

Respiratory support in preterm infants:

A review of the evidence comparing Nasal High Flow and CPAP

1. Post-extubation respiratory support
2. Primary support of respiratory distress

NHF vs CPAP for noninvasive ventilation in preterm infants

Evidence for post-extubation

- Established evidence base supporting this application in neonates greater than 28 weeks gestational age (GA)
- Comparative trials have found no difference in clinical outcomes between Nasal High Flow (NHF) and Continuous Positive Airway Pressure (CPAP)
 - The use of NHF is associated with less nasal trauma and no differences in adverse outcomes
- Most NHF studies were conducted using flow between 3-8 L/min

Evidence for primary treatment

- Emerging evidence base for this application
- CPAP remains the gold standard for treatment in neonates less than 28 weeks GA
- For more mature preterm infants, NHF with 'rescue' CPAP may be considered
 - The use of NHF is associated with less nasal trauma and no differences in adverse outcomes
- Most NHF studies were conducted using flow between 3-8 L/min

1. NHF vs. CPAP for post-extubation

Summary of RCTs & Cochrane Review

A Randomized Controlled Trial to Compare Heated Humidified High-Flow Nasal Cannulae with Nasal Continuous Positive Airway Pressure Postextubation in Premature Infants

**Setting:**

Single center in Australia
(Melbourne)

**Population:**

132 infants
<32 weeks GA

**Intervention:** NHF

(Vapotherm, starting flow 8 L/min)

Comparator: nCPAP

(Hudson prongs, starting pressure 7-8 cmH₂O)

**Primary outcome:**

Extubation failure within 7 days

Key Points

- This study found no statistically significant difference in the rates of extubation failure between therapies, within 7 days
- NHF resulted in significantly less nasal trauma compared to CPAP

Heated, Humidified High-Flow Nasal Cannula Versus Nasal CPAP for Respiratory Support in Neonates

**Setting:**

Four centers in the USA and one center in China

**Population:**

432 infants
>28 weeks GA

**Intervention:** NHF

(Vapotherm, F&P Healthcare, Comfort Flo
Starting flow 3 – 5 L/min)

Comparator: nCPAP

(Bubble CPAP, Infant Flow, Ventilator
Starting pressure 5 – 6 cmH2O)

**Primary outcome:**

Extubation failure within 72 hours

Key Points

- This study found no statistically significant difference in the rates of extubation failure between therapies, within 72 hours
- NHF resulted in significantly less nasal trauma compared to CPAP

High-Flow Nasal Cannulae in Very Preterm Infants after Extubation (HIPERSPACE – A noninferiority trial)

**Setting:**

Three centers in Australia
(Melbourne, Brisbane and Adelaide)

**Population:**

303 infants
< 32 weeks GA

**Intervention:** NHF

(F&P Healthcare, starting flow 5-6 L/min)

Comparator: nCPAP

(Bubble CPAP, starting pressure 7 cmH2O)

**Primary outcome:**

Treatment failure within 7 days

Key Points

Non-inferiority trials assess if a new treatment has similar efficacy to, or is no worse than, an established therapy. The premise is that the new treatment has some other benefit and might be favored over the standard treatment, even if the efficacy is the same or lower

- Margin of non-inferiority = 20%
- NHF was found to be non-inferior to CPAP in terms of treatment failure within 7 days
- Intubation rate in the NHF group was slightly lower than in the CPAP group (non-significant difference; 17.8% vs. 25.2%, $p=0.12$)
- 'Rescue CPAP' probably avoided intubation for approx. half the babies in whom NHF had failed
- NHF resulted in significantly less nasal trauma compared to CPAP
- Caution for subgroup of infants < 26 weeks GA

High flow nasal cannula for respiratory support in preterm infants (Review)

**Scope:**

Six studies were included in the post-extubation analysis (a total population of 934 infants)

This review includes data on primary treatment and post-extubation. This slide focuses on the post-extubation data only

