Table of Contents

Reviews: Overview of Nasal High Flow Literature

R1  Review: NHF therapy Mechanisms of Action  2
R2  Review: Early use of NHF therapy  4
R3  Review: Integrated use of NHF therapy  6
R4  Review: Implementing NHF therapy  8

Summaries: Key Randomized Controlled Trials

S1  Summary: Testa et al. 2014; Milési et al. 2017; Sarkar et al. 2018  9
S2  Summary: Franklin et al. 2018  11
Key References


R1. Review: NHF therapy Mechanisms of Action


Aim
• To summarize key literature describing the physiological and clinical outcomes associated with the use of NHF therapy in infants across various hospital settings

Introduction
• NHF therapy is a form of noninvasive respiratory support, delivering conditioned (heated and humidified) gas flow to patients via appropriately-sized nasal cannula. In order to reduce the entrainment of room air and dilution of administered oxygen, air and oxygen should be delivered at a flow rate which meets or exceeds the peak inspiratory demand of the patient (Schibler et al. 2016).

• A flow rate of 2 L/kg/min is suggested for infants with a body weight of between 3 and 10 kg (Milési et al. 2014; Schibler et al. 2016). Franklin et al. 2018 extended this approach to infants up to 12.5kg. This dose by weight approach to setting the flow rate has not been validated in the literature for neonates, older children, or adults.

• In recent years, there has been an increase in the use of NHF therapy for infants with respiratory distress across various hospital settings, including the ED, the ward, and in the PICU (Canares et al. 2014; Mikalsen et al. 2016; Schibler et al. 2016).

• The existing body of evidence suggests that the early and integrated use of NHF across the hospital is associated with physiological and clinical benefits. Use of NHF early in the course of respiratory failure reduces the escalation of care, reduces the need for PICU admission, and has been associated with a decreased rate of intubation and the need to transfer infants to the PICU (McKiernan et al. 2010; Mikalsen et al. 2016; Schibler et al. 2016).

Mechanisms of Action

Washout of anatomical dead space
• NHF therapy facilitates washout in the nasopharyngeal anatomical dead space (Dysart et al. 2009). The nasopharynx contains gas rich in CO₂ at the end of exhalation during normal breathing. This gas is then re-breathed in the next respiratory cycle, reducing the efficacy of gas exchange. Continuous flow of fresh gas in the nasopharynx washes out CO₂-rich gas from the nasopharyngeal dead space. During the next inspiration, CO₂ re-breathing is minimized and oxygenation may be improved (Schibler et al. 2016).

Generates low level of positive airway pressure
• A study of 26 infants with acute bronchiolitis admitted to a PICU demonstrated that NHF therapy (and the use of a pacifier to limit air leak from the mouth) was associated with the generation of a clinically relevant pharyngeal pressure (Milési et al. 2013). NHF therapy at a flow rate ≥2 L/kg/min was associated with a pharyngeal pressure of ≥4 cm H₂O. This resulted in an approximately 50% reduction in respiratory effort among the studied infants.

• Positive pressure at the beginning of inspiration may compensate for the inspiratory burden associated with end-expiratory pressure and facilitate inspiratory flow. Positive pressure during expiration may prevent small airway collapse, increase the expiratory time, and reduce the end-expiratory pressure (Milési et al. 2014).
Reduction in the work of breathing

- Pham et al. 2015 demonstrated in infants with bronchiolitis (n = 12) admitted to a PICU that infants treated with NHF therapy at a rate of 2 L/kg/min significantly off-loaded the diaphragm compared with receiving no therapy. NHF therapy, compared with before NHF use, significantly decreased the work of breathing, as shown by the significant reductions in the pressure-rate product and the pressure-time product (p = 0.004 and p = 0.003, respectively).

Warming and humidifying the respiratory gas

- A major role of the nasopharynx and the epithelium lining the upper airway is to provide moisture and remove debris while warming the inspiratory gas. NHF therapy uses humidified (100% relative humidity) and adequately heated (maintained at 34 to 37 °C) gas.

Improves respiratory outcomes

- A study in neonates and infants (n = 27) with moderate-to-severe bronchiolitis treated with NHF therapy (2 L/kg/min) in a pediatric ward demonstrated that median SpO₂ significantly increased by 1-2 points after changing from standard oxygen to NHF therapy (p < 0.001) (Bressan et al. 2013). Median end tidal CO₂ and respiratory rate decreased by 6 to 8 mmHg and 13 to 20 breaths per minute, respectively, in the first 3 hours of NHF therapy (p < 0.001) and remained steady thereafter.

