Neonatus 2016 - What is next mode of respiratory support after stabilization?

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Neonatus 2016 - What is next mode of resp. support after stabilization?

SUPPORTING BREATHING AFTER BIRTH
Origins of respir. distress of prematurity

The preterm infant has

- Asynchronous breathing
- Highly compliant thorax wall
- Collapsible airways
- Surfactant deficiency/atelectasis

Intrinsic coping mechanism

- Increase in respiratory rate
- Increased tone of diaphragm
- Prem. termination of expiration
- Active closure of glottis
CHOOSING THE RIGHT KIND OF RESPIRATORY SUPPORT
Unit No. 3: avoided mech. ventilation, used nasal CPAP had lowest BPD rates!

NORTH AMERICAN TERTIARY CENTRE
COMPARISON OF PRETERMS
RESPIRATORY OUTCOMES

Avery M et al. Pediatrics 1987
CPAP or MV at birth: CPAP = less death and/or BPD at 36/40 weeks cGA - NNT: 25\textsuperscript{a} to 35\textsuperscript{b}!

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Avoid ventilation</th>
<th>Control group</th>
<th>Weight</th>
<th>Odds Ratio [95% CI]</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BPD/death</td>
<td>Total</td>
<td>BPD/death</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>COIN (2008)</td>
<td>108</td>
<td>307</td>
<td>122</td>
<td>303</td>
<td>19.8% [0.58, 1.12]</td>
</tr>
<tr>
<td>CNRN (2009)</td>
<td>53</td>
<td>74</td>
<td>54</td>
<td>72</td>
<td>4.0% [0.40, 1.75]</td>
</tr>
<tr>
<td>SUPPORT (2010)</td>
<td>323</td>
<td>663</td>
<td>353</td>
<td>653</td>
<td>45.5% [0.65, 1.00]</td>
</tr>
<tr>
<td>CURPAP (2010)</td>
<td>22</td>
<td>103</td>
<td>23</td>
<td>105</td>
<td>4.9% [0.50, 1.87]</td>
</tr>
<tr>
<td>DRM (2011)</td>
<td>68</td>
<td>223</td>
<td>138</td>
<td>425</td>
<td>17.4% [0.64, 1.29]</td>
</tr>
<tr>
<td>AMV (2011)</td>
<td>15</td>
<td>108</td>
<td>17</td>
<td>112</td>
<td>3.8% [0.43, 1.91]</td>
</tr>
<tr>
<td>Take Care (2013)</td>
<td>25</td>
<td>74</td>
<td>30</td>
<td>67</td>
<td>4.6% [0.32, 1.24]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>614</td>
<td>1552</td>
<td>737</td>
<td>1737</td>
<td>100% [0.71, 0.96]</td>
</tr>
</tbody>
</table>

Test for overall effect: $Z = 2.55$ (p = 0.01)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.27$; df = 6 (p = 0.97); $I^2 = 0\%$

- Favoring avoiding ventilation
- Favoring control group

\textsuperscript{a} Schmölzer GM et al. BMJ 2013; 347: f5980
\textsuperscript{b} Fischer HS et al. Ped. 2013; 132: e1351-60
Respiratory Support in Preterm Infants at Birth

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CPAP for STABILIZING BABIES AT BIRTH = STANDARD of CARE

CPAP IS GREAT - WHY WORRY?

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Doing CPAP well isn’t all that easy!

Prospective study with decubitus score staging
Swiss NICU with wide experience in CPAP use

CPAP-related Nasal Trauma
occurs in > 40% of VLBWI Neonates

High-flow nasal cannula an alternative to CPAP?
High-Flow Nasal Cannula Therapy – HFNC or nasal HFT

Application of high gas flows of heated & humidified medical air or an air oxygen mix via nasal prongs.

What are high flow rates?