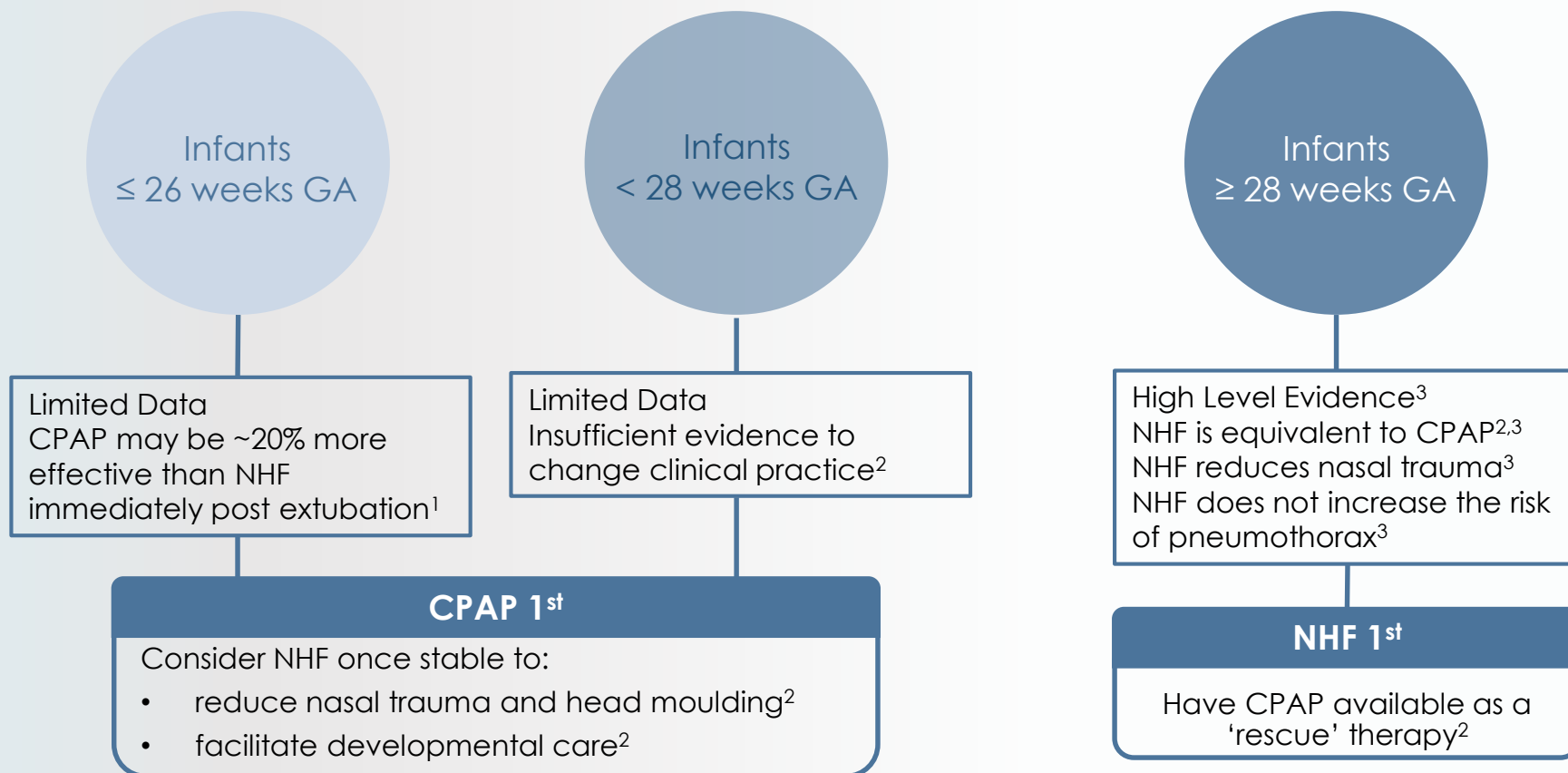


Cochrane Reviews “...are systematic reviews of primary research and are internationally recognized as the highest standard in evidence-based health care. All the existing primary research on a topic that meets certain criteria is searched for and collated, and then assessed using stringent guidelines, to establish whether or not there is conclusive evidence about a specific treatment.” (Cochrane Collaboration, 2016)

Key Points

- In the evidence to date comparing NHF to CPAP therapy, there is:
 - No difference in rates of death or chronic lung disease
 - No difference in rates of treatment failure or reintubation
 - A small reduction in the rate of reintubation in infants 28-32 weeks GA with NHF
 - Note: Relatively few infants < 28 weeks GA included in trials
 - A small reduction in rate of pneumothorax with NHF
 - A significant reduction in nasal trauma with NHF

Post-extubation: NHF or CPAP?