KEY POINTS

- Proposed physiological effects with NHF therapy include:
  - Wash-out of the anatomical dead space
  - Low level positive airway pressure
  - Improved work of breathing
  - Warming and humidifying of the respiratory gases
  - Improvement of respiratory outcomes
AIM

- To understand the key literature supporting the rationale for using NHF early in the course of respiratory failure in infants.

INTRODUCTION

- Most mild-to-moderate respiratory distress conditions with an oxygen requirement appear to benefit from therapies that provide airway pressure, such as CPAP (Schibler et al. 2016). However, respiratory support modes like CPAP, intubation, and mechanical ventilation (MV) have traditionally been restricted to the PICU setting.

- Increasing physiological evidence shows that low levels of positive airway pressure are observed when flow rates of 2 L/kg/min are delivered to infants with a body weight of 3-10 kg (Milési et al. 2014; Schibler et al. 2016). Therefore, NHF is being considered more frequently for use in lower acuity settings to support inspiratory effort, deliver oxygen, and provide low-level positive airway pressure (Schibler et al. 2016).

- Several studies have evaluated the early use of NHF in the course of respiratory failure (Bressan et al. 2013; Mayfield et al. 2016; Wing et al. 2012) in the ED or wards.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Patient Population</td>
<td>ED</td>
<td>ED and ward</td>
<td>ED and ward</td>
</tr>
<tr>
<td>Study Design</td>
<td>Observational (Retrospective cohort)</td>
<td>Prospective pilot</td>
<td>Prospective, observational pilot</td>
</tr>
<tr>
<td>Intervention</td>
<td>Cohort 1: Before NHF (2-10 L/min)</td>
<td>NHF (2 L/kg/min)</td>
<td>NHF (2 L/kg/min)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Cohort 2: After NHF, before guidelines</td>
<td>Standard therapy (2 L/min)</td>
<td>None</td>
</tr>
<tr>
<td>Study Outcomes</td>
<td>Need for intubation, ventilation, and/or PICU admission</td>
<td>Indicators of treatment success</td>
<td>Indicators of treatment success</td>
</tr>
</tbody>
</table>
RESULTS

1. Rate of intubation

Patients who received NHF therapy in the ED on admission experienced significantly lower intubation rates compared with those who received NHF when escalated and admitted to the PICU (7.6% vs. 18.1%, p = 0.047) (Wing et al. 2012).

2. Admission to the PICU

Fewer patients were admitted to the PICU when NHF therapy was initiated in the ED or ward compared with those who received standard therapy (13% vs. 87%) (Mayfield et al. 2014).

3. Physiological indicators of treatment success

Mayfield et al. (2014) found that heart rate (HR) and respiratory rate (RR) could be used to predict NHF therapy success or the need for escalation. An improvement of these parameters within an hour of initiation of treatment may indicate the likelihood of therapy success.

KEY POINTS

• The early use of NHF in infants was associated with a decreased need for intubation and a decreased number of PICU admissions.

• Non-responders to NHF, who are likely to require treatment escalation, can be identified early after treatment initiation by monitoring the heart rate (HR) and respiratory rate (RR).

• The early use of NHF therapy in EDs and wards may result in significant cost savings due to the reduced number of patients admitted to the PICU.
Wing et al. 2012; Kepreotes et al. 2017

AIM
• To demonstrate how the integrated use of NHF therapy in infants with moderate respiratory distress across EDs and wards prevents subsequent admission to the PICU.

INTRODUCTION
• Respiratory illnesses are a leading cause of ED admissions and subsequently to the ward or to the PICU (Wing et al. 2012).

• Studies have shown that NHF therapy has improved the management of infants with moderate bronchiolitis, often removing the need for intubation and reducing the number of infants experiencing treatment failure and an escalation of care (Kepreotes et al. 2017; Wing et al. 2012).