• > 1 L/min according to Cochrane Review

  • Clinical trials: used much higher flows (2-8 L/min)

Respiratory mechanics during NCPAP and HHHFNC at equal distending pressures

Lavizzari A et al. ADC F&N 2014
doi:10.1136/archdischild-2013-305855
Surge in nHFT use in tertiary Australasian (AU & NZ) NICUs

Surge in use of nHFT in tertiary NICUs world wide

- UK: 56% to **87%** between 2012 - 2015
  

- Germany: **93%**
  
  (Hepping, Z Geburtshilfe Neonatol. 2015)

- Japan: **58%**
  
  (Motojima, Pediatr Int. 2016)

- Australia and New Zealand: 15% to **58%** within 3 years
  
  (Roberts C, ADC F&N 2016)
Surge in use of nHFT in NICUs worldwide:

- Germany: 93% (Hepping, Z Geburtshilfe Neonatol. 2015)
- Japan: 58% (Motojima, Pediatr Int. 2016)
- Australia and New Zealand: 15% to 58% within 3 years (Roberts C, ADC F&N 2016)

Nasal high flow: going viral?

"Like sneezing and Susan Boyle", ice bucket challenge...
HOW GOOD IS THE EVIDENCE FOR THE USE OF nHFT IN NEONATES?
Meta-Analysis: HFNC vs CPAP (Mostly relating to post-extubation support)

Figure 1. Forest plot of comparison: 1 HFNC versus CPAP soon after birth for treatment or prophylaxis of RDS, outcome: Treatment failure within 7 days of trial entry.

Figure 2. Forest plot of comparison: 3 HFNC versus CPAP to prevent extubation failure, outcome: 3.3 Death.

Figure 3. Forest plot of comparison: 3 HFNC versus CPAP to prevent extubation failure, outcome: 3.2 C^-

Figure 4. Forest plot of comparison: 3 High Flow Nasal Cannula versus CPAP to prevent extubation failure, outcome: Treatment failure.


**Figure 6.** Forest plot of comparison: 3 HFNC versus CPAP to prevent extubation failure, outcome: Nasal trauma.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HFNC Events</th>
<th>Total</th>
<th>CPAP Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell 2006</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Yoder 2013</td>
<td>4</td>
<td>102</td>
<td>15</td>
<td>115</td>
<td>11.5%</td>
<td>0.30 [0.10, 0.88]</td>
</tr>
<tr>
<td>Mostafa-Gharebaghi 2014</td>
<td>14</td>
<td>42</td>
<td>27</td>
<td>43</td>
<td>21.7%</td>
<td>0.53 [0.33, 0.86]</td>
</tr>
<tr>
<td>Manley 2013</td>
<td>60</td>
<td>152</td>
<td>82</td>
<td>151</td>
<td>66.9%</td>
<td>0.73 [0.57, 0.93]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>316</td>
<td></td>
<td>329</td>
<td></td>
<td>100.0%</td>
<td>0.64 [0.51, 0.79]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>78</td>
<td></td>
<td>124</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.56, df = 2 (P = 0.17); I² = 44%
Test for overall effect: Z = 4.09 (P < 0.0001)

**Figure 7.** Forest plot of comparison: 3 HFNC versus CPAP to prevent extubation failure, outcome: Pneumothorax.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HFNC Events</th>
<th>Total</th>
<th>CPAP Events</th>
<th>Total</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins 2013</td>
<td>0</td>
<td>67</td>
<td>1</td>
<td>65</td>
<td>12.9%</td>
</tr>
<tr>
<td>Liu 2014</td>
<td>1</td>
<td>71</td>
<td>2</td>
<td>79</td>
<td>16.0%</td>
</tr>
<tr>
<td>Manley 2013</td>
<td>1</td>
<td>152</td>
<td>4</td>
<td>151</td>
<td>34.0%</td>
</tr>
<tr>
<td>Mostafa-Gharebaghi 2014</td>
<td>1</td>
<td>42</td>
<td>3</td>
<td>43</td>
<td>25.1%</td>
</tr>
<tr>
<td>Yoder 2013</td>
<td>0</td>
<td>107</td>
<td>1</td>
<td>119</td>
<td>12.0%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>439</td>
<td></td>
<td>457</td>
<td></td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>3</td>
<td></td>
<td>11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.25, df = 4 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.86 (P = 0.06)