1. Manley, et al. N Engl J Med. 2013.

2. Manley et al. Clin Perinatol. 2016.

3. Wilkinson et al. Cochrane Database Syst Rev. 2016.

Post-extubation: NHF or CPAP?

- High level evidence supports the use of NHF post-extubation in infants ≥ 28 weeks GA^{1,2,3,4,5}
- Expert clinical judgement must always be used to select the appropriate therapy for an individual neonate

GESTATIONAL AGE																	
23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
CPAP						NHF with 'rescue' CPAP available											
<ul style="list-style-type: none"> ○ CPAP remains the gold standard Currently no robust evidence supporting NHF in this population 						<ul style="list-style-type: none"> ○ High level evidence indicates that NHF is equivalent to CPAP^{4,5} ○ Consider NHF immediately post-extubation because of a significant reduction in nasal trauma, with no difference in rates of treatment failure, intubation, death or CLD ○ CPAP can be used as a 'rescue' therapy if needed 											

1. Yoder et al. Pediatrics 2013.

2. Manley et al. N Engl J Med. 2013.

3. Collins et al. J Pediatr. 2013.

4. Manley et al. Clin Perinatol. 2016.

5. Wilkinson et al. Cochrane Database Syst Rev. 2016.

2. Primary support of respiratory distress

Summary of RCTs

Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants (HIPSTER)

**Setting:**

Four centers in Australia and five centers in Norway

**Population:**

564 infants (recruitment stopped early)
>28 weeks GA

**Intervention:** NHF

(F&P Healthcare & Vapotherm, starting flow 6-8 L/min)

Comparator: nCPAP

(Bubble or variable flow, starting pressure 6 -8 cmH2O)

**Primary outcome:** Treatment failure within 72 hours.

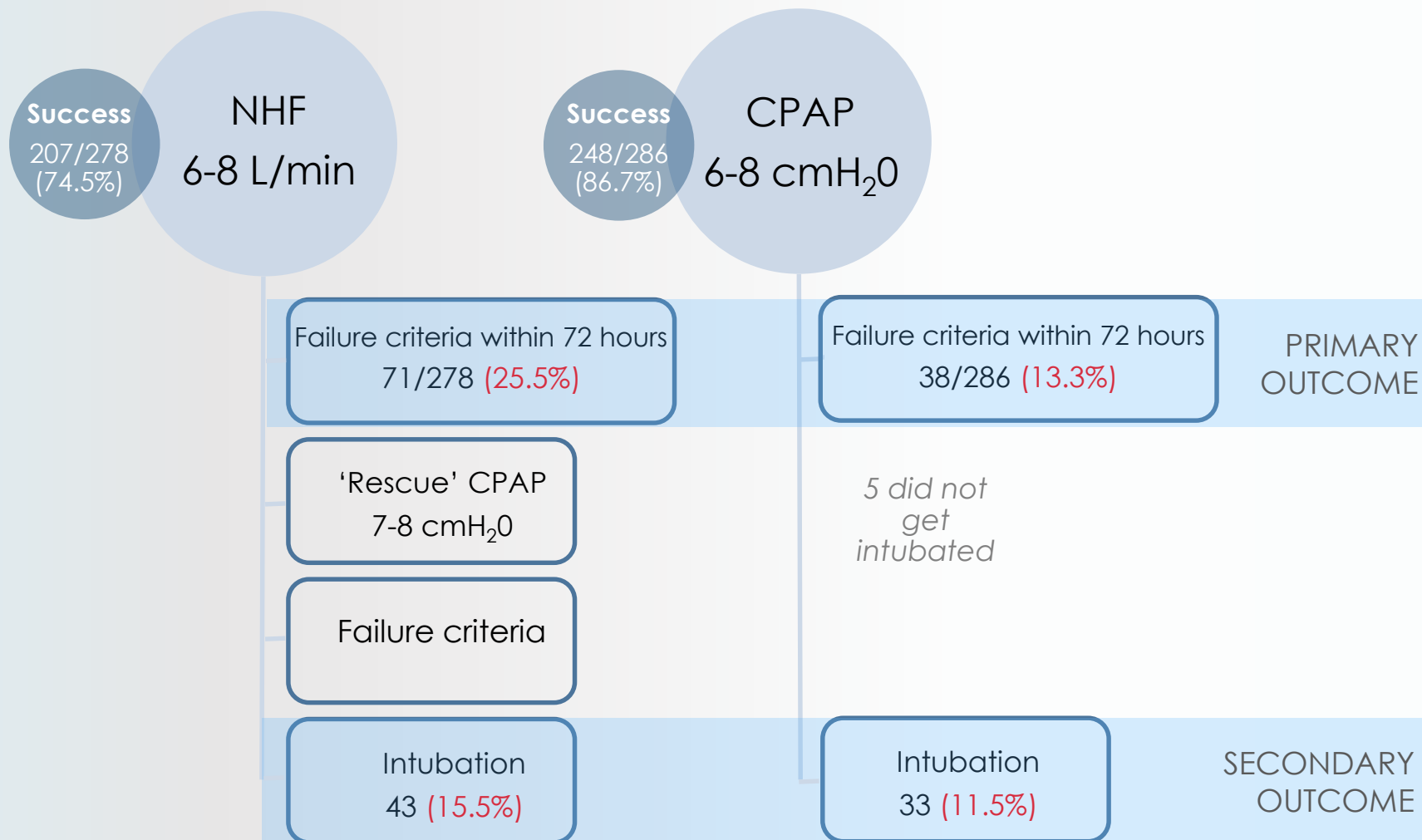
Infants meeting one or more of the following criteria while on maximal support are classified as 'therapy failure':

