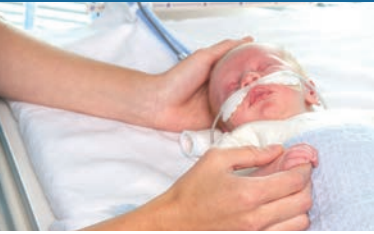


Infant Nasal High Flow: Clinical Paper Summaries



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## Research in high flow therapy: mechanisms of action

### AIM:

To review proposed mechanisms for the efficacy of nasal high flow (NHF) therapy.

### DETAILS:

NHF oxygen therapy is being increasingly utilized in a variety of patients with different diseases. The precise mechanisms by which NHF oxygen therapy alters gas exchange and influences the respiratory system have not been fully elucidated. However, available data suggest that there are five contributors to the effectiveness of NHF oxygen therapy.

**Washout of nasopharyngeal deadspace:** The most common reasons for needing to switch to invasive ventilation are hypercapnia and apnoea secondary to hypercapnia. Therefore, if deadspace in the nasopharyngeal cavity (and overall deadspace) is reduced, alveolar ventilation will be a greater fraction of minute ventilation. NHF oxygen therapy has been shown to have an immediate effect on ventilation rates and to improve oxygenation, indicating that deadspace is reduced. In addition, the results of animal studies of tracheal gas insufflation (TGI) support the notion that deadspace washout is a lung protective strategy for acute lung injury.

**Reduced work of breathing (WOB):** The nasopharyngeal surface area, distensibility of the nasopharynx and gas volume all contribute resistance to gas flow. NHF oxygen therapy provides nasopharyngeal gas flows that are equal to, or greater than, a patient's peak inspiratory flow thereby decreasing resistance which in turn translates into a reduction in resistive WOB. The effects of NHF oxygen therapy on expiration are not as well understood. However, it is speculated that expiratory efforts may be assisted secondary to a potential Coanda effect.

**Improved mechanics:** Even short periods inspiring gas at ambient temperature and humidity can significantly decrease pulmonary compliance and conductance during mechanical ventilation in infants. Improved respiratory compliance has been documented in infants receiving NHF oxygen therapy for respiratory support. These results indicate that, by reducing distending pressure and therefore also functional residual volume, adequate conditioning of inspired gases during NHF oxygen therapy affects physiological responses in the lung.

**Reduced metabolic cost of gas conditioning:** There is an energy cost associated with conditioning of inspired gases by the upper airway. This cost is higher when gas is cooler and drier. Furthermore, the increase in minute ventilation that often accompanies lung pathologies means that the volume of gas requiring conditioning is greater. Use of a NHF oxygen therapy system that warms and humidifies inspired gas presumably reduces the energy required for gas conditioning.

**Provision of distending pressure:** Ventilatory mechanics can be improved by providing distending pressure to the lungs which then improves lung compliance and gas exchange. There is the potential for continuous positive airway pressure (CPAP) to be generated during NHF oxygen therapy. This is dependent on the leak rate which is in turn highly dependent on the relationship between the size of nasal prongs and the nose, and requires the mouth to be closed. One clinical study in infants receiving NHF oxygen therapy showed that pharyngeal pressure was correlated with flow and inversely correlated with infant size.

### CONCLUSION:

Delivery of warmed and humidified gases using NHF oxygen therapy is a viable treatment option, which is comfortable for the patient and minimizes deterioration of nasopharyngeal structures.

### KEY POINTS:

- The five proposed mechanisms for the efficacy of NHF oxygen therapy are: washout of nasopharyngeal deadspace; reduced WOB, improved mechanics; reduced metabolic cost of gas conditioning; and provision of distending pressure.
- HFT can be regarded as a viable device for gas conditioning.
- Numerous studies have established the safety and efficacy of NHF in acute care.
- There are some studies which demonstrated the application of NHF beyond conventional oxygen therapy.

## DEFINITIONS:

Coanda effect	A term originating from the field of aeronautical engineering. The Coanda effect is an entrainment effect whereby high-speed fluid from a nozzle entrains fluid from the body that it enters. An obstruction to this action by a wall/barrier causes a low-pressure area on one side of the jet, causing a deflection in flow, redirecting flow to the barrier
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
Functional residual volume	The volume in the lungs at the end-expiratory position
Hypercapnia	The presence of an abnormally high level of carbon dioxide in the circulating blood
Mechanical ventilation	The use of an invasive artificial airway to mechanically assist or replace spontaneous breathing, when patients cannot do so on their own
Minute ventilation	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
Nasal high flow (NHF) oxygen therapy	A technique to provide a high flow of heated, humidified oxygen and air to patients requiring respiratory support, delivered through nasal cannulae
Tracheal gas insufflation (TGI)	An adjunctive ventilatory technique that delivers fresh gas into the trachea either continuously or only during a specific segment of the respiratory cycle
Work of breathing (WOB)	The force required to expand the lung against its elastic properties



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## High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence

### AIM:

To review evidence for the use of high-flow nasal cannula (HFNC) oxygen therapy in preterm infants based on data drawn from 19 studies identified by literature searching.

### DETAILS:

HFNC delivers humidified gas via nasal prongs, which are available in a variety of sizes. The use of HFNC oxygen therapy in preterm infants is increasing in popularity. Indications where HFNC is being used include: primary support for respiratory distress syndrome (RDS), treatment of apnoea of prematurity (AOP), and weaning from nasal continuous positive airway pressure (nCPAP). HFNC may offer some advantages over nCPAP in terms of ease of application and better facial access.

**Pressure generation:** Pressures generated by HFNC appear to be less than or similar to those usually delivered with nCPAP. The pressures will vary depending on the presence of mouth leak, and also in the presence of nasal obstruction. Results from studies predicting pressure during HFNC oxygen therapy vary and should be interpreted with caution due to the number of methodological limitations and design differences.

**Respiratory mechanics:** Beneficial effects of HFNC include the generation of distending pressure, and reduced thoraco-abdominal asynchrony and respiratory effort. Heating and humidification of inspired gases is important for achieving these benefits. Comparisons between HFNC and nCPAP have demonstrated comparable effectiveness of the two strategies.

**Prevention of extubation failure:** HFNC has been suggested as an alternative to nCPAP for prevention of extubation failure in the neonatal intensive care unit. However, there has been little published evidence to support this to date. HFNC did not perform well compared with nCPAP in one study<sup>1</sup>, but the flow rates used were much lower than those currently used in clinical practice. Another study reported an advantage for HFNC over nCPAP<sup>2</sup>, while a different trial showed that extubation failure was similar with the two devices<sup>3</sup>. Larger, prospective randomized, controlled clinical trials are currently underway which will potentially provide more reliable and useful data.

**Treating RDS or AOP:** Data from small trials suggest that HFNC has beneficial effects when used to treat RDS or AOP<sup>4-7</sup>. In the only comparative clinical trial, there was no difference in intubation rate, duration of hospitalization and the combined outcome of death or bronchopulmonary dysplasia in infants treated with HFNC or nCPAP [unpublished data].

**Weaning from nCPAP:** Available data are conflicting. One study showed similar outcomes with continuation of nCPAP or changing to HFNC while another reported clinically important increases in days on oxygen and duration of respiratory support in patients switched to HFNC oxygen therapy compared with continued on nCPAP.

**Safety:** With the exception of early issues with bacterial contamination of the Vapotherm HFNC device, which have since been addressed, few important adverse outcomes have been reported during HFNC oxygen therapy. Nasal trauma appears to be reduced compared with nCPAP when HFNC is used. However, the safety of HFNC in preterm infants has yet to be clearly defined and further data from larger, randomized studies are required.

**Recommendations:** Evidence for the feasibility of HFNC oxygen therapy as an alternative treatment for preterm infants is growing, although no long-term data are currently available. However, surveys show widespread use of HFNC in this population. It is recommended that only heated, humidified HFNC systems be used to prevent drying of the airway mucosa and maintain secretion quality. Flow rates should be  $\geq 2$  L/min and prongs should be selected so that the nares are not completely occluded. An appropriate balance between efficacy and safety can be achieved by using a starting flow rate of 4-6 L/min.

## CONCLUSION:

Further research is needed to clearly define whether HFNC oxygen therapy is effective and safe compared with nCPAP. NCPAP is the current standard of care for non-invasive respiratory support. The results of on-going studies investigating the use of HFNC as post-extubation support and for the treatment of RDS are required before any recommendation can be made about the widespread use of HFNC to treat preterm infants.

## KEY POINTS:

- Evidence for the feasibility of HFNC oxygen therapy as an alternative respiratory support treatment for preterm infants is growing.
- Heated, humidified HFNC systems with flow rates  $\geq 2$  L/min should be used.
- Widespread use of HFNC oxygen therapy to treat preterm infants cannot yet be recommended due to lack of data.