<table>
<thead>
<tr>
<th></th>
<th>Wing et al. 2012</th>
<th>Kepreotes et al. 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Setting</td>
<td>ED</td>
<td>ED or ward</td>
</tr>
<tr>
<td>Patient Population</td>
<td>848 patients, &lt; 18 years old (mean 4.6 years) with ARI</td>
<td>202 infants, &lt; 24 months old with moderate bronchiolitis</td>
</tr>
<tr>
<td>Study Design</td>
<td>Observational (Retrospective cohort)</td>
<td>RCT</td>
</tr>
<tr>
<td>Intervention</td>
<td>Cohort 1: Before NHF introduction (2-10 L/min)</td>
<td>NHF (1 L/kg/min)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Cohort 2: After NHF introduction but without a guideline for use</td>
<td>Standard therapy (2 L/min)</td>
</tr>
<tr>
<td></td>
<td>Cohort 3: After NHF introduction and implementation of a guideline for use</td>
<td></td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Need for intubation, ventilation, and/or PICU admission</td>
<td>Time to wean off oxygen</td>
</tr>
</tbody>
</table>

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R3. Review: Integrated use of NHF therapy

RESULTS
1. Increased adoption of NHF with protocol
Introducing an NHF guideline significantly increased the use and adoption of the therapy in the ED. This trend was also observed in the PICU (Wing et al. 2012).

2. Decreased ED intubation rate
The early use of NHF in the ED was found to significantly decrease intubation rates. There was no difference in intubation rates in the PICU (Wing et al. 2012).

3. Treatment failure and transfer to the PICU
NHF therapy was associated with lower treatment failure when used in the wards compared with standard therapy. However, there was no significant difference between the two treatment groups in the transfer to the PICU (Kepreotes et al. 2017).

KEY POINTS
• NHF therapy may be a safe and effective therapy for infants with ARI as it reduces the need for intubation and mechanical ventilation (Wing et al. 2012)
• NHF therapy was associated with significantly lower rates of escalation of care due to treatment failure when compared with standard oxygen therapy administered to infants with bronchiolitis.
• Use of NHF early in the course of respiratory failure in the ED may reduce the need for admission to the PICU.

### Use of NHF, % patients

<table>
<thead>
<tr>
<th>Wing et al. 2012</th>
<th>Cohort 1 (n = 190)</th>
<th>Cohort 2 (n = 289)</th>
<th>Cohort 3 (n = 369)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED</td>
<td>0</td>
<td>8</td>
<td>19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PICU</td>
<td>0</td>
<td>18</td>
<td>23</td>
<td>0.08</td>
</tr>
</tbody>
</table>

### Intubation rate, % patients

<table>
<thead>
<tr>
<th>Wing et al. 2012</th>
<th>Cohort 1 (n = 190)</th>
<th>Cohort 2 (n = 289)</th>
<th>Cohort 3 (n = 369)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED</td>
<td>11</td>
<td>10</td>
<td>2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PICU</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>0.90</td>
</tr>
</tbody>
</table>

### Treatment failure within 24 h, % patients

<table>
<thead>
<tr>
<th>Kepreotes et al. 2017</th>
<th>NHF (n = 101)</th>
<th>Standard Therapy (n = 101)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>33</td>
<td>0.0016</td>
<td></td>
</tr>
</tbody>
</table>

### Transfer to PICU, % patients

<table>
<thead>
<tr>
<th>Kepreotes et al. 2017</th>
<th>NHF (n = 101)</th>
<th>Standard Therapy (n = 101)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>12</td>
<td>0.41</td>
<td></td>
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</tbody>
</table>
AIM

• To review the use and implementation of NHF therapy in pediatric literature. The following collates data from published literature, but does not overrule expert clinical judgment in patient management.

INTRODUCTION

• NHF appears feasible in most infant populations currently managed with noninvasive ventilation (NIV) and may be better tolerated than conventional NIV options (Milési et al. 2014).

• The most prevalent population in the body of literature is infants with bronchiolitis. A large RCT by Franklin et al. (the PARIS trial) found that the early use of NHF in the ED is associated with significantly less treatment failure resulting in escalation of care, compared to standard oxygen therapy.

• Smaller trials have included patients with ARI caused by other respiratory illness including asthma/reactive airway disease, pneumonia, and croup (Wing et al. 2012).

INITIATING NHF THERAPY

• NHF therapy has been used to manage moderate respiratory distress in infants in EDs, in pediatric wards, and in PICUs (Franklin et al. 2018; Mayfield et al. 2014; Milési et al. 2013; Wing et al. 2012).