Mostly relating to post-extubation support

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nHFT FROM BIRTH – FIRST AND CONFLICTING STUDIES
nHFT for stabilization of premature infants in delivery room

Design

single centre feasibility study of nHFT for initial respiratory support of babies born at < 30 weeks

Methods: Pilot observational trial

n = 28 preterm infants

HFNC (Vapotherm®) gas flow 6-7 L/min, FiO₂ <0.4

rescue: as per NLS algorithm

Primary outcomes

Successful transfer and clinical stability

Results

• Successful transition 24/28 patients

• Transition failure:
  – 24/28 (85%) infants with GA > 26+0/40 successfully transitioned on HFNC

• No difference reg. pulmonary and extra-pulmonary outcomes from standard of care

Reynolds P et al. ADC F&N 2016; 101: F284-7
nHFT as primary support for mild to moderate RDS

**Design**

*single centre RCT* of HFNC vs CPAP or BiPAP as initial support in *mild/moderate* RDS

**Methods:** Non-inferiority trial

n = 316 babies 29+0 - 36+6/40

RDS severity score & FiO₂ >0.3: HFNC (Vapotherm®) gas flow 4-6 L/min,

or nCPAP od BiPAP 4-6 cmH₂O

**Primary outcome**

Need for MV within 72hrs after birth

**Results**

- MV within 72 hrs of birth:
  - 17/158 (10.8%) HFNC
  - 39/151 (9.5%) nCPAP n.s.
  - statistically n.s. (95% CI 8.4 (-6.0 – 8.6)

- Non-pulmonary outcomes:
  No statistically sig. difference

**Conclusion**

- HFNC efficacy and safety - similar to CPAP/BiPAP

Lavizzari A et al. JAMA Pediatrics, online 08.08.2016
HIPSTER Trial: nHFT as primary support for preterm infants with RDS

**Design**

- **multicentre RCT** of HFNC vs CPAP as initial support with pre-surfactant, pre-CPAP RDS

**Methods:** Non-inferiority trial

- n = 700 (intention to treat) babies
- ≥28+0 – 36+0 weeks

with RDS, no previous surfactant and no CPAP > 4hrs

- HFNC (Optiflow Junior®) gas flow 6-8 L/min,
- or nCPAP 7-8 cmH₂O

**Primary outcome**

- Intubation, FiO₂ 0.4 or higher, resp.
- Acidosis, hypercarbia
- Inferiority margin 10%

**Results**

- **Recruitment stopped** at n = 564!
- Higher treatment failure in nHFT group (25.5% vs 13.3%), but:
  - No sig. diff. intubation rates
  - No sig. diff. in oxygen need (nHFT 74.6% vs CPAP 78.9%)
- Non-pulmonary outcomes:
  - No statistically sig. difference

**Conclusion**

- **nHFT inferior** to nCPAP when used as primary support
NON-INVASIVE POSITIVE PRESSURE VENTILATION (NIPPV)

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Large RCT (n= 1009 ELBW) investigating primary unsynchronised NIPPV: no sig. benefit over nCPAP!