- **Increased Oxygen Requirement** ($\text{FI}_{\text{O}_2} \geq 0.4$)
- **Respiratory Acidosis** ($\text{pH} \leq 7.2$ with PCO_2 60mm Hg [8.0kPa])
- **Apneas** (≥ 2 within 24 hours requiring PPV, or ≥ 6 within 6 hours requiring intervention)
- **Urgent Intubation** (Clinician decision)

Key Points

- Non-inferiority trial design.
 - Margin of 10%
- First RCT looking at NHF vs. CPAP for primary treatment in infants

Study design and results



Key Points and considerations

Key Points

- The primary outcome (treatment failure) favors CPAP by a margin of >10%, therefore NHF is not non-inferior
- Risk difference: 10%
95% CI, 5.8-18.7, $p < 0.001$
 - There was no significant difference in the rates of intubation between therapies (3.9%, 95% CI, -17-9.6, $p = 0.15$).

To consider

- Using **NHF first** (with 'rescue' CPAP) resulted in:
 - less nasal trauma
 - fewer air leaks during treatment
 - fewer emergency intubations
- Using **CPAP first** resulted in
 - approximately one less day of respiratory support
 - fewer infants needing brief supplemental oxygen
- Approximately 8 out of 10 infants ≥ 32 weeks GA were managed on NHF alone

Heated, Humidified High-Flow Nasal Cannula vs Continuous Positive Airway Pressure for Respiratory Distress Syndrome of Prematurity. A Randomized Clinical Noninferiority Trial

**Setting:**

Single center in Italy (Milan)

**Population:**

316 infants
>29 weeks GA

**Intervention:** NHF

(Vapotherm, starting flow 4 – 6 L/min)

Comparator: nCPAP

(SiPAP (Viasys Healthcare), starting pressure 4 -6 cmH₂O)

**Primary outcome:**

Treatment failure requiring intubation and mechanical ventilation within 72 hours