• The prong diameter should be about half that of the nostril. Some studies have used a pacifier to reduce air leaks through the mouth (Milési et al. 2014).

• A flow rate of 2 L/kg/min is suggested for infants with a body weight of between 3 and 10 kg (Milési et al. 2014). This “dose by weight” approach has been extended to infants up to 12.5kg in a recent RCT (Franklin et al. 2018), however there is no evidence to support this approach in neonates, older children or adults.

• FiO2 should be set to achieve target saturation between 92% and 98% (Franklin et al. 2018).

• NHF should be delivered with adequately conditioned (heated and humidified) gas (Milési et al. 2014).

CONSIDERATIONS

• In addition to appropriate monitoring of the patient, physiological parameters such as HR and RR may be helpful in evaluating therapy success or the need for escalating care (Franklin et al. 2018, Milési et al. 2014)

• Treatment failure occurs when a set of pre-defined criteria is met, which necessitates an escalation of treatment or level of care (admission to the PICU from ED/ward) for the patient. In Franklin et al. (2018), treatment failure was defined as meeting three out of the four following criteria: persistent tachycardia, persistent tachypnea, increasing use of oxygen, and/or hospital early warning tool.

WEANING NHF THERAPY

• Weaning is initiated at the clinician’s discretion.

• In Franklin et al. (2018), FiO2 was decreased to room air while the flow rate was maintained at 2 L/kg/min. Once FiO2 had reached 21%, with SpO2 maintained between 92% and 98% (or 94% to 98% in some hospitals) for four hours, nasal cannulae were removed.
AIM
To evaluate the key RCTs investigating the use of NHF therapy and comparing it to other modes of noninvasive respiratory support (CPAP, low-flow oxygen therapy, etc.) in infants with respiratory distress.

INTRODUCTION

- Of particular interest are the following three RCTs:

<table>
<thead>
<tr>
<th>Study Setting</th>
<th>Patient Population</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testa et al. 2014</td>
<td>89 infants, &lt; 18 months old</td>
<td>Single-center RCT</td>
<td>NHF (2 L/kg/min)</td>
<td>Standard O₂ (2 L/min)</td>
<td>PaCO₂ elimination</td>
</tr>
<tr>
<td>Milési et al. 2017</td>
<td>142 infants, &lt; 6 months old</td>
<td>Multi-centre RCT</td>
<td>NHF (2 L/kg/min)</td>
<td>CPAP (7 cmH₂O)</td>
<td>Treatment failure within 24h</td>
</tr>
<tr>
<td>Sarkar et al. 2018</td>
<td>31 patients, 28 days to 12 months old</td>
<td>Pilot RCT</td>
<td>NHF (2 L/kg/min)</td>
<td>CPAP (4-8 cm H₂O)</td>
<td>Reduction of the need of MV</td>
</tr>
</tbody>
</table>

RESULTS

1. Treatment failure
Treatment failure rates with NHF and the comparator differed across the three RCTs. Testa et al. (2014) found no treatment failure in the NHF group compared with the standard O₂ group. Milési et al. (2017) found that treatment failure was higher in the NHF group than in the CPAP group. However, Sarkar et al. (2018) found no significant difference between NHF and CPAP.

2. Intubation rate
There was no significant difference in intubation rate between NHF and the comparator respiratory support across all three RCTs.
3. Nasal trauma

Only two of the RCTs evaluated the rate of nasal trauma (Milési et al. 2017; Sarkar et al. 2018). Although not statistically significant, NHF was associated with less nasal trauma than CPAP. Testa et al. (2014) had no reports of nasal ulcers with NHF therapy.

### Nasal Trauma, % patients

<table>
<thead>
<tr>
<th></th>
<th>Milési et al. 2017</th>
<th>Sarkar et al. 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHF (n = 71)</td>
<td>2.8</td>
<td>27</td>
</tr>
<tr>
<td>CPAP (n = 71)</td>
<td>8.5</td>
<td>75</td>
</tr>
<tr>
<td>P-value</td>
<td>0.27</td>
<td>0.021</td>
</tr>
</tbody>
</table>

4. Adverse outcomes i.e. death, pneumothorax

There was no difference in the adverse event profiles with NHF when compared with either CPAP or standard O₂ therapy.