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## DEFINITIONS:

Apnea of prematurity (AOP)	A phenomenon that occurs in premature babies when the part of the central nervous system that controls breathing is not yet mature enough to allow continuous breathing. This results in large bursts of breath followed by periods of shallow or stopped breathing.
High-flow nasal cannula (HFNC) oxygen therapy	A device designed to provide a high flow of heated, humidified oxygen and air to patients requiring respiratory support, delivered through nasal cannulae.
Nasal continuous positive airway pressure (nCPAP)	A technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilator circuit.
Noninvasive ventilation (NIV)	The delivery of ventilatory support without the need for an invasive artificial airway.
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.



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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 heated humidified (HH) high-flow nasal cannula (HFNC) oxygen therapy increases the rate of successful extubation in premature infants following endotracheal positive pressure ventilation, compared with conventional nasal continuous airway pressure (nCPAP) oxygen therapy.

### METHOD:

In this prospective study, conducted at the Mercy Hospital for Women in Melbourne, Australia, premature infants (born at <32 weeks' gestational age) who required endotracheal intubation and positive pressure ventilation and were considered ready for extubation were randomized to HH HFNC (Vapotherm) or nCPAP (Hudson Respiratory Care) oxygen therapy; patients were also stratified by gestational age (<28 weeks vs. 28–31.6 weeks).

In the HFNC group, nasal cannulae with a 1.5mm external diameter were used and patients were extubated to a flow rate of 8 L/min; flow rate was weaned to a minimum of 4 L/min. nCPAP was delivered via bi-nasal prongs with an external diameter of 3.7–4.6 mm and a positive end-expiratory pressure (PEEP) of 8 cm H<sub>2</sub>O or 7 cm H<sub>2</sub>O for FiO<sub>2</sub> values of >0.3 and <0.3, respectively; PEEP was weaned to a minimum of 5 cm H<sub>2</sub>O. Oxygen saturation targets for both groups were 85–92%. The assigned respiratory support was continued until it was no longer required or patients were switched to non-humidified low-flow sub-nasal oxygen ≤0.2 L/min.

The primary outcome measure was 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 PCO<sub>2</sub> >66 mmHg); sustained increase in FiO<sub>2</sub> of >15% from extubation. Patients were re-intubated at the treating physician's discretion. Secondary outcome measures included nasal trauma, the duration of respiratory support, supplemental oxygen requirement, and bronchopulmonary dysplasia. Nasal trauma was assessed using the sum of thrice-daily nasal trauma score recordings during the 7 days after extubation; nasal trauma at the internal and external nares, philtrum and septum were rated from 0 (normal) to 3 (skin tear).

### RESULTS:

Between 1 January 2009 and 31 July 2009 a total of 132 infants were randomized to either HFNC (n=67) or nCPAP (n=65). The baseline characteristics of the HFNC and nCPAP groups were similar with the exception of sex; although there were more male infants in the nCPAP group (63% vs. 49% for HFNC); no relationship was seen between sex and the primary outcome.

HFNC and nCPAP oxygen therapy were associated with similar extubation failure rates at 7 days (see table). Stratification of patients by gestational age (<28 weeks vs. ≥28 weeks) also showed no significant difference between HFNC and nCPAP therapy in extubation failure rates at 7 days; overall extubation failure rates were higher among infants born at <28 weeks' gestational age than those born at 28–32 weeks (44% vs. 15%; p<0.001). HFNC oxygen therapy was associated with significantly reduced nasal trauma compared with nCPAP. Furthermore, at 7 days after extubation, 20% of the infants randomized to nCPAP switched to HFNC oxygen therapy due to nasal trauma. No significant differences were seen in bronchopulmonary dysplasia rates or the durations of supplemental oxygen and respiratory support (see table).

Variable	HFNC (n=67)	nCPAP (n=65)	p-value
Extubation failure at 7 days (primary outcome), % pts.	22	34	NS
Apnoea, % pts.	21	26	NS
Acidosis, % pts.	0	5	NS
FiO <sub>2</sub> increase >15%, % pts.	10	18	NS
Nasal trauma score first week, mean (SD)	3.1 (7.2)	11.8 (10.7)	<0.01
BPD at 36 weeks' gestation, % pts.	36	43	NS
Respiratory support, mean completed weeks (SD)	33.5 (2.88)	34.3 (3.51)	NS
Supplemental oxygen, mean completed weeks (SD)	36.9 (2.54)	38.0 (3.26)	0.06

BPD, bronchopulmonary dysplasia; HFNC, high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure; NS, not significant; pts., patients; FiO<sub>2</sub>, fraction of inspired oxygen; SD, standard deviation

## DISCUSSION:

HFNC and NCPAP oxygen therapy were associated with similar rates of extubation failure at 7 days in this study. The extubation failure rate with nCPAP oxygen therapy in this study was lower than expected based on historical controls at the same institution (34% vs. 50% in 2004–2006); this difference may be due to the change in the standard nCPAP delivery device used from a single nasopharyngeal prong to bi-nasal prongs in late 2005.

Nasal trauma was significantly reduced with HFNC versus nCPAP oxygen therapy. Although damage to the nasal mucosa caused by the bi-nasal prongs used in nCPAP is usually mild and resolves after cessation of treatment, in some cases disfigurement and long-term functional effects may occur. Nasal trauma may also be associated with an increased risk of nosocomial sepsis; however, further study is required before conclusions can be drawn. Larger randomized controlled trials of HFNC oxygen therapy in preterm infants are warranted, particularly those born at <28 weeks' gestational age as this subgroup has a higher rate of extubation failure.

## CONCLUSION:

HFNC and nCPAP oxygen therapy are associated with similar rates of extubation failure at 7 days in premature infants, although nasal trauma is reduced with the use of HFNC.

## KEY POINTS

- HFNC oxygen therapy is associated with a similar rate of extubation failure at 7 days to nCPAP oxygen therapy in premature infants undergoing extubation.
- HFNC oxygen therapy significantly reduces nasal trauma compared with NCPAP therapy.

## DEFINITIONS:

Apnea of prematurity	A phenomenon that occurs in premature babies when the part of the central nervous system that controls breathing is not yet mature enough to allow continuous breathing. This results in large bursts of breath followed by periods of shallow or stopped breathing
Endotracheal tube (ETT)	A tube inserted through the mouth or nose into the trachea to maintain an unobstructed airway
Fraction of inspired oxygen (FiO <sub>2</sub> )	The fraction of oxygen in inspired gas
Heated humidifier (HH)	A device that actively adds heat and water vapor to inspired gas
High-flow nasal cannula (HFNC) oxygen therapy	Nasal cannula (a small, half-moon shaped plastic tube, the ends of which fit into the nostrils of a patient) designed to deliver gas at a high flow rate
Nasal delivery of continuous positive airway pressure (nCPAP)	A technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilator circuit
Nosocomial infections	Infections acquired in the hospital inpatient environment, not resulting from the reasons for which the patient was admitted
Partial pressure of carbon dioxide (PCO <sub>2</sub> )	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
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
Premature infant	A baby born before 37 weeks' gestation



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## High-flow nasal cannulae vs. nasal CPAP for post-extubation respiratory support of very preterm infants: results of the HIPERSPACE trial

### AIM:

To determine whether the use of high-flow nasal cannula (HFNC) oxygen therapy for post-extubation respiratory support in premature infants is associated with a lower rate of failure than conventional nasal continuous airway pressure (nCPAP) oxygen therapy.

### METHOD:

This prospective non-inferiority study was conducted at three tertiary perinatal centers in Australia. Premature infants (born at <32 weeks' gestational age) were randomized to HFNC or nCPAP oxygen therapy as post-extubation respiratory support and patients were also stratified by gestational age (<26 weeks vs. ≥26 weeks). In the HFNC group, infants were extubated to a flow rate of 5–6 L/min whereas in the nCPAP group, the treatment was calibrated to deliver a positive end-expiratory pressure of 7 cm H<sub>2</sub>O. Those in whom HFNC treatment failed could be switched to nCPAP 7 cm H<sub>2</sub>O and infants in whom nCPAP failed were re-intubated.

The primary outcome measure was treatment failure within 7 days, defined by pre-specified failure criteria. A predefined margin of 20% for non-inferiority was used. Secondary outcome measures included the rate of re-intubation within 7 days, the incidence of death, bronchopulmonary dysplasia or pneumothorax, and the duration of hospitalization.