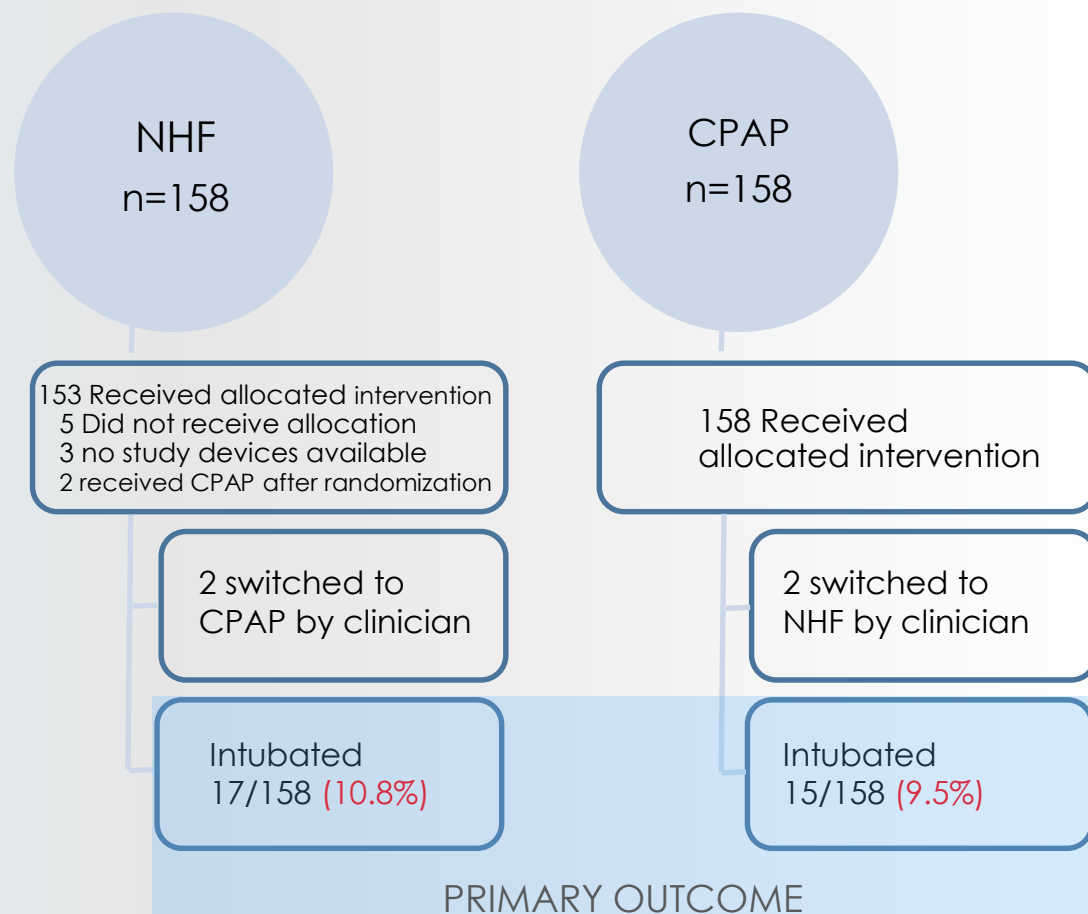
Criteria for intubation and mechanical ventilation assessed within 72 hours:

- **Oxygen Requirement** (persistent FiO₂ of >0.4)
- **Respiratory Acidosis** (persistent PCO₂ >70 mmHg [8.66kPa] with a pH <7.2)
- **Severe Apnea** (>4 per hour or >2 apnea per hour requiring PPV)

Key Points

- Non-inferiority trial design
 - Margin of 10%
- Second RCT looking at NHF vs. CPAP for primary treatment in infants

Study design and results



Primary outcome for this study:

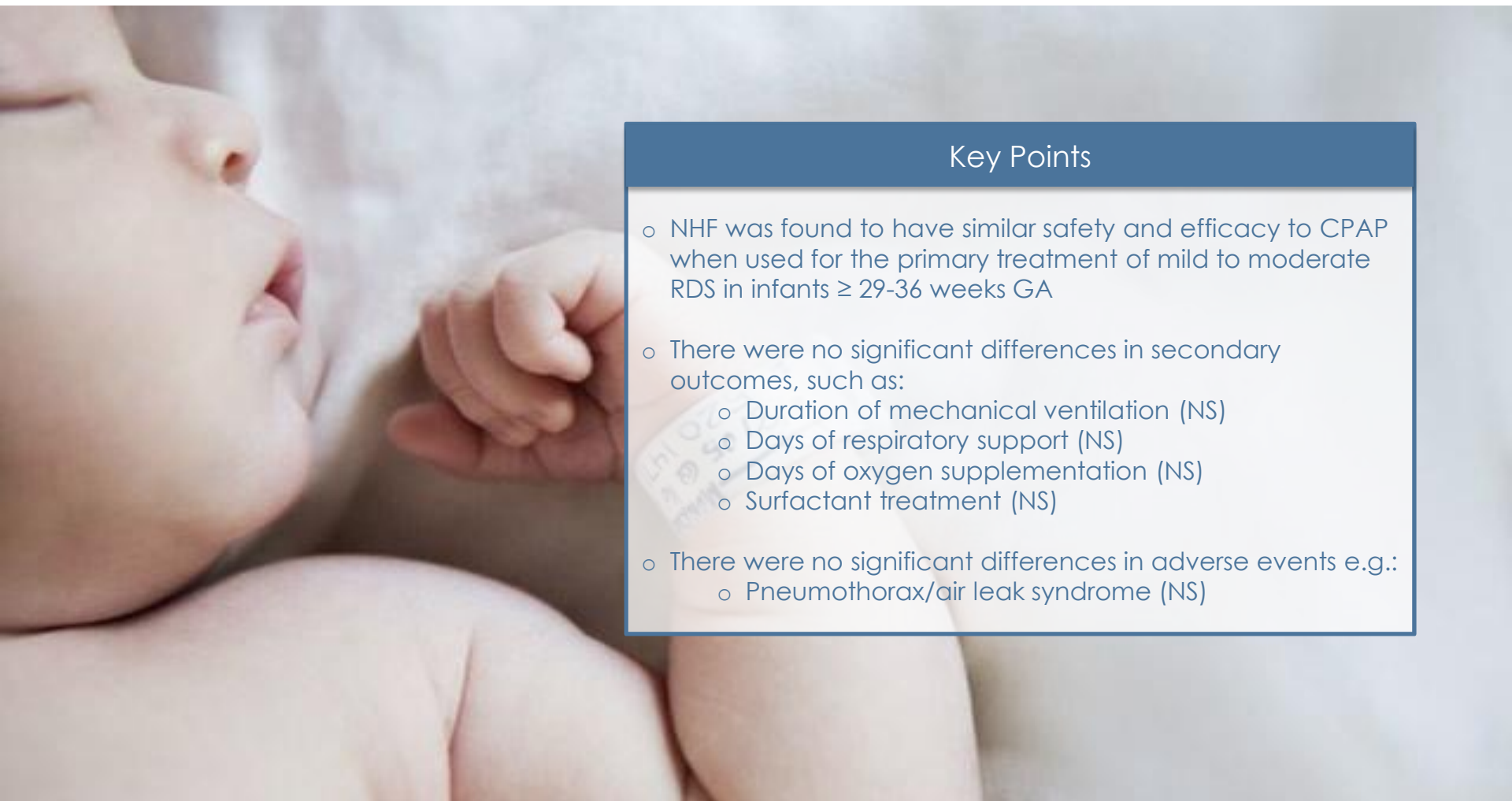
- Intubation and mechanical ventilation within 72 hours

Comparison to Roberts et al.

Key differences:

- Criteria for surfactant use
- Different primary outcome (intubation vs. failure of initial therapy)
- Population (≥ 29 vs ≥ 28 weeks GA)

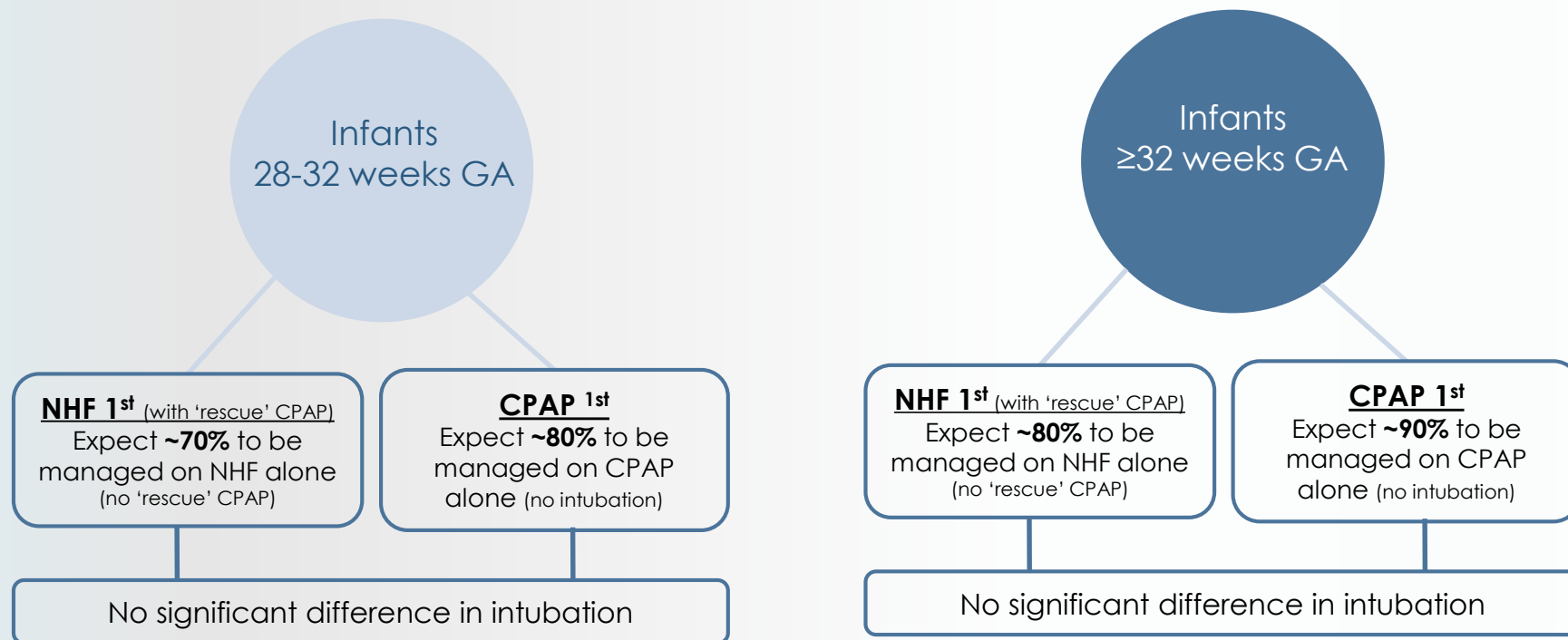
Key Points and conclusions



Key Points

- NHF was found to have similar safety and efficacy to CPAP when used for the primary treatment of mild to moderate RDS in infants ≥ 29 -36 weeks GA
- There were no significant differences in secondary outcomes, such as:
 - Duration of mechanical ventilation (NS)
 - Days of respiratory support (NS)
 - Days of oxygen supplementation (NS)
 - Surfactant treatment (NS)
- There were no significant differences in adverse events e.g.:
 - Pneumothorax/air leak syndrome (NS)

Primary support: NHF or CPAP?



Other considerations if using NHF first:

- Expect a lower rate of nasal trauma, fewer emergency intubations and fewer pneumothoraces while on NHF
- Expect an extra day of respiratory support
- Expect more infants to require brief supplemental oxygen during admission with NHF

Primary support: NHF or CPAP?

- NHF therapy has a higher success rate in more mature preterm infants^{1,2}
- CPAP remains the gold standard for less mature preterm infants
- Expert clinical judgement must always be used to select the appropriate therapy for an individual neonate

GESTATIONAL AGE																	
23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
CPAP 1 st						CPAP 1 st OR NHF 1 st (NHF once stable) (with 'rescue' CPAP available)						NHF 1 st (with 'rescue' CPAP available)					
<ul style="list-style-type: none"> ○ CPAP remains the gold standard as there is currently no robust evidence supporting NHF in this population 						Two options <ul style="list-style-type: none"> ○ CPAP 1st: Therapy success ~8/10¹ ○ NHF 1st: (with 'rescue' CPAP). Therapy success ~7/10¹ No significant difference in intubation rate^{1,2} 						<ul style="list-style-type: none"> ○ NHF 1st: 8/10 infants likely to be managed successfully on NHF¹ (with 'rescue' CPAP) ○ Consider using NHF first because of high therapy success rate and lower rate of nasal trauma, with no significant difference in intubation^{1,2} 					

1. Roberts et al. N Engl J Med. 2016

2. Lavizzari et al. JAMA Pediatrics. 2016.

Reference list

Section1: NHF for post-extubation

1. Collins C, Holberton J, Barfield C. et al. A Randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. J Pediatr. 2013 May;162(5):949-54
2. Yoder B, Stoddard R, Li M. et al. Heated, humidified high-flow nasal cannula versus basal CPAP for respiratory support in neonates. Pediatrics 2013 May;131(5)
3. Manley B, Owen L, Doyle L. et al. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2013 Oct 10;369(15):1425-33
4. Wilkinson D, Andersen C, O'Donnell C. et al. Cochrane Database Syst Rev. 2016 Feb 22;2:CD006405



Section 2: NHF for primary support

1. Roberts CT, Owen LS, Manley BJ. et al. Nasal high-flow therapy for primary respiratory support in preterm infants. N Engl J Med. 2016 Sep 22;375(12):1142-51.
2. Lavizzari A, Colnaghi M, Ciuffini F. et al. Heated, humidified high-flow nasal cannula vs continuous positive airway pressure for respiratory distress syndrome of prematurity. A randomized clinical noninferiority trial. JAMA Pediatrics. Published online August 8, 2016.