**KEY POINTS**

- The evidence indicates that the rate of treatment failure with NHF is lower compared to that with standard O₂ therapy, but not CPAP.
- The use of NHF resulted in lower rates of nasal trauma, with no additional risk of adverse events, compared with CPAP.
- There was no significant difference in the rate of intubation and escalation of care between the NHF and comparator groups.
AIM
To investigate whether the early use of NHF compared with standard oxygen therapy (SOT) reduces the need to escalate the level of care in infants with bronchiolitis.

METHOD

Patient group
- Infants < 12 months old presenting to the ED with bronchiolitis and hypoxia (SpO2 < 92%/94%, dependent on hospital guideline).

Study design
- Prospective open-label, multi-center randomized controlled trial conducted in 17 EDs and associated general pediatric wards across Australia and New Zealand.

Outcome measures
- Primary outcome: Treatment failure during hospital admission requiring escalation of respiratory support and/or PICU admission. Escalation of therapy occurred if 3 out of 4 criteria were met: persistent tachycardia, hypoxemia, and/or hospital early warning tool activated.
- Secondary outcomes included transfer to tertiary institution, admission to intensive care, length of hospital stay, duration of oxygen therapy, intubation rates, and adverse events

Treatment regimen
- Infants were randomized to receive NHF therapy or SOT via nasal cannulae.
- NHF was delivered at a rate of 2 L/kg/min using Optiflow™ Junior (Fisher & Paykel Healthcare Ltd)
  - FiO2 was adjusted to maintain SpO2 between 92% (or 94%) and 98%.
  - NHF was stopped once infants were able to maintain SpO2 in the target range on room air for at least 4 hours.
- SOT was delivered at flow rates of up to a maximum of 2 L/min to maintain SpO2 between 92% (or 94%) and 98%.
- Parameters recorded included SpO2, heart rate, respiratory rate, respiratory effort, oxygen/FiO2 administered, NHF flow rate, therapy and medications, temperature, and blood pressure.
RESULTS

A total of 1,472 infants were enrolled over a three-year period. Baseline characteristics were similar between the groups. Respiratory syncytial virus was the most common viral cause and premature birth was the most common coexisting condition.

Outcomes

- The primary outcome of treatment failure was significantly different between groups. Escalation of care was required in 87 of 739 infants (12%) on NHF therapy and 167 of 733 infants (23%) on SOT (p < 0.001).
- Rescue therapy with NHF was given to all infants in the SOT group requiring escalation of therapy.
  - 102 of 167 infants (61%) responded to rescue NHF therapy and 65 were transferred to the PICU.
- 12 infants required intubation: 4 in the SOT group and 8 in the NHF group (p = 0.39).
- There was no significant difference in the length of hospital stay, length of ICU stay, or the duration of oxygen therapy.
- No serious adverse events were reported - one pneumothorax in each group.

CONCLUSIONS AND KEY POINTS

Early use of NHF across the ED and pediatric ward is an effective strategy in reducing the escalation of therapy and level of care required in young infants with bronchiolitis, compared with standard oxygen therapy.

- Please note, Fisher & Paykel Healthcare Limited provided product support for this study and has a consultancy arrangement with the primary investigator for this study, under which payment is provided.
GLOSSARY

100% RELATIVE HUMIDITY
The maximum amount of water a gas can hold at a given temperature

ACUTE RESPIRATORY INSUFFICIENCY (ARI)
Impaired lung function that leads to decreased oxygen uptake and inadequate delivery of oxygen to the body's tissues

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 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 airways (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

ED
Emergency Department

FRACTION OF INSPIRED OXYGEN (FiO₂)
The proportion of oxygen in the air that is inspired

HEART RATE (HR)
The amount of heartbeats over a specified time period

HEATED, HUMIDIFIED GAS
Air that has been heated and humidified prior to delivery by noninvasive ventilation, typically to 37 °C and 100% Relative Humidity

INFANT
Children greater than 1 month to 2 years of age

INTUBATION
The insertion of an endotracheal tube or tracheostomy tube into the trachea

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

NHF
Nasal high flow

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

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

PICU
Pediatric intensive care unit

PNEUMOTHORAX
Air of gas in the pleural space

PRP
Pressure-rate product

PTP
Pressure-time product

RCT
Randomized controlled trial

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 (RR)
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

WORK OF BREATHING (WOB)
The force required to expand the lung against its elastic properties
For more information please contact your local Fisher & Paykel Healthcare representative