### RESULTS:

A total of 303 premature infants were randomized to either HFNC (n=152) or nCPAP (n=151). The baseline infant characteristics of the HFNC and nCPAP groups were similar, with a mean gestational age and birth weight of 27.7 weeks and 1041g in the HFNC group, and 27.5 weeks and 1044g in the nCPAP group, respectively. Maternal characteristics were also similar between the groups.

HFNC and nCPAP oxygen therapy were associated with similar treatment failure rates at 7 days (see table). When infants were stratified by gestational age (<26 weeks vs. ≥26 weeks) the risk of treatment failure at 7 days was higher among infants born at <26 weeks' gestational age than those born at 26–32 weeks (risk difference: 20.0% vs. 5.0%); however, this difference was still not considered clinically significant.

Compared with nCPAP, HFNC oxygen therapy was associated with significantly reduced nasal trauma (p=0.009). No significant differences between treatment groups were seen in the rates of death, bronchopulmonary dysplasia or pneumothorax, or the duration of hospitalization.

Variable	HFNC (n=152)	nCPAP (n=151)	Risk difference, % (95% CI)
Treatment failure at 7 days (primary outcome), n (%)	52 (34.2)	39 (25.8)	8.4 (-1.9, 18.7)
Infants <26 weeks gestational age	-	-	20.0 (-1.9, 41.8)
Infants ≥26 weeks gestational age	-	-	5.0 (-4.9, 14.9)
Re-intubation within 7 days, n (%)	27 (17.8)	38 (25.2)	

CI, confidence interval; HFNC, high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure

### CONCLUSION:

The results of the HIPERSPACE study indicate that oxygen therapy delivered by HFNC and nCPAP oxygen therapy are associated with similar rates of treatment failure at 7 days in premature infants, with HFNC non-inferior to nCPAP. For non-invasive respiratory support of premature infants, HFNC therapy is an increasingly popular alternative to nCPAP as it is perceived to be more comfortable for infants and easier to use than nCPAP. Furthermore, HFNC appears to be safe and reduces the incidence of nasal trauma compared with nCPAP. Further studies are warranted.

## KEY POINTS

- HFNC oxygen therapy is non-inferior to nCPAP oxygen therapy and is associated with a similar rate of treatment failure at 7 days when administered as post-extubation respiratory support in premature infants.
- HFNC oxygen therapy was associated with significantly less nasal trauma compared with nCPAP therapy.

## DEFINITIONS:

High-flow nasal cannula (HFNC) oxygen therapy	Nasal cannula (a small, half-moon shaped plastic tube, the ends of which fit into the nostrils of a patient) designed to deliver gas at a high flow rate
Nasal delivery of continuous positive airway pressure (nCPAP)	A technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilator circuit
Premature infant	A baby born before 37 weeks' gestation

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## High flow nasal cannulae therapy in infants with bronchiolitis

### AIM:

To determine if heated humidified nasal high flow (NHF) oxygen therapy was associated with decreased rates of intubation in infants with bronchiolitis admitted to a paediatric intensive care unit (PICU).

### METHOD:

In this retrospective study, the charts of 115 infants (age 0.5-24.0 months) with bronchiolitis were reviewed to examine the effect of the introduction of the NHF oxygen therapy system (MR850; Fisher & Paykel Healthcare) in the PICU. Fifty-seven infants were included for analysis in the "before" group (controls) and the outcomes of 58 infants were analyzed after the introduction of NHF therapy.

Use of the NHF system was at the discretion of the attending physician in the PICU. Both infant and pediatric cannulae were available and the size used was selected to fit the child's nares without occlusion.

The primary objective of the study was to determine whether the availability of NHF oxygen therapy was associated with a decrease in the need for intubation. Secondary outcomes included changes in respiratory measures and whether certain subgroups of infants showed greater benefit (see table below).

### RESULTS:

There were no differences between groups in terms of age, weight, gestational age, sex, RSV status, and Paediatric Index of Mortality (PIM2) score; however, more infants in the control group were premature (gestational age <37 weeks; 40% versus 19% of infants in the NHF group). Before the introduction of the NHF system, 57.9% of infants presenting with bronchiolitis received nasal cannula oxygen as their primary means of respiratory support. After the introduction of the NHF system, this was used in 87.9% of infants.

Data for the primary and secondary endpoints are reported in the table. The reduction in the intubation rate, as assessed using logistic regression analysis, was statistically significant both in the unadjusted analysis and after adjustment for age, weight and RSV status ( $p=0.043$  and  $p=0.049$ , respectively). The  $p$  value after adjustment for age, weight, RSV status and gestational age was 0.072.

Multivariate logistic regression analysis showed that infants with a history of prematurity may benefit more from NHF therapy; the intubation rate in formerly premature infants in the control group was 34.8% compared with 9% in the NHF group but patient numbers were too small to allow statistical comparison. Infants who received NHF oxygen therapy had a greater decrease in respiratory rate one hour after initiation of treatment than those who did not ( $p<0.001$ ); this effect persisted after adjustment for age, weight, gestational age and requirement for intubation. Infants who did not experience a clinically significant reduction in respiratory rate after the initiation of NHF were more likely to require intubation. The decrease in respiratory rate one hour after initiation of NHF was  $14 (\pm 15)$  versus  $1 (\pm 17)$  breaths/minute in infants who didn't versus did require intubation, respectively.

	Controls (n=57)	NHF oxygen therapy (n=58)	Absolute risk reduction	Adjusted decrease in risk of intubation with NHF
Intubation rate, n (%)	13 (23)	5 (9)	14%	65%

*Adjusted = regression analysis adjusted for age, weight, respiratory syncytial virus status and gestational age.*

### DISCUSSION:

There was a reduction in the need for intubation in infants who presented to the PICU with viral bronchiolitis after the introduction of NHF oxygen therapy which persisted after adjustment for age, weight and RSV status. The reduction in respiratory rate observed in patients who were successfully managed with NHF oxygen therapy supports the hypothesis that NHF oxygen therapy decreases work of breathing and delivers continuous positive airway pressure (CPAP), both of which contribute to a reduced requirement for intubation. After the introduction of NHF the median PICU stay for children with bronchiolitis decreased from 6 to 4 days indicating that by decreasing the need for intubation in this group of infants the length of hospital stay also decreases.

## CONCLUSION:

NHF oxygen therapy decreased the intubation rate in infants with bronchiolitis. In addition, this method of respiratory support was well tolerated.

## KEY POINTS:

- Use of NHF oxygen therapy for respiratory support in infants with bronchiolitis decreases the need for intubation.
- The mechanism of the beneficial effect of NHF oxygen therapy is likely to be decreased work of breathing and delivery of CPAP.

## DEFINITIONS:

95% confidence interval (CI)	A statistical measure showing that 95% of the results for that parameter lie within the range quoted
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
Nasal high flow (NHF) oxygen therapy	A technique to provide a high flow of heated, humidified oxygen and air to patients requiring respiratory support, delivered through nasal cannulae
Pediatric Index of Mortality (PIM2)	A mortality prediction model for children in intensive care
Pediatric intensive care unit (PICU)	A hospital facility providing intensive nursing and medical care for critically ill pediatric patients



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## Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery

### AIM:

To describe the experience with the use of nasal high flow oxygen therapy (NHF) in the treatment of infants aged <24 months with respiratory distress admitted to the pediatric intensive care unit (PICU). To compare the ventilatory practices at this PICU with those of all other PICUs in Australia and New Zealand.

### METHOD:

A retrospective database review was performed to identify all infants aged <24 months who had received NHF within 24 hours of admission to the PICU over the period January 2005 to December 2009 (n=298). A humidified NHF system was used with a low-resistance cannula [BC3780 and RT329; Fisher & Paykel Healthcare]. Underlying disease was classified as: viral bronchiolitis (n=167); other lung disease (72); upper airway obstruction (8); neuromuscular conditions (10); cardiac conditions (24); or other (17). Respiratory support subgroups were classified as: NHF alone; NHF + noninvasive ventilation (NIV); NHF + NIV + invasive ventilation (INV); NHF + INV. Risk factors for escalation to NIV or INV were investigated.

Specific to infants admitted with viral bronchiolitis, local changes in ventilation practices during the study period were assessed retrospectively using case records from the PICU's own database. The data from this PICU were then compared with case records from the Australian New Zealand Paediatric Intensive Care (ANZPIC) registry for infants with viral bronchiolitis admitted during 2008.

### RESULTS:

The number of infants who needed additional respiratory support with NIV or INV is detailed in the table below. Infants in the NHF group had a significantly lower PIM2 ROD score and fraction of inspired oxygen (FiO<sub>2</sub>) on admission compared with the NHF + NIV group (p<0.01). PICU length of stay was also shorter in the NHF group compared with the NHF + NIV group (p<0.01).