A Trial Comparing Noninvasive Ventilation Strategies in Preterm Infants


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nasal IPPV</th>
<th>Nasal CPAP</th>
<th>Odds Ratio</th>
<th>Odds Ratio Adjusted for Strata (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: death at &lt;36 wk of post-menstrual age or BPD</td>
<td>191/497 (38.4)</td>
<td>180/490 (36.7)</td>
<td>1.07</td>
<td>1.09 (0.83–1.43)‡</td>
<td>0.56</td>
</tr>
<tr>
<td>Components of primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death at &lt;36 wk of postmenstrual age</td>
<td>34/504 (6.7)</td>
<td>41/503 (8.2)</td>
<td>0.82</td>
<td>0.81 (0.51–1.31)§</td>
<td>0.39</td>
</tr>
<tr>
<td>Survival with BPD</td>
<td>157/463 (33.9)</td>
<td>139/449 (31.0)</td>
<td>1.14</td>
<td>1.17 (0.86–1.57)‡</td>
<td>0.32</td>
</tr>
<tr>
<td>Death at &lt;36 wk of postmenstrual age or BPD according to older NIH criteria in 20 infants</td>
<td>197/504 (39.1)</td>
<td>193/503 (38.4)</td>
<td>1.03</td>
<td>1.03 (0.79–1.35)‡</td>
<td>0.82</td>
</tr>
</tbody>
</table>
NASAL HIGH-FREQUENCY OSCILLATORY VENTILATION
Nasal, non-invasive HFOV

• Definition: “supra-glottic application of HFO”, sometimes called “super-CPAP”*
• Single- and binasal prongs
• Studies:
  – Hoehn T. et al. 2000: Case Report
  – Colaizy T. et al. 2008: Case Series
  – Czernik C. et al. 2011: retrospective cohort study
  – Mukerji A. et al. 2013: promising in vitro study CO₂ elimination

* Czernik C at al. 2011
Nasal, non-invasive HFOV

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TRIAL AWAITED: Nasal CPAP or Nasal High Frequency for RDS in Premature Neonates: Randomized Controlled Multicentre Trial. Pers. communication Prof. P. Rimensberger, Geneva

* Czernik C at al. 2011

CO₂ elimination
WHAT ABOUT INTUBATION AND SURFACTANT?
Surfactant application: INSURE vs. via small endotracheal catheters?

Meta-Analysis (1837 citations) on min. inv. Surfactant techniques - Conclusion:

The use of endotracheal catheters may provide comparable results to the InSurE method!

Surfactant application: INSURE vs. via small endotracheal catheters?

The use of endotracheal catheters may provide comparable results to the INSURE method!

Conclusion: The use of endotracheal catheters may provide comparable results to the INSURE method.

If you need to ventilate, use Volume Guarantee (VG) modes to prevent alveolar over distension.

CHOOSING THE RIGHT KIND OF RESPIRATORY SUPPORT

Neonatus 2016 - What is next mode of resp. support after stabilization?
## Choice of Respiratory Support should match the Pathophysiology of Neonatal Lung Disease

<table>
<thead>
<tr>
<th>Birth, early days of life</th>
<th>Extubation, de-escalation of resp. support</th>
<th>Continuation of respiratory support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase of alveolar/FRC recruitment</td>
<td>Risk of acute alveolar collapse</td>
<td>Immature respiratory drive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impaired respiratory muscle function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper airway obstruction/ collapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low pulmonary compliance/ CLD</td>
</tr>
</tbody>
</table>

### CPAP
- COIN Trial
- SUPPORT
- VON Trial, etc.

*nHFT*
Mounting evidence for its use: Lavizzari, Reynolds VS Roberts

**GA >28/40 nHFT non-Inferior to CPAP**
- B. Manley’s Trial
- C. Collin’s Trial
- B. Yoder’s Trial


### HFNC, as easy handling, low side effects and is the parental & nursing satisfaction
- C. Klingenberg et al. 2014
- C. Roberts et al. 2014
- Clinical trials by Yoder, Collins and Manley
Conclusions

• CPAP currently remains the gold standard for all breathing infants at birth, of all gestational ages

• Consider short mech. vent. (VG-Mode) following minimal invasive surfactant application

• Recent studies and meta-analyses show sufficient evidence for nHFT post extubation and CPAP

• Promising results reg. use of nHFT as primary treatment for RDS, possible for mild to moderate RDS

• Caution for using nHFT:
  • as primary treatment for severe RDS
  • in extremely low gestational age infants (<27/40)

Roehr Poznan, 2016
Dziekuje!