratory support for preterm infants with respiratory distress.

METHOD

Randomized controlled trial
- Single center in Italy
- 316 infants ≥ 29 weeks GA,
  Non-inferiority trial design with a margin of 10%

NHF
- Starting flow of 4-6 L/min

nCPAP
- Starting pressure 4-6 cmH₂O

Primary outcome
- Treatment failure requiring intubation and mechanical ventilation within 72 hours

KEY POINTS

- Second RCT investigating NHF for primary treatment in infants.
- Primary outcome: Intubation within 72 hours
- Secondary outcome: Intubation

RESULTS

NHF (n=158)
- 153 received allocated intervention
- 5 did not receive allocation
- 3 no study devices available
- 2 received CPAP after randomization
- 2 switched to CPAP by clinicians
- Intubation criteria
- Intubated 17/158 (10.8%)

CPAP (n=158)
- 158 received allocated intervention
- 2 switched to NHF by clinicians
- Intubation criteria
- Intubated 15/158 (9.5%)

There were no significant differences in the secondary outcomes, i.e.
- Duration of mechanical ventilation
- Days of respiratory support
- Days of oxygen supplementation
- Surfactant treatment

PRIMARY OUTCOME:
Intubation rate was within the margin of non-inferiority, therefore NHF is non-inferior to CPAP (P value =0.71)
Differences in study design between Roberts et al. vs. Lavizzari et al.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Surfactant use</strong></td>
<td>NHF 14.4% CPAP 10.5%</td>
<td>NHF 44.3% CPAP 46.2%</td>
</tr>
<tr>
<td></td>
<td>Low usage/threshold not specified</td>
<td>High usage /low threshold</td>
</tr>
<tr>
<td></td>
<td>Infants intubated for surfactant were</td>
<td>Infants who received INSURE* were not</td>
</tr>
<tr>
<td></td>
<td>deemed to have met the primary outcome</td>
<td>considered to have met failure criteria and</td>
</tr>
<tr>
<td></td>
<td>of therapy failure</td>
<td>remained in the study</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Failure of initial therapy</td>
<td>Intubation and mechanical ventilation</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>≥28 weeks GA</td>
<td>≥29 weeks GA</td>
</tr>
</tbody>
</table>

* INtubate SURfactant Extubate
The study compared NHF and CPAP as primary respiratory support for preterm infants in special care nurseries.

**METHODS**

Randomized controlled trial
- 754 preterm neonates, >32 weeks GA, <24 hours old with respiratory distress
- Non-inferiority trial design with margin of 10%

**NHF**
- Starting flow of 6 L/min, max 8 L/min

**Bubble CPAP**
- Starting pressure 6 cm H$_2$O, max 8 cm H$_2$O

**Primary outcome**
- Treatment failure within 72 hours

**Secondary outcomes**
- Intubation, NICU admission, duration of respiratory support, supplemental oxygen and hospitalization

**KEY POINTS**
- RCT to investigate NHF as primary treatment in neonates >32 weeks
- Primary outcome: treatment failure within 72 hours
- Secondary outcome: intubation
Results

**THERAPY SUCCESS**

<table>
<thead>
<tr>
<th>NHF (n=381)</th>
<th>CPAP (n=373)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy failure</td>
<td>Therapy failure</td>
</tr>
<tr>
<td>78/381 (20.5%)</td>
<td>38/373 (10.2%)</td>
</tr>
<tr>
<td>‘Rescue’ CPAP</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>Intubation</td>
</tr>
<tr>
<td>21 (5.5%)</td>
<td>22 (5.9%)</td>
</tr>
</tbody>
</table>

**PRIMARY OUTCOME:**
Initial therapy failure was higher with NHF compared to CPAP (margin >10%), therefore NHF is not non-inferior to CPAP

**SECONDARY OUTCOME:**
There was no significant differences in intubation rates and other secondary outcomes between the two groups
Towards a Clinical Practice Guideline
**NHF in practice**

Two recent publications have explored the current practices of >25 leading international NHF researchers. Consensus has been captured on therapy practices for **NHF initiation, escalation, weaning, flow rates, nare occlusion, humidification, contraindications, populations**

### CONSENSUS 1: (Published in 2016)

**Evidence Support and Guidelines for Using Heated, Humidified, High-Flow Nasal Cannulae in Neonatology**  
*Oxford Nasal High-Flow Therapy Meeting, 2015*

<table>
<thead>
<tr>
<th>Country</th>
<th>Authors</th>
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<tbody>
<tr>
<td>USA</td>
<td>Bradley Yoder, Haresh Kirpalani, Soraya Abbasi, Richard Polin, Martin Keszler</td>
</tr>
<tr>
<td>UK</td>
<td>Kevin Ives, Ed Juszczak, Elane Boyle, Eleri Adams, Faith Ernery, Amit Gupta, Charles Roehr, Peter Reynolds</td>
</tr>
<tr>
<td>Italy</td>
<td>Anna Lavizzari, Paolo Tagliabue, Gianluca Lista</td>
</tr>
<tr>
<td>Germany</td>
<td>Roland Wauer, Roland Hentschel</td>
</tr>
<tr>
<td>Israel</td>
<td>Amir Kugelman</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Michelle Muir (FPH)</td>
</tr>
<tr>
<td>Australia</td>
<td>Andreas Schibler, Peter Davis</td>
</tr>
<tr>
<td>Norway</td>
<td>Claus Klingenberg</td>
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</tbody>
</table>

### CONSENSUS 2: (Published in 2017)

**Original Article**  

Consensus approach to nasal high-flow therapy in neonates

<table>
<thead>
<tr>
<th>Country</th>
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<tbody>
<tr>
<td>USA</td>
<td>Bradley Yoder, Michael McQueen</td>
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<td>Israel</td>
<td>Amir Kugelman</td>
</tr>
<tr>
<td>Australia</td>
<td>Brett Manley, Clare Collins</td>
</tr>
</tbody>
</table>
• NHF is effective for post-extubation support for most neonates ≥28 weeks GA
• NHF is an effective alternative to prolonged CPAP
• Limited evidence for primary treatment but can be considered depending on GA and $O_2$ requirements

Heat & humidify
34-37 °C
100% RH

Initial gas flow of
4-6 L/min

Clear gap around the nares

Further studies

Well-designed, randomized studies are needed in many other areas to optimize the safe and effective use of neonatal NHF therapy.

- Safety and efficacy of NHF in extremely preterm infants, infants with other neonatal lung disorders
- Effects of different initial flow rates
- Effects of different weaning protocols
- Cost-benefit analyses compared to other NIV modes
- NHF in the delivery room and during transport
- NHF in resource-limited countries
- NHF in the home
- Approaches to oral feeding on NHF therapy

Our key message today

• Be aware of the importance of interface choice on therapy delivery
  – Be clear about what therapy you are intending to deliver – pressure or flow?

• Understand that non-sealed “CPAP” is not delivering the pressure and is really just a form of NHF.

• Consider using true sealed CPAP and NHF as part of evidence based strategies of care
  1. Focus on doing CPAP well and becoming expert in it’s delivery
  2. Introduce NHF (4-6 L/min) in line with the evidence, to reduce nasal trauma and help with ease of use concerns