Across the whole group (n=298) there was an overall reduction in respiratory rate and heart rate after NHF commencement (p<0.001). Infants who could be maintained on NHF showed a decrease of >20% in both heart rate and respiratory rate within 90 minutes of the initiation of NHF (both p<0.05 vs. baseline). This rapid response was not evident in the NHF+NIV group. Also, infants with bronchiolitis had the greatest change in heart rate and respiratory rate after initiation of NHF oxygen therapy compared with infants who had other underlying conditions.

The intubation rate for viral bronchiolitis at the study site was 37% in 2005 and 7% in 2009. In comparison, the ANZPIC registry data reported an intubation rate of 28% for viral bronchiolitis in 2008.

The incidence of adverse events including pneumothorax, gastric distension and mucosal injury was monitored. No such events occurred during NHF therapy.

	Ventilation requirement after initiation of NHF, n (%)		
	NHF alone	NHF + NIV	Combined data for patients escalated to INV (NHF + NIV + INV and NHF + INV)
Bronchiolitis (n=167)	120 (72%)	41 (25%)	6 (4%)
Other lung disease (n=72)	55 (76%)	9 (13%)	8 (12%)
Cardiac disorders (n=24)	11 (46%)	1 (4%)	12 (50%) <sup>a</sup>
Other disorders (n=17)	6 (35%)	4 (24%)	7 (41%) <sup>a</sup>
Neuromuscular conditions (n=10)	8 (80%)	1 (10%)	1(10%) <sup>b</sup>
Upper airway obstruction (n=8)	6 (75%)	0 (0%)	2(25%) <sup>b</sup>
Overall (n=298)	206 (69%)	56 (19%)	36 (12%)

<sup>a</sup> Significantly higher incidence of INV (p<0.05) versus infants with bronchiolitis and infants with other lung disease; <sup>b</sup> Incidence of INV not compared with other disease groups because of small patient numbers.

## DISCUSSION:

Viral bronchiolitis is the most common reason for non-elective admission to the PICU. This retrospective analysis showed an increase in the proportion of infants with viral bronchiolitis treated with NHF from 13% in 2005 to 66% in 2009. Although it is difficult to demonstrate a cause and effect relationship using a retrospective analysis, a significant reduction in the need for intubation and mechanical ventilation was seen during this period, from 37% in 2005 to 7% in 2009, whereas the ANZPIC registry showed a markedly higher intubation rate of 28%. This suggests that the reduced intubation rate at the study institution is unlikely to have been due to an overall improvement in the standard of care over time. Also, admission criteria to the PICU did not change over the study period. A multicenter randomized controlled trial comparing NHF therapy with standard care is required to definitively assess the efficacy of this intervention in a PICU setting.

## CONCLUSION:

NHF is an efficient method of respiratory support and oxygen delivery for infants with respiratory distress. The introduction of NHF to the PICU was associated with a reduction in the requirement for INV in infants with viral bronchiolitis.

## KEY POINTS:

- Early improvement in heart rate and respiratory rate (reductions of >20% within 90 minutes) is predictive of the success of NHF oxygen therapy in infants with respiratory distress admitted to the PICU.
- The introduction of NHF oxygen therapy in the PICU coincided with a significant reduction in the need for intubation in infants with viral bronchiolitis.

## DEFINITIONS:

ANZPIC	Australian New Zealand Paediatric Intensive Care registry
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
Fraction of inspired oxygen (FiO <sub>2</sub> )	The fraction of oxygen in inspired gas
Nasal high flow oxygen therapy (NHF)	A technique to provide a high flow of heated, humidified oxygen and air to patients requiring respiratory support, delivered through nasal cannulae
Invasive ventilation (INV)	The use of an invasive artificial airway to mechanically assist or replace spontaneous breathing, when patients cannot do so on their own
Noninvasive ventilation (NIV)	The delivery of ventilatory support without the need for an invasive artificial airway
Pediatric Intensive Care Unit (PICU)	A hospital facility providing intensive nursing and medical care for critically ill pediatric patients
Pediatric Index of Mortality (PIM2)	A mortality prediction model for children in intensive care



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## High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study

### AIM:

To describe the utilisation, clinical experience and safety of humidified high flow nasal cannula (HHFNC) devices in premature infants, and compare them to non-invasive respiratory support with nasal continuous positive airway pressure (nCPAP).

### METHOD:

A retrospective database review was performed at 2 regional referral medical centres in the US. In the first part of the study, the change in frequency of usage of HHFNC and nCPAP was determined by comparing August 2003 to June 2004 (era 1) with August 2004 to June 2005 (era 2); the outcomes of infants treated during these 2 periods were also compared. In the second part of the study, the outcomes of a cohort of infants < 30 weeks' gestational age were compared across the 2 time periods.

nCPAP support, using pressures of 3-8 cm H<sub>2</sub>O, was provided by one of the following: Arabelles (Hamilton Medical, Inc.); InfantStar (Infrasonics) or Infant Flow Driver (Viasys Healthcare Inc.). HHFNC was generated using the VapoTherm 2000i (VapoTherm Inc.); high flow was defined as rates >2 L/min. Both nCPAP pressure and HHFNC flow rates were adjusted by clinicians as required. Oxygen saturation was 85-92%.

### RESULTS:

Utilisation of nCPAP fell from 19% in era 1 to 3.5% in era 2 ( $p < 0.001$ ), and there was a corresponding increase in the usage of HHFNC (from 14% in era 1 to 64% in era 2;  $p < 0.001$ ); similar significant trends were observed when infants aged  $\geq 30$  or < 30 weeks' gestational age were analysed. Compared with era 1, more infants treated during era 2 had gram-negative bacteraemia (14% vs. 6%) although the difference did not reach statistical significance. There was no association between the use of antenatal corticosteroids or delivery via caesarean section, and the rates of re-intubation or bronchopulmonary dysplasia. Key outcomes for infants aged <30 weeks' gestation are presented in the table. In an analysis of infants 26 to 29 6/7 weeks' gestational age, there was a significantly lower re-intubation rate in era 2 versus era 1 (6% vs. 35%;  $p < 0.001$ ).

Infants <30 weeks' gestational age	Era 1	Era 2
Ventilator days per patient	19.4	9.9 <sup>a</sup>
Bronchopulmonary dysplasia (infants)	34%	32%

<sup>a</sup>  $p < 0.05$  vs era 1.

### DISCUSSION:

Use of HHFNC has increased markedly in recent years. Improved ease of use, better tolerability and less nasal trauma compared with nCPAP are likely reasons for this. However, despite widespread clinical acceptance, published data on the efficacy and tolerability of HHFNC are scarce. Data from this retrospective analysis show that HHFNC appears to be associated with similar outcomes to nCPAP. Despite concern that using HHFNC in infants <30 weeks' gestational age may increase the risk of bronchopulmonary dysplasia; the current results did not show a difference between HHFNC and nCPAP in the rate of this complication. Generation of pressure at higher flows is another concern, particularly in very small infants, as is the potential for work of breathing to increase during use of HHFNC compared with nCPAP. While further studies of airway pressures are required, no cases of pneumothorax were documented during HHFNC therapy in this study. The VapoTherm 2000i device used for HHFNC in this study has since been recalled due to concerns about increased gram-negative bacteraemia in infants receiving early respiratory therapy with HHFNC versus nCPAP. The rate of gram-negative bacteraemia was somewhat higher in era 2 than in era 1, but this increase cannot be directly attributed to the use of HHFNC in the current study. Further investigation is warranted.

### CONCLUSION:

HHFNC appears to be an effective and well tolerated therapeutic alternative to nCPAP in premature infants.

### KEY POINTS:

- Use of HHFNC as a respiratory therapy in premature infants has increased markedly in recent years.
- Respiratory outcomes appear to be similar in infants treated with HHFNC compared with nCPAP.
- Re-intubation rates are lower in infants aged < 30 weeks' gestation treated with HHFNC versus CPAP.
- Further study is required to assess airway pressures generated by HHFNC devices in premature neonates, and to determine whether the use of HHFNC contributes to the development of gram-negative bacteremia.

### DEFINITIONS:

HHFNC	Humidified high-flow nasal cannula - nasal cannula (a small, half-moon shaped plastic tube, the ends of which fit into the nostrils of a patient) designed to deliver humidified gas at a high flow rate
nCPAP	Nasal delivery of continuous positive airway pressure – a technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilatory circuit
Bronchopulmonary dysplasia	A form of chronic lung disease that develops in preterm neonates treated with oxygen
Re-intubation	Intubation that is required subsequent to previous weaning from mechanical ventilation
Premature infant	A baby born before 37 weeks' gestation



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## Use of high-flow nasal cannula support in the emergency department reduces the need for intubation in pediatric acute respiratory insufficiency

### AIM:

To determine whether the use of high-flow nasal cannula (HFNC) oxygen therapy reduces the need for endotracheal intubation among pediatric patients with acute respiratory insufficiency (ARI) presenting to the emergency department (ED) and subsequently admitted to the intensive care unit (ICU). In addition, the number of days' use of HFNC oxygen therapy and mechanical ventilation (MV), length of ICU stay and mortality were assessed.

### METHOD:

This was a retrospective study of all patients aged <18 years admitted to the pediatric ICU from the pediatric ED with ARI at a single center between January 2006 and December 2009, in the USA. Acute respiratory insufficiency was defined as any acute respiratory illness severe enough to warrant admission to the ICU. Patients were excluded if they had primary central nervous system causes of ARI or a pre-existing tracheostomy, or if they were receiving non-invasive ventilation support at home, intubated prior to arrival in the ED, or not considered candidates for HFNC oxygen therapy.

Patients were assigned to one of three cohorts, depending on the date of admission. Cohort 1 was admitted before the availability of HFNC oxygen therapy (January 2006 through December 2006), cohort 2 was admitted after HFNC therapy became available but before implementation of an institutional guideline on its use and before HFNC therapy was widely used in the ED (January 2007 through June 2008) and cohort 3 was admitted after HFNC therapy was available and the guidelines were implemented, when HFNC was readily available in both the ICU and ED (July 2008 through December 2009). Data were obtained from chart review.

The HFNC system comprised a humidifier (Fisher & Paykel 850) and a continuous flow circuit (Fisher & Paykel RT 329 for children and infants; Fisher & Paykel RT 202 for adolescents). Flow ranges were 2–10 L/min for children and infants, and 5–50 L/min for adolescents; cannula sizes ranged from infant (maximum flow rate 7 L/min) to large adult (maximum flow rate 50 L/min).

### RESULTS:

The study included 848 admissions meeting the inclusion criteria; cohorts 1, 2 and 3 included 190, 289 and 369 patients, respectively. There were no significant differences in baseline characteristics of patients in the three cohorts. Mean ages were 4.1–4.8 years and 39–47% of patients in each cohort were female. The most common primary diagnoses were asthma or reactive airway disease (34–47%), bronchiolitis (23–27%) and pneumonia (16–22%).

Following the introduction of the guidelines, the use of HFNC oxygen therapy increased significantly in the ED (19% of patients in cohort 3 versus 8% in cohort 2;  $p < 0.0001$ ) and a non-significant increase was seen in the ICU (23% vs. 18%;  $p = 0.08$ ). The HFNC utilization ratio (HFNC days/total patient days) also increased after the guidelines were introduced (0.35 for cohort 3 vs. 0.19 for cohort 2;  $p < 0.0001$ ).

The use of HFNC oxygen therapy according to guidelines was associated with reduced intubation rates in the ED and overall, and a non-significant reduction in the number of intubations in the ICU, compared with before HFNC became available (see table). After adjustment for baseline characteristics, an 83% reduction in ED intubations was seen in cohort 3 compared with cohort 1 ( $p = 0.001$ ). No significant difference in intubation rates was seen between cohorts 1 and 2. Initiation of HFNC oxygen in the ED rather than in the ICU was associated with a reduction in the rate of subsequent intubation (7.6% vs. 18.1%;  $p = 0.047$ ). HFNC success rates (no requirement for intubation or non-invasive ventilation during illness) did not change significantly after the introduction of the guidelines (88% for cohort 3 versus 84% for cohort 2). There were no significant differences in total ventilator days, the duration of ICU stay, or mortality rates. Guideline-based HFNC oxygen therapy (cohort 3) was associated with reduced intubation rates across ARI types (including asthma/reactive airway disease and bronchiolitis), with the exception of croup. Intubation was performed in 30 patients for whom HFNC was unsuccessful and 75 patients in whom HFNC was not tried.

HFNC oxygen therapy was generally well tolerated and accepted by patients. One patient experienced a major complication attributed to HFNC, bilateral pneumothoraces which developed within several hours of initiation of treatment, occurred prior to the introduction of the guidelines and was considered likely to have been due to improper fitting of the cannula.

	Cohort 1 (n=190)	Cohort 2 (n=289)	Cohort 3 (n=369)	p-value
<b>Utilisation, % pts.</b>				
HFNC				
Initiated in ED	0	8	19	p<0.0001
Initiated in ICU	0	18	23	p=0.08
Total	0	25	42	p<0.0001
Mechanical ventilation				
Intubation in ED	11	10	2	p<0.001
Intubation in ICU	5	5	6	p=0.90
Total	16	16	8	p=0.004
<b>Utilisation ratios</b>				
HFNC	–	0.19	0.35	p<0.0001
Ventilator	0.41	0.32	0.21	p<0.001

### DISCUSSION:

This appears to be the first study to demonstrate that HFNC oxygen therapy in the paediatric ED is beneficial across different ages and diagnoses of ARI. The use of HFNC oxygen therapy was associated with reduced MV rates in children with ARI compared with the period before HFNC became available. Intubation rates also significantly decreased after HFNC oxygen therapy became readily available in the ED and guidelines on its use were implemented. The lack of significant difference in intubation rates following the introduction of HFNC without guidelines and with limited availability in the ED (cohort 2) compared with pre-HFNC (cohort 1) suggests that guidelines, including an education programme, and greater availability of the HFNC equipment were responsible for its increased use in the paediatric ED and consequently lower intubation rates. HFNC oxygen therapy is potentially cost saving due to reduced use of MV, which leads to reductions in costs associated with administration, sedation, and the management of ventilator-associated complications such as nosocomial pneumonia and airway injury.

### CONCLUSION:

Early initiation of HFNC oxygen therapy reduces the need for endotracheal intubation and mechanical ventilation in paediatric patients with ARI. Introduction of institutional guidelines on the use of HFNC oxygen therapy increases the rate of its use in the ED and reduces the rate of intubation.

### KEY POINTS

- Early initiation of HFNC oxygen therapy is associated with reduced need for intubation or mechanical ventilation in paediatric patients with ARI.
- Guidelines on the use of HFNC oxygen therapy and its availability in the ED are associated with reduced intubation and mechanical ventilation rates.
- Early use of HFNC oxygen therapy is not associated with increased durations of mechanical ventilation or PICU stay.

## DEFINITIONS:

95% confidence interval	A statistical measure showing that 95% of the results for that parameter lie within the range quoted
Endotracheal tube (ETT)	A tube inserted through the mouth or nose into the trachea to maintain an unobstructed airway
Heated humidifier (HH)	A device that actively adds heat and water vapor to inspired gas
High-flow nasal cannula (HFNC)	Nasal cannula (a small, half-moon shaped plastic tube, the ends of which fit into the nostrils of a patient) designed to deliver gas at a high flow rate
Intensive care unit (ICU)	A hospital facility providing intensive nursing and medical care for critically ill patients
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
Nasal oxygen cannula	A small, half-moon shaped plastic tube, the ends of which fit into the nostrils of a patient, which is used to deliver oxygen at a concentration higher than that in ambient air
Noninvasive ventilation (NIV)	The delivery of ventilatory support without the need for an invasive artificial airway

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## Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomized, masked, crossover trial

### AIM:

To examine the effects of high-flow gas therapy via nasal cannula in the presence or absence of humidification following extubation in infants in a neonatal intensive care unit (NICU).

### METHOD:

Eligible infants in the NICU were those undergoing planned extubation to a high-flow ( $\geq 1$  L/min) nasal cannula. Patients were randomised to receive either heated humidification (HH) for the first 24 hours then no humidification (standard high-flow) for the next 24 hours ( $n = 15$ ) or no humidification then humidification ( $n = 15$ ). At the end of each 24-hour treatment period the nasal mucosa was examined using a speculum and otoscope by a neonatologist unaware of treatment allocation who assigned a score from 1 (completely normal mucosa) to 5 (occluded with thick mucus and oedema, and/or haemorrhagic). A research nurse (also unaware of treatment allocation) scored respiratory effort on a scale of 0 (no retractions) to 3 (severe retractions). Retractions at 5 locations were scored, so the total respiratory effort score was 0 (no retractions in any of the 5 locations) to 15 (severe retractions in all 5 locations).

### RESULTS:

Two patients failed treatment during the first 24 hours, while they were receiving standard high flow therapy. They required re-intubation because of increasing carbon dioxide pressure and fraction of inspired oxygen. No patients initially receiving HH failed therapy during the first 24 hours. However, 5 patients failed treatment during the second 24 hours when receiving standard high-flow therapy; all were switched back to HH (median time to switch 9.5 hours). No cases of pneumothorax or respiratory infection was reported during the study. Respiratory and mucosal findings are reported in the table.

	HH	Standard high-flow
Nasal gas flow (L/min)	3.1	1.8 <sup>a</sup>
Fraction of inspired oxygen	0.31	0.32
Respiratory rate (breaths/min)	52	54
Nasal examination score	2.7	7.8 <sup>b</sup>
Respiratory effort score	1.2	2.0 <sup>c</sup>
Patients with an increase in respiratory effort score	0	6 <sup>c</sup>

<sup>a</sup> $p < 0.01$  vs. HH, <sup>b</sup> $p < 0.005$  vs. HH, <sup>c</sup> $p < 0.05$  vs. HH

### DISCUSSION:

The HH delivers molecular water vapour through a nasal cannula with nearly 100% relative humidity at body temperature. In this study, use of HH during high-flow nasal cannula gas therapy in recently extubated neonates was associated with improved outcomes in terms of mucosal health, respiratory effort and success of nasal cannula therapy. Despite higher gas flow rates during the use of HH, the nasal mucosa was less damaged. This is likely to be the result of the higher humidity and temperature of the inspired gas.

### CONCLUSION:

The use of humidity during high-flow nasal cannula therapy preserves the nasal mucosa, reduces respiratory effort, avoids re-intubation and has no recognised complications in recently extubated patients in the NICU.

## KEY POINTS:

- This study compared that effect of humidified nasal cannula (Vapotherm®) with non-humidified nasal cannula.
- This humidification allowed higher flows to be delivered to the neonate via nasal cannula, than non-humidified group.
- The non-humidified group had far worse outcomes in the nasal exam (i.e. caused more inflammation, swelling and bleeding), even though the nares were being subjected to less flow.
- Respiratory effort scores were significantly decreased in the humidified group.
- Infants in the non-humidified group had 7 failures (where patients required alternative respiratory therapies). Two of which resulted in the infant being intubated, however no such failures were reported during humidification.

## DEFINITIONS:

Speculum	A medical instrument for dilating a bodily passage or cavity in order to examine the interior.
Otoscope	A medical device used to look into the ears, nose and mouth.
Odema	Swelling caused be excess fluid.
Hemorrhagic	Bleeding (excessively)
Pneumothorax	Condition in which air escapes from the lungs into the chest cavity and compresses the lungs.
Mucosa	A collective term for the cells and mucous membranes that line the walls of the nares and airway.



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## Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates

### AIM:

To determine the safety and efficacy of heated humidified high flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) when used as non-invasive respiratory support in neonates with respiratory dysfunction.

### METHOD:

This was a randomized, controlled, unblinded, multicenter trial. Infants included were between 28 and 42 weeks gestational age, had a birth weight  $\geq 1000\text{g}$ , and there was an intention to manage them with non-invasive respiratory support either from birth (initiated within the first 24 hours of life), or at any age following a period of mechanical ventilation. Infants were randomized to heated humidified HFNC or nCPAP, and stratified according to birth weight (1000-1999g and  $\geq 2000\text{g}$ ) and age at randomization ( $\leq 7$  days vs.  $> 7$  days).

No specific device was mandated for the study; heated humidified HFNC was provided using the Comfort Flo (Hudson RCI™), Fisher & Paykel Healthcare and VapoTherm devices, whilst nCPAP was provided via interfaces including bubble and Infant Flow nCPAP System (CareFusion). Initial flow rate for heated humidified HFNC was determined according to current infant weight: 1000-1999g infants received 3 L/min, 2000-2999g infants received 4 L/min, and  $\geq 3000\text{g}$  infants received 5 L/min. Within each weight category, flow rate could be increased by  $\leq 3$  L/min above the initial flow rate. The starting pressure for nCPAP was 5-6 cm H<sub>2</sub>O or a pressure equivalent to the positive end-expiratory pressure level on ventilator support. Pressure could be increased to a maximum of 8 cm H<sub>2</sub>O. nCPAP could be discontinued when the heated humidified HFNC flow rate was  $< 2$  L/min or nCPAP was 4-5 cm H<sub>2</sub>O and the infant remained stable. Oxygenation and ventilation targets were 85-98% for oxygen saturation (SpO<sub>2</sub>), and 40-65 mmHg for partial pressure of carbon dioxide (PCO<sub>2</sub>).

The primary outcome of the study was failure of study support mode (defined as the need for intubation within the first 72 hours of treatment). Secondary endpoints included rates of bronchopulmonary dysplasia (BPD), total ventilator days, days on supplemental oxygen, and a need for delayed intubation.

### RESULTS:

Between December 2007 and April 2012, 432 infants were enrolled in the study and randomized to either heated humidified HFNC (n=212) or nCPAP (n=220). Demographic characteristics between groups were similar. More than 90% of infants were  $< 7$  days of age at randomization, and the most common diagnosis was respiratory distress syndrome.

There was no significant difference between groups in the primary outcome of failure of support within 72 hours (see table), and the reasons for early failure and intubation were similar between groups (increasing respiratory distress: 83% in both heated humidified HFNC and nCPAP groups [p=0.951]; increased fraction of inspired oxygen [FiO<sub>2</sub>]: 39% and 50% in the heated humidified HFNC and nCPAP groups [p=0.539]; and severe apnea: 22% and 11% in the heated humidified HFNC and nCPAP groups [p=0.438]). 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 HFNC (see table). At 7 days post-study entry, significantly more infants receiving heated humidified HFNC than nCPAP remained on the treatment. 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.

Variable	Heated humidified HFNC	nCPAP	p-value
Early respiratory failure, % pts	11	8	NS
Need for reintubation, % pts	15	11	NS
Remaining on therapy 7 days post-study entry, % pts	23	9	<0.001
BPD, % pts	20	16	NS
Home O <sub>2</sub> , % pts	19	18	NS
Median days on positive pressure support	6	4	<0.001
Median days on study mode	4	2	<0.001
Median days on supplemental O <sub>2</sub>	10	8	NS

BPD, bronchopulmonary dysplasia, HFNC, high flow nasal cannula; nCPAP, nasal continuous positive airway pressure; NS, not significant; O<sub>2</sub>, oxygen; pts, patients.

#### CONCLUSION:

The results of this study show that there was no difference in early support failure rates or several respiratory outcomes in infants with respiratory dysfunction treated with HFNC or nCPAP. HFNC appears to have a similar efficacy and safety profile to nCPAP when used to treat infants with respiratory dysfunction. The same results were found whether heated humidified HFNC was used as initial therapy or post-extubation. Patients receiving HFNC were treated significantly longer than patients receiving nCPAP, but there was no evident reason for this difference found when caregivers were asked to assess patient comfort, device humidification or ease of use. Despite the difference in length of treatment between groups, there were no long-term effects in the heated humidified HFNC group versus the nCPAP group based on the results of the other endpoints examined.

#### KEY POINTS

- Heated humidified HFNC appears to have a similar efficacy and safety profile to nCPAP when used in infants with a gestational age  $\geq 28$  weeks and respiratory dysfunction, irrespective of whether heated humidified HFNC was used as initial therapy or after extubation.
- Patients receiving heated humidified HFNC were treated significantly longer than patients receiving nCPAP, but no reason for this difference was found.
- Despite this difference, there were no long-term effects in the heated humidified HFNC group versus the nCPAP group based on the results of the other endpoints examined.

## DEFINITIONS:

Fraction of inspired oxygen (FiO <sub>2</sub> )	The proportion of oxygen in the air that is inspired
Heated humidifier (HH)	A device that actively adds heat and water vapor to inspired gas
High-flow nasal cannula (HFNC)	A technique to provide a range of flows of heated, humidified oxygen and air to patients requiring respiratory support, delivered through nasal cannulae
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
Nasal delivery of continuous positive airway pressure (nCPAP)	A technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilator circuit
Oxygen saturation by pulse oximetry (SpO <sub>2</sub> )	Oxygen saturation as measured by pulse oximetry
Partial pressure of carbon dioxide (PCO <sub>2</sub> )	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

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## Nasopharyngeal airway pressures in bronchiolitis patients treated with high-flow nasal cannula oxygen therapy

### AIM:

To measure nasopharyngeal pressures according to flow rates in infants with moderate to severe bronchiolitis receiving heated humidified high-flow nasal cannula (HFNC) oxygen therapy. The secondary objective was to assess clinical improvement with HFNC oxygen therapy.

### METHOD:

This prospective observational study was conducted at a single pediatric emergency department (ED) in the USA between 2009 and 2011. A convenience sample of non-premature infants aged from 1 month to 1 year presenting to the ED was enrolled. Patients were required to have a clinical diagnosis of moderate to severe bronchiolitis and a Respiratory Distress Assessment Instrument (RDAI) score of >10 at baseline. Patients were initially treated in the ED with oxygen given via face mask, intravenous fluids and/or aerosolized  $\beta_2$  agonists or epinephrine; RDAI score was determined 20 minutes after the last dose of aerosolized treatment and patients enrolled in the study if the score remained  $\geq 10$ .

Oxygen therapy was delivered using HFNC (Fisher & Paykel) with outer diameters of 0.2cm for infants aged <2 months and 0.3cm for those aged 2–12 months. Oxygen was delivered via a standardized wall unit, oxygen blender and flow meter through a heated humidifier (Fisher & Paykel). The initial flow rate was 1 L/min and this was increased by 0.5 L/min until clinical improvement, defined as a Respiratory Assessment Change Score (RACS) of  $\geq 4$ , was seen (maximum 8 L/min). The inspired oxygen concentration was adjusted by the attending physician according to individual patients' needs. Nasopharyngeal pressure was monitored continuously using a solid-state tip pressure transducer inserted in the nasopharynx 1cm less than the distance between the tragus and the tip of the nose. Mean nasopharyngeal pressure was calculated over a period of 20 seconds after each change in flow rate for both open- and closed-mouth states.

### RESULTS:

Twenty-five patients were enrolled. The mean age and bodyweight were 78.1 days and 5.3kg, respectively, and 56% were male. The mean baseline nasopharyngeal pressure was 0.20 cm H<sub>2</sub>O.

A linear increase in nasopharyngeal pressure with flow rate of 0.45 cm H<sub>2</sub>O per 1L/min increase in flow rate was observed. The rate of increase in pressure was higher with flow rates of up to 6 L/min and above 6 L/min. Rapid stabilization of nasopharyngeal pressure was observed after increase in flow rate. At flow rates up to 6 L/min, the generated pressure was significantly different for open- versus closed-mouth states (see table). Flow rate ( $p < 0.001$ ), but not age or sex, was found to be significantly associated with the nasopharyngeal pressure generated. Clinical improvement occurred at a mean nasopharyngeal pressure of 3.4 cm H<sub>2</sub>O.

A significant improvement in RDAI scores was seen following HFNC therapy, with a mean reduction from 14.5 (SD 1.4) pre-therapy to 10.4 (SD 1.2) post-therapy ( $p < 0.001$ ). Most (23) patients were considered to have significant improvement in their condition post-therapy and were admitted to the regular pediatric ward; two patients required admission to the pediatric intensive care unit.

HFNC oxygen therapy was well tolerated, with transient discomfort during insertion of the transducer and nasal cannula being the only adverse effect; this resolved within a few minutes.

HFNC flow rate	Nasopharyngeal pressure (cm H <sub>2</sub> O), mean		Difference (cm H <sub>2</sub> O), mean
	Closed-mouth	Open-mouth	
2 L/min	0.80	0.68	0.12 <sup>a</sup>
4 L/min	1.72	1.57	0.15 <sup>a</sup>
6 L/min	2.74	2.47	0.27 <sup>b</sup>

*a p < 0.05 for difference; b p < 0.001 for difference HFNC, high-flow nasal cannula*

## DISCUSSION:

This is the first prospective study to determine the relationship between nasopharyngeal pressure and heated humidified HFNC oxygen therapy in full-term infants with bronchiolitis. This study showed that nasopharyngeal pressure increases linearly with flow rates up to 6 L/min in children with bronchiolitis receiving HFNC oxygen therapy, a finding consistent with studies in premature infants. The study also found that nasopharyngeal pressure was significantly different for open- and closed-mouth states, but was not affected by bodyweight. Flow was affected by pressure but not patients' age or sex. Although the study was not designed to assess the efficacy and safety of HFNC oxygen therapy, clinical improvements were observed and treatment was well tolerated.

The findings of this study suggest that HFNC may be useful in non-premature infants with respiratory distress and management of bronchiolitis, and further study is therefore warranted.

## CONCLUSION:

Nasopharyngeal pressure increases linearly with the flow rate of HFNC oxygen therapy in non-premature infants with moderate to severe bronchiolitis. HFNC oxygen therapy appears to improve clinical outcome in this patient population.

## KEY POINTS:

- In infants receiving heated humidified HFNC oxygen therapy, nasopharyngeal pressure increases linearly with flow rate.
- Nasopharyngeal pressure is significantly different in the open- and closed-mouth states.
- Heated humidified HFNC oxygen therapy may improve clinical outcome in infants with moderate to severe bronchiolitis.

## DEFINITIONS:

Fraction of inspired oxygen (FiO <sub>2</sub> )	The fraction of oxygen in inspired gas
High-flow nasal cannula (HFNC)	Nasal cannula (a small, half-moon shaped plastic tube, the ends of which fit into the nostrils of a patient) designed to deliver gas at a high flow rate
Heated humidifier (HH)	A device that actively adds heat and water vapor to inspired gas
Intensive care unit (ICU)	A hospital facility providing intensive nursing and medical care for critically ill patients
Respiratory Assessment Change Score (RACS)	The sum of the change in RDAI and a standardized score for change in respiratory rate (1 unit for every 10% decrease in RR over 5% from baseline)
Respiratory Distress Assessment Instrument (RDAI)	A validated 6-item scoring tool for assessing respiratory distress in patients with bronchiolitis. Scores range from 0 to 17, with higher scores indicating greater severity of respiratory distress.
Fraction of inspired oxygen (FiO <sub>2</sub> )	The fraction of oxygen in inspired gas

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## Work of breathing using high-flow nasal cannula in preterm infants

### AIM:

To investigate the work of breathing (WOB) in preterm infants treated with a high-flow nasal cannula (HFNC) or nasal continuous positive airway pressure (nCPAP).

### METHOD:

Eighteen preterm infants (birth weight <2.0 kg) received respiratory support with HFNC and nCPAP in a random order. The indication for respiratory support was mild respiratory distress syndrome, chronic lung disease and/or apnoea of prematurity. Respiratory support was given via Inca nasal prongs (Ackrad Laboratories). HFNC therapy was given at rates of 3, 4 and 5 L/min, and CPAP (Infant Bird Ventilator, Viasys Healthcare) was given at 6cm H<sub>2</sub>O. Data were collected over the last 30 seconds of each 5-minute treatment period. Respiratory inductance plethysmography was used to record chest wall and abdominal movements, oesophageal pressure was measured using an oesophageal catheter to approximate pleural pressures.

### RESULTS:

There were no significant differences between nCPAP and the 3 different levels of HFNC with respect to WOB, tidal volume, respiratory rate and phase angle. Compliance was significantly higher with HFNC 5 L/min compared with nCPAP ( $p = 0.03$ ). End-distending pressures during HFNC did not vary significantly versus nCPAP except for HFNC 5 L/min ( $p < 0.05$ ). Mean end distending pressures were below 2 cmH<sub>2</sub>O from baseline readings in all cases.

### DISCUSSION:

HFNC therapy has been used as an alternative to nCPAP, assuming comparable respiratory support; however, very few data exist. Data from this study showed no significant difference between HFNC and nCPAP in terms of WOB. There has been some concern about overdistension and potential harm from pneumothoraces with HFNC therapy. However, in this study, increases in end-distending pressures were small.

### CONCLUSION:

HFNC therapy provides similar respiratory support to nCPAP at 6cm H<sub>2</sub>O in preterm neonates requiring mild respiratory support. However, additional data on the effects of HFNC therapy, specifically outcomes data, length of hospital stay, and rates of chronic lung disease, infection and pneumothorax, are required.

### KEY POINTS:

- The HFNC used in this study (Vapotherm<sup>®</sup>) is being used to wean from and in some cases an alternative to nCPAP, especially in mild respiratory dysfunction.
- The positive end distending pressures generated in infants during HFNC is comparable to that of nCPAP. This is unsurprising as the flows used in standard nCPAP and those used in HFNC are similar in this study.
- There were no significant differences between nCPAP and HFNC in all other measured respiratory factors (WOB, V<sub>t</sub>, RR and phase angle)
- Because end distending pressure can be delivered via nasal cannula, some form of pressure relief is always recommended.

## DEFINITIONS:

HFNC	High flow nasal cannula
nCPAP	Nasal Continuous positive air pressure – one positive pressure is applied for the whole respiratory cycle and delivered via nasal prongs
Respiratory Distress Syndrome	An illness most commonly associated with prematurity, where the alveolar sacs have a tendency to collapse on exhalation, due in part to a lack of surfactant
Chronic Lung Disease	A general term for long-term respiratory problems in premature infants. It is also known as bronchopulmonary dysplasia (BPD)
Apnoea of Prematurity	A common condition in neonates where breathing ceases momentarily
Inductance Plethysmography	A way on measuring respiratory parameters using electrical bands placed around the chest
Pleural Pressure	The pressure surrounding the lung, within the pleural space
Phase Angle	The degree of difference between the rib cage and abdominal movement during breathing. A measurement often used to indicate respiratory distress.
Compliance	The ease of lung expansion
End Distending Pressure	Pressure in the lungs at the end of expiration
Over Distension	An injury caused by over inflation of the lung
Pneumothoraces	Condition in which air escapes from the lungs into the chest cavity and compresses the lungs



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## Effect of HFNC flow rate, cannula size, and nares diameter on generated airway pressure: an in vitro study

### AIM:

To investigate the effect of high flow nasal cannula (HFNC) flow rate settings on delivered airway pressure with different nasal prong-to-nares diameters in an active neonatal lung model.

### METHOD:

HFNC oxygen therapy [RT329; Fisher & Paykel] was supplied to a test lung set to simulate normal to moderately affected lungs of a 1-3kg infant. Fixed flow rates of 0, 1, 2, 3, 4, 5 and 6 L/min were tested. Two different sizes of nasal cannulae were used [Fisher & Paykel], a neonatal cannula (outer prong diameter 3mm) and an infant cannula (outer prong diameter 3.7mm). Each cannula was tested using 7 different simulated nare openings (internal diameter 3-7mm). Resulting ratios of prongs to nares were 0.43-1.06, with corresponding nares occlusion of 18.4-100.0%. Full or partial mouth closure was simulated by closing a Teflon stopcock (5mm orifice situated midway between the nares/prongs and the test lung) by 100% or 50%, respectively.

### RESULTS:

Overall, when the mouth-leak valve was set to the open position there was an increase in airway pressure as both the prong-to-nares diameter ratio and HFNC flow rate increased, and cannula flow was almost exactly the same as HFNC flow from 0-5 L/min. Under the same conditions, when there was full nasal occlusion the maximum airway pressure was <1.7 cm H<sub>2</sub>O at the highest flow rate tested (6 L/min). Airway pressures were higher in the mouth closed versus mouth open condition, but remained <10 cm H<sub>2</sub>O even at 6 L/min. When the mouth-leak valve was closed and the prong-to-nares ratio was >0.9 (equivalent to 85-100% occlusion of the nares), airway pressures quickly reached those that would trigger the pressure-release valve at flow rates of <2 L/min.

### DISCUSSION:

There is a trend towards utilisation of alternatives to endotracheal ventilation to provide respiratory support in premature infants. The aim is to reduce the incidence of chronic lung disease in these children. Noninvasive ventilation options include nasal continuous positive airway pressure, nasal intermittent positive-pressure ventilation and HFNC oxygen therapy. Use of a heated and humidified HFNC system is the only one of these which does not require close fitting of nasal prongs within the nares. Adequate but not excessive positive pressure support requires a balance between prong size of the nares and the flow rates of the gas. Selection of the correct nasal prong-to-nares ratio helps to ensure delivery of the appropriate level of pressure support.

### CONCLUSION:

The data generated in this *in vitro* study indicate that an appropriate nasal prong-to-nares ratio and an integrated pressure-release valve are important for safe and effective delivery of HFNC oxygen therapy in preterm infants.

### KEY POINTS:

- For HFNC to be safe and effective in preterm infants, selection of an appropriate nasal prongs-to-nare ratio is important.
- An integrated pressure-release valve is an important component of a safe and effective HFNC system for use in preterm infants.

## DEFINITIONS:

High-flow nasal cannula (HFNC) oxygen therapy	A device designed to provide a high flow of heated, humidified oxygen and air to patients requiring respiratory support, delivered through nasal cannulae
Nasal continuous positive airway pressure (NCPAP)	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)	The delivery of positive pressure ventilatory support via the nose without the need for an invasive artificial airway
Noninvasive ventilation (NIV)	The delivery of ventilatory support without the need for an invasive artificial airway

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## Pharyngeal pressure with high-flow nasal cannulae in premature infants

### AIM:

To measure pharyngeal pressure in premature infants receiving high-flow nasal cannula (HFNC) therapy at flow rates of 2-8 L/min.

### METHOD:

Eighteen infants (10 female; median corrected gestational age 33.6 weeks; median weight 1.619kg) who were receiving HFNC for the treatment of respiratory distress syndrome, chronic lung disease or apnoea of prematurity were included in the study. Pharyngeal pressures were measured using a 0.21cm diameter catheter with a single solid-state catheter-tip pressure transducer (CTO-1; Gaeltec). The catheter was inserted into one nostril to a distance 1cm less than the measured distance from tip of nose to tragus, to ensure positioning in the nasopharynx. Flow rate was increased sequentially to a maximum of 8 L/min, then decreased to a minimum of 2 L/min. Stable recording of >20 seconds was observed before changing parameters. Mean pharyngeal pressure over the longest period of stable recording was calculated. Short, narrow-calibre, tapered nasal cannulae (Fisher and Paykel Healthcare) were connected to a standard humidifier base (MR850; Fisher and Paykel) and circuit without a pressure-limiting valve (Oxygen Therapy System RT329; Fisher and Paykel). Pressures were recorded with the mouth in the resting position (passive) and with the mouth actively closed (by gently placing a finger under the infant's chin). Cannulae were chosen to comfortably fit into the patient's nostrils without occluding them. Neonatal cannulae (outer diameter 0.14cm) were used in 13 infants, infant cannulae (0.19cm) were used in 2 infants, and paediatric cannulae (0.27cm) were used in the remaining 3 patients.

### RESULTS:

There was a significant linear relationship between pharyngeal pressure and flow rate ( $p < 0.001$ ), that was not affected by adjustment for infant weight or mouth closure. The average increase in pressure for each 1 L/min increase in flow was 0.8cm H<sub>2</sub>O. There was also a significant association between infant weight and pressure ( $p = 0.001$ ), with average pressure decreasing by 1.4cm H<sub>2</sub>O for each 1kg increase in body weight. No association between mouth closure and pharyngeal pressure was observed. The relationship between pharyngeal pressure, flow and bodyweight could be expressed as:  $2.6 + 0.8 F - 1.4 \text{ wt}$  (where F is flow in L/min and wt is bodyweight in kg).

### DISCUSSION:

The pressures recorded in this study are lower than those reported previously. Both cannula diameter and measurement technique may have contributed to the differences. HFNC is an alternative to nasal continuous positive airway pressure (nCPAP). Changes in pharyngeal pressure relative to flow rate have also been documented with nCPAP, with mouth closure increasing pharyngeal pressure by 1.1cm H<sub>2</sub>O. In contrast, mouth closure had no effect on pharyngeal pressure during HFNC in this study. One of the safety concerns with HFNC is that the pressures transmitted may lead to barotrauma. While this trial was not designed to answer that question, the ranges of pressures generated during HFNC were within the range of commonly used nCPAP pressures. However, pressures of >10cm H<sub>2</sub>O were documented in 2 infants during HFNC therapy. Therefore, it may be prudent to limit the flows used during HFNC therapy in preterm infants, particularly those with a bodyweight of 1kg.

### CONCLUSION:

This study increases understanding of the pressures generated during HFNC therapy in preterm infants, and the variables affecting these pressures. The results may help guide appropriate flow levels for use in infants of different bodyweights.

### KEY POINTS:

- No studies have previously examined pressures generated during the use of HFNC in premature infants.
- There was a significant relationship between flow rate and pharyngeal pressure.
- There was a significant inverse relationship between body weight and pharyngeal pressure.
- In the majority of patients, pressures generated during HFNC were similar to those commonly used for nCPAP.
- Generation of pressures >10cm H<sub>2</sub>O in 2 patients indicate that it may be prudent to limit flows used during HFNC therapy, particularly in premature infants with a bodyweight of <1kg.

## DEFINITIONS:

HFNC	High-flow nasal cannula – nasal cannula (a small, half-moon shaped plastic tube, the ends of which fit into the nostrils of a patient) designed to deliver gas at a high flow rate
NCPAP	Nasal delivery of continuous positive airway pressure – a technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilator circuit
Premature infant	A baby born before 37 weeks' gestation
Respiratory distress syndrome	A lung disease of the new-born, 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
Apnoea of prematurity	A phenomenon that occurs in premature babies when the part of the central nervous system that controls breathing is not yet mature enough to allow continuous breathing. This results in large bursts of breath followed by periods of shallow or stopped breathing
Barotrauma	Trauma caused by rapid or extreme changes in air pressure